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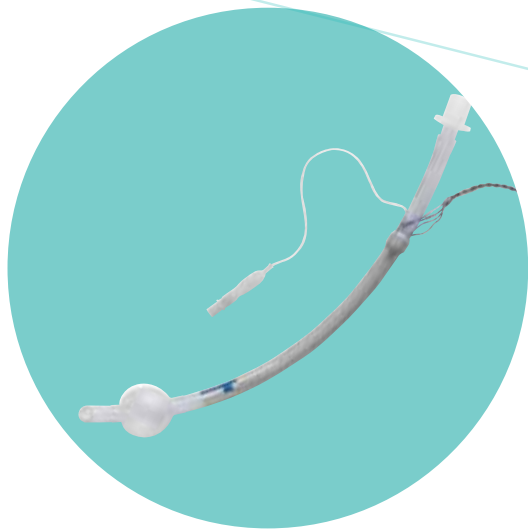
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Volume 7 Issue 1 December 2014

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Welcome to Volume 7 Issue 1 of Journal of ENT Masterclass 2014

In its eleventh year ENT Masterclass® has evolved into a truly international training platform; ENT Masterclass® 'Australia' was launched in April 2014 at Sydney led by Prof Carsten Palme and Faruque Riffat and was a resounding success. Other new courses launched in 2014 were the Consultant's Revalidation ENT Masterclass®, National GP ENT Masterclass® and the DOHNS Revision Masterclass. The ENT Masterclass® Academic Travelling club is being planned for its first venture to India in December 2014.

The January 2015 ENT Masterclass® faculty now includes Professor Javier Gavilan (Spain), Dr Carsten Palme (Australia), Dr Faruque Riffat (Australia), Professor Oliver Kaschke (Germany), Professor Mumtaz Khan (USA) and Professor Scharukh Jalisi (USA). It is commendable that they have all volunteered for this innovative training platform, by contributing their time and paying for all their own expenses. The generosity and the enthusiasm of the 70 voluntary faculty members from 4 different continents across 12 different courses is vital for the ongoing successful delivery of a world class training service.

The updated, 3rd edition of the Cyber textbook for ENT Surgery was launched in May 2014, with 364 surgical videos. It has been very well received and along with the webcasts of the archived courses they are the most popular resources on our website with several thousand hits from over 70 countries every month. The training platform remains free and over the last ten years, over £1.8 million of educational resources have been provided to ENT trainees.

The Journal of ENT Masterclass is now in its seventh year and has reached new heights. The Chairman of the Editorial Board, Prof Pat Bradley has announced his plan to step down next year after an illustrious term. On behalf of the ENT Masterclass team I would like to thank Pat for his tremendous contribution to this concept of free training since the launch of ENT Masterclass in 2004. He has always been available to guide the various training modalities as they have developed over the years. We wish him all the best in retirement.

The Editorial Board has seen the entry of Mr James England, Prof J P O'Neill, and Prof Mumtaz Khan. I would like to thank Mr Rory-Walsh and Mr Derek Skinner for their valuable support over the years, who are now stepping down after completing their terms in the Editorial Board. The addition of Sub-Editors in 2013 for different sections proved very successful, with a nice variety of articles for the 7th Edition. The seventh Journal comes out with 25 key articles from UK and abroad and we are thankful for all those who have contributed to this successful publication. The past 6 editions of the journal are available in pdf format from the website:

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We welcome ideas and comments on our work as this is an evolving platform, which considers feedback as its key to innovation.

The support of the faculty, volunteers, sponsors, delegates, well-wishers and Doncaster & Bassetlaw NHS Foundation trust remains instrumental in maintaining this high standard free training platform.

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Mr M Shahed Quraishi, FRCS, FRCS (ORL, H&N)

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Recurrent ear infections in children

Mary-Louise Montague

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Abstract:

Acute otitis media (AOM) is a common illness in childhood and becomes recurrent in up to 20%. Recurrent acute otitis media (RAOM) is associated with significant negative impact on quality of life for the affected child and their care-givers. This review article considers the definition, epidemiology, and pathogenesis of RAOM in children. It focuses in particular on the investigation of children referred to the ENT clinic and treatment options available taking into consideration recent updates to the evidence base. Optimal management of RAOM remains a clinical challenge. A logical stepwise approach to management considering all treatment modalities including modification of risk factors is appropriate. Research priorities in the management of RAOM include the role of adenoidectomy and its relative benefits in different age groups of children and the optimal antibiotic for prophylaxis and duration of prophylaxis.

Key words

Otitis media, recurrent acute otitis media, children

J ENT Masterclass 2014; 7 (1): 5 - 9.

Introduction

Strictly speaking the complete spectrum of recurrent ear infections in children encompasses diagnoses of otitis externa and recurrent acute otitis media. In children with recurrent episodes of ear infection associated with otorrhoea, a diagnosis of chronic suppurative otitis media, either mucosal or squamous (i.e. cholesteatoma) must also be considered and excluded. The focus of this review however will be on recurrent acute otitis media in childhood.

Definitions

Acute otitis media (AOM) refers to inflammation of the middle ear of rapid onset resulting in an infected effusion and presenting with one or more local or systemic signs and symptoms of acute infection¹. AOM becomes a recurrent problem in up to 20% of children. Recurrent acute otitis media (RAOM) has been defined as three or

more episodes of AOM in the preceding 6 months, or four or more episodes in the preceding 12 month period with complete resolution of symptoms and signs between episodes of infection².

Epidemiology

AOM is one of the most common paediatric infectious diseases second only to viral upper respiratory tract infections. It is most common between the ages of three months and three years with the peak incidence between six and eighteen months of age. It is seen most frequently in the winter months. Approximately 70% of children will have had an episode of AOM by the age of two years and 90% of children will have had at least one infection by the age of six-years³.

The risk factors for this condition can be classified into those that are either host-related or environmental. With respect to host-related risk factors a first episode of AOM at a young age and especially under the age of six months is associated with recurrence. Boys appear to be more otitis prone than girls³. RAOM is reportedly more common in native Americans, Canadian Eskimos and Australian aborigines but these differences need to be interpreted with caution as they may be due to variability in socioeconomic status, accessibility of medical care and differences in climate⁴. Craniofacial abnormalities including cleft palate and submucous cleft palate are known risk factors. Immunodeficiency secondary to congenital or acquired immune deficiency, immunoglobulin deficiencies or immunosuppressive drug therapies also confer risk. Syndromic diagnoses, in particular Down syndrome and Turners syndrome are associated with recurrent ear infections. A genetic predisposition to RAOM must exist as evidenced by twin studies⁵.

Considering environmental risk factors it is clear that climate and season play a part with episodes of infection being more common in autumn and winter, this mirroring the increase in viral upper respiratory tract infections. Evidence from metanalysis of otitis media risk factor

studies confirm an increased risk of otitis media from passive smoke exposure, child care outside the home and formula feeding in preference to breast feeding for three or six months⁶. It is also more common in lower socioeconomic groups probably related to damp over-crowded living accommodation and in children who use a pacifier.

In summary AOM and RAOM are infectious diseases which are multifactorial in aetiology and which result from an interaction between viral and bacterial microbial load, eustachian tube dysfunction and an immature host immune response.

Pathogenesis

An antecedent viral URTI usually disrupts eustachian tube function by causing oedema and blockage. This results in stasis of middle ear secretions. The middle ear mucosa subsequently becomes inflamed and a middle ear effusion is produced in which bacterial pathogens proliferate. In infants and children the eustachian tube is shorter, lacks stiffness and is more horizontally orientated. This probably allows for easier access to the middle ear by potential pathogens. Although viral infection is important in the pathogenesis of AOM, the majority of cases will develop subsequent bacterial colonisation, and therefore AOM should be considered to be a predominantly bacterial infection. The most commonly implicated bacterial pathogens are shown in Figure 1. Organisms other than Pneumococcus, Haemophilus Influenzae and Moraxella Catarrhalis and less commonly implicated include Group A Streptococci, Staphylococcus Aureus, and Gram negative organisms such as Pseudomonas Aeruginosa. It is worth noting that 20% of middle ear isolates prove to be culture negative.

Diagnosis

AOM is typically preceded by an upper respiratory tract infection and presents with fever, otalgia, otorrhoea if perforation has occurred and hearing loss. Otalgia has the highest diagnostic predictive value. Vomiting or diarrhoea, anorexia and irritability are non-specific features but may in fact be the only indication of infection in infants. The

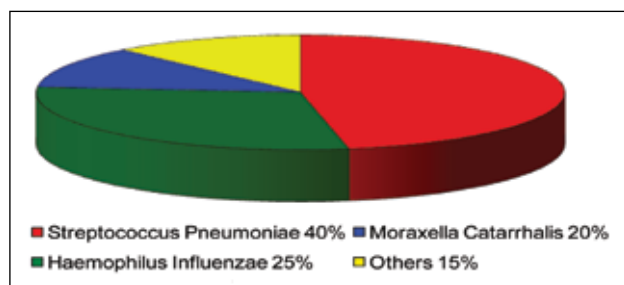


Figure 1: Bacterial pathogens implicated in AOM and RAOM.

clinical findings in children with RAOM referred to the ENT outpatient clinic will depend largely on the timing of presentation to the clinic. In the acute phase at otoscopy the tympanic membrane will be bulging and hyperaemic with opacification and loss of normal ossicular landmarks. The normal light reflex will be dull or absent. Between episodes there may be a tympanic membrane perforation with or without otorrhoea or a persistent effusion. The tympanic membrane is often normal in appearance between episodes. It is imperative to look in the mouth and assess the palate and in the nose looking for any possible source of infection. All children referred merit age appropriate audiological assessment and tympanometry.

Management

Having established a diagnosis of RAOM management options require consideration and full discussion with parents or carers. A logical stepwise approach can be adopted in counselling and individualising management plans as outlined in Figure 2. A large part of the management centres on the assessment and modification of risk factors. Thereafter management options include treatment of individual episodes, antibiotic or chemoprophylaxis, immunoprophylaxis, and surgery or indeed any combination of these strategies.

There is some evidence from non-randomised controlled trials that health promotion and education with an emphasis on prolonging breastfeeding, limiting pacifier use, eliminating passive smoke exposure and postponing daycare of young children until over the age of six months can have a positive influence on RAOM.

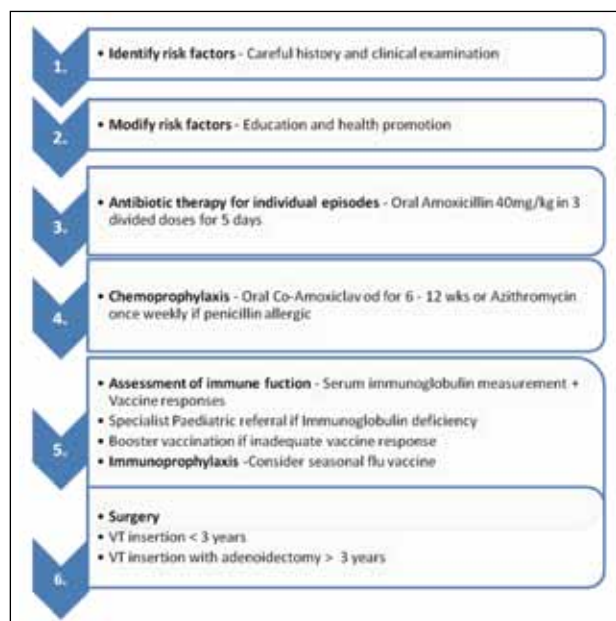


Figure 2: A stepwise approach to the management of recurrent acute otitis media in children.

There may be some children in whom it is appropriate to simply treat each AOM episode as it occurs whilst waiting for the child to grow out of the problem. This really depends on the frequency of episodes and the impact of the condition on parents or carers. This management strategy aims to shorten the duration of each episode of AOM. Treatment of individual episodes of AOM is outlined in the Scottish Intercollegiate Guidelines Network Guideline Number 66⁷. This guideline places emphasis on watchful waiting versus immediate antibiotic therapy and favours symptomatic treatment of pain and fever with paracetamol and ibuprofen in the first 48 to 72 hours. It does recommend antibiotic therapy in the event of failure of watchful waiting after 48 to 72 hours. It does not make any specific recommendations with respect to very young children, under 2 years, those with a cochlear implant, Down Syndrome, cleft palate or known immunodeficiency. Many paediatric otolaryngologists would favour immediate recourse to antibiotic therapy in these groups. The antibiotic of choice is amoxicillin delivered orally in a conventional five day course at dosage levels indicated in the British National Formulary. It is the most effective oral agent against *Streptococcus Pneumoniae*. It is safe, inexpensive and its taste is acceptable to the paediatric population. It does not however provide antimicrobial cover for beta-lactamase producing *Haemophilus Influenzae* or *Moraxella Catarrhalis*. All the focus is on the *Pneumococcus* as it is the most common initial bacterial pathogen and the most common isolate after failed therapy. AOM episodes where pneumococcus is the causative organism are not only least likely to self resolve but are also most likely to cause severe otitis media and suppurative complications. This gram positive diplococcus has a polysaccharide capsule which contributes to its virulence.

Although often prescribed oral decongestants and antihistamines have no proven benefit and are generally not recommended.

Chemoprophylaxis has had a long record of efficacy during the winter upper respiratory tract infection season. There is no consensus on the choice of antibiotic or duration of prophylaxis with Amoxicillin, Co-Amoxiclav, Trimethoprim, Azithromycin and others all having been tried for anything from 6 weeks to 6 months. Once daily oral amoxicillin, is the most commonly adopted regimen. Some favour a single daily dose of Co-Amoxiclav for a period of three months. This affords the addition of clavulanate and whilst this provides no additional coverage for pneumococcus compared to amoxicillin it does afford excellent coverage for beta lactamase positive *Haemophilus Influenzae* and *Moraxella Catarrhalis*. A 2006 Cochrane review analysed 16 studies of long-term antibiotic use for

AOM and found such use prevented 1.5 episodes of AOM per year, reducing in half the number of AOM episodes during the period of treatment⁸. Antibiotic prophylaxis has been shown to be effective in reducing otitis media recurrence, recurrence frequency and total recurrence time⁹. This must be countered against the growing evidence that long-term antibiotic prophylaxis for RAOM is associated with the emergence of resistant *Pneumococcus*. In some children hypersensitivity reactions preclude continued antibiotic prophylaxis and in others compliance with prophylaxis is uncertain.

Assessment of immune function has a part to play in some children. This involves measurement of serum immunoglobulin levels including Immunoglobulin G subclasses with the main interest being in the serum Immunoglobulin G2 level. Vaccine responses to *Pneumococcus* and *Haemophilus Influenzae* are also assessed. This should be considered when breakthrough infections occur during antibiotic prophylaxis or if there is further RAOM upon completion of antibiotic prophylaxis¹⁰. RAOM occurring alongside infections in other systems should also raise suspicion of an underlying immunodeficiency. Identified immunoglobulin deficiencies or deficient vaccine responses warrant specialist paediatric referral or booster vaccinations respectively.

7-valent pneumococcal conjugate vaccine (Prevenar) is immunogenic in children under two years and its use in unselected cohorts has been shown to be associated with an 8% reduction in AOM frequency and a 24% reduction in the need for grommet insertion¹¹. More recent research into its use in children with AOM onset before 6 months of age, implying a high risk for RAOM, resulted in AOM incidence being reduced by 26%, emergency visits reduced by 36% and halved the need for ventilation tubes compared to unvaccinated controls¹². 23-valent polysaccharide pneumococcal vaccine (Pneumovax) provides marginal benefit for children over the age of two years. Another vaccine that appears to lower the risk of AOM in children is the live-attenuated intranasal influenza vaccine. One team of researchers found that children who were given the vaccine before the start of the flu season were 43% less likely to develop AOM than children who were not vaccinated¹³.

Surgical treatment options include ventilation tube insertion alone or ventilation tube insertion with concurrent adenoidectomy. Ventilation tubes appear to play a significant role in maintaining a disease-free state in the first six months after insertion¹⁴. Rosenfeld and Bluestone

recorded 67% fewer episodes of AOM in children with ventilation tubes compared to controls in 2003¹⁵.

Ventilation tubes should be considered at the outset for those children in whom the burden of RAOM has been significant with significant carer anxiety or reduced quality of life. Ventilation tubes should also be considered for those children who either cannot tolerate antibiotic prophylaxis or who have had break-through infections whilst on or upon withdrawing antibiotic prophylaxis. Most parents or carers, having been counselled regarding post-operative risks, consider the post-ventilation tube perforation rate of 2% associated with short-term tubes and the potential post-ventilation tube otorrhoea rate of up to 20% to be offset by the potential for improved quality of life for the child and whole family, reduced need for antibiotic therapy and improved hearing.

Concurrent adenoidectomy with ventilation tube insertion has previously been thought to confer no major advantage over tubes alone in preventing otitis media in children under the age of two years¹⁶. The current evidence is somewhat conflicting though with a recent report that children under 2 years with RAOM were likely to benefit from adenoidectomy with no significant benefit conferred in children over the age of 2 years with RAOM¹⁷. Other researchers reported that adenoidectomy with ventilation tube insertion may be superior to ventilation tubes alone in reducing the chance of future tube insertions and the risk of RAOM after tube extrusion in children older than four years¹⁸. The benefit of concurrent adenoidectomy appears to be greatest for these older children irrespective of adenoid size¹⁹. Emerging evidence regarding the presence of nasopharyngeal biofilm-producing otopathogens as a factor favouring RAOM²⁰ might explain this finding. Those in the UK who believe that the adenoids may influence AOM and recurrence by either physical obstruction of the eustachian tube or as a potential reservoir of pathogenic bacteria not unreasonably offer adjuvant adenoidectomy in children over the age of three years. Some also favour techniques such as suction diathermy adenoidectomy and coblation adenoidectomy that afford more complete adenoid reduction whilst minimising both intra-operative blood loss and risk of post-operative bleeding.

More recent evidence has emerged that a vitamin D deficit is common in children with RAOM and is associated with an increase in the occurrence of AOM when serum 25-hydroxy vitamin D levels are less than 30ng/ml²¹. The administration of vitamin D supplementation to restore serum values to greater than 30ng/ml is associated with a significant reduction in the risk of uncomplicated AOM.

Whilst this is a novel finding and reaches statistical significance the benefit of vitamin D supplementation must be considered to be modest as treated children experienced only one episode less of AOM than controls.

Recent years have also seen research into the association of otitis media including RAOM with gastroesophageal reflux disease (GORD). Whilst the prevalence of GORD in children with RAOM may be higher than the overall prevalence for children, a cause-effect relationship between pepsin or pepsinogen in the middle ear and otitis media remains unclear²². It would therefore not be appropriate to endorse antireflux therapy for RAOM based on the currently available evidence.

Conclusion

RAOM results in multiple primary and acute care consultations, antibiotic prescriptions and surgery in children. It has a significant negative impact on the quality of life of the affected child and their caregivers. All children with RAOM should be referred to an Otolaryngologist. This requires primary care providers and paediatricians and other professionals in secondary care to be aware of the criteria for diagnosis of RAOM. Management plans need to be individualised in order to obtain the best outcomes for each child and their caregivers. ENT surgeons require greater clarity about the role of adenoidectomy in managing children with RAOM and its relative benefits in different age groups of children. The research agenda in RAOM should also provide evidence-based guidance on the most appropriate antibiotic to employ for prophylaxis and the optimum duration of prophylaxis.

In addition to the short-term aims of minimising pain, pyrexia and parental anxiety the longer-term aim of preventing complications should remain high on the agenda for these children.

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Evidence-based management of paediatric epistaxis

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Abstract

Epistaxis is an extremely common presentation in children. The most common aetiology is nasal colonisation with *Staphylococcus aureus*, leading to inflammation with crusting (and therefore digital trauma) in the early stages, progressing to new vessel formation in the septal mucosa. More serious causes such as bleeding disorders and tumours should be considered. An evidence-based approach to treat recurrent nosebleeds in children would involve use of an antiseptic nasal cream, with the addition of silver nitrate cautery when prominent new vessels are visible.

Key words

Epistaxis, paediatrics, silver nitrate cautery, Chlorhexidine/Neomycin cream (Naseptin)

J ENT Masterclass 2014; 7 (1): 10 - 13.

Introduction

Epistaxis is a common presentation in children, affecting up to 56 % aged 6 -10 yrs and around 9 % of the teenage population^{1,2}.

Children may be more prone to nose bleeds due to the extensive vascular supply and increased frequency of upper respiratory tract infections¹. The natural history of the problem is one of intermittent, recurrent and usually minor nose bleeds that mostly resolve spontaneously but which can cause alarm³. The incidence of having an underlying bleeding disorder causing epistaxis has been reported as only 0.7% to 3.5%, however, these figures are from adult retrospective studies which only included routine coagulation studies⁴.

Aetiology

The most common site of epistaxis is the anterior septum (Little's area). Multiple aetiologies have been postulated for this and in the past most cases were labelled as idiopathic⁵. However, recent evidence has led to the hypothesis that the primary event is colonisation of the nasal vestibule and anterior mucosa with *Staphylococcus aureus*, which leads to low grade chronic inflammation manifesting as crusting. Evidence for this includes a case-control study of children with recurrent epistaxis showing *Staphylococcus aureus* to be more prevalent than in the noses of control children from the fracture clinic⁶, plus trials showing that antiseptic cream is effective⁷ while simple emollient ointment is not³. Digital trauma is the inevitable consequence of an irritated, itchy, crusty nose in a young child. With prolonged inflammation comes new vessel formation, visible as prominent veins on the surface of the nasal mucosa in Little's area⁸.

Epistaxis is a known complication of the incorrect application of topical steroid sprays for rhinitis. If the spray is directed medially towards the nasal septum it can cause local trauma, so the solution is always to instruct patients to apply nasal sprays holding the bottle in the opposite hand (right hand for left nostril and vice versa) as this ensures the spray is directed laterally towards the turbinates and away from the septum⁹.

At the same time it has to be kept in mind that an epistaxis can be a presenting feature of tumours such as juvenile angiofibroma (in teenage boys) or rhabdomyosarcoma (in younger children).

Epistaxis may be a presenting feature of a coagulation disorder, typically Von Willebrand's disease. Some studies have suggested the prevalence of Von Willebrand's disease

may be 5-10% in children with recurrent epistaxis when full coagulation studies including tests for Von Willebrand's disease are performed^{2,4}. Hereditary haemorrhagic telangiectasia causes recurrent epistaxis but it is uncommon for the bleeds to start until teenage. Nosebleeds often occur in children with thrombocytopenia due to chemotherapy or haematological disorder, although the underlying problem is usually well-known and it is rare for a haematological disorder such as this to present primarily with epistaxis.

Clinical Presentation

Epistaxis can present as an acute spontaneous episode or patients can have complaints of chronic intermittent episodes. It is important that a thorough history is obtained keeping in mind the age of patient, laterality, trauma, any familial bleeding disorders. The history should also include history of unexpected bruising or bleeding from other parts of the body. Associated nasal symptoms such as blockage, discharge or pain should alert the clinician to the possibility of a tumour¹⁰.

Medications should be documented including topical nasal steroid sprays and anti-coagulants (mostly in children with congenital heart disease)¹⁰.

Examination and Investigations

Detailed examination of the nasal cavity should be performed. Anterior rhinoscopy in children can be easily done with an otoscope which is familiar and non-threatening to the child, whilst providing good light and a degree of magnification for the examiner. Flexible nasoendoscopy after application of topical anaesthesia can be used in slightly older and compliant children to have a more in depth view of the posterior nasal cavity.

Prominent visible vessels are seen in approximately 40 – 50% of children with recurrent nose bleeds⁸. Crusting of the mucosa of the anterior septum is also prevalent in patients with recurrent epistaxis. Distortion of nasal anatomy, masses and polyps all suggest tumour.

The role of blood tests is controversial. Full blood count and coagulation studies are rarely informative for the vast majority of uncomplicated children presenting for the first time. However, if a child continues to have recurrent epistaxis, in spite of adequate treatment (such as cautery) or if the history suggests a bleeding disorder, then a full coagulation study should be done in combination with a specific test for Von Willebrand's disease⁴.

Suspected tumours should lead to urgent imaging (usually MRI scanning) in the first instance, followed by

examination under anaesthetic with biopsy depending on the results of the scan. MRI alone may be diagnostic for angiofibroma, and may be followed up by angiography at the discretion of the operating surgeon.

MANAGEMENT OPTIONS

Acute Nose Bleed

In an acute setting ABCDE line of management should be adapted. Patients who have epistaxis due to trauma should be managed holistically.

In case of an acute episode, measures including pressure application should be attempted. Parents and health care staff are usually poorly informed with effective first aid manoeuvres and a demonstration of the Hippocratic method for arresting a nosebleed (pressure on the septum via application of pressure on the soft part of the nose) is worthwhile¹⁰.

If the child continues to bleed then silver nitrate cautery under local anaesthetic may be required. Co-phenylcaine should be applied on a cotton wool pledget placed in the nose as children can find sprays quite distressing. Packing, balloon tamponade and embolisation are very rarely required in children.

In children with known coagulation disorders or thrombocytopenia (such as those on an oncology ward) cautery and traditional non-absorbable packing should be avoided, as they tend not to be effective. The best option here is to insert a small wad of an absorbable haemostatic agent (such as Kaltostat, Nasopore or Surgicel) into the nose and just leave it.

Chronic intermittent nose bleeds

There have been a few studies including randomised controlled trials to ascertain which treatment option should be the first line treatment option with patients with recurrent epistaxis. A Cochrane review from 2012 by Qureishi concluded that there is still not enough evidence to compare the effectiveness of these treatment options¹¹.

However, there is some evidence available. A prospective, single blind, randomised controlled trial, comparing neomycin/chlorhexidine cream with no treatment in 103 patients showed significantly greater resolution of symptoms at 8 weeks in the treatment arm compared to controls⁷. A similar trial of petroleum jelly versus no treatment showed no difference³.

Calder in 2009 conducted a randomised controlled trial comparing silver nitrate cautery with antiseptic nasal

cream to antiseptic treatment alone in children with visible prominent vessels on the nasal septum. 109 patients participated in this study and the treatment arm showed a small but statistically significant benefit¹².

Another much smaller randomised controlled trial of 48 patients comparing silver nitrate cautery and neomycin/chlorhexidine cream showed no statistically significant difference between the two treatment arms¹³, although in clinical practice it would be unusual to perform cautery and not also use antiseptic cream.

A randomised controlled trial of a 101 patients confirmed that 75 % AgNO₃ was more effective than 95 % AgNO₃ when used with and neomycin/chlorhexidine cream. However, in the long term the difference becomes less marked¹⁴. Long term follow up of a previously-mentioned trial also showed that epistaxis tends to recur over time, presumably as the Staphylococci are reintroduced to the nose¹⁵.

The findings of the various trials are summarised in Table 1.

Conclusion

Paediatric epistaxis is common and can usually be managed with antiseptic cream to eradicate Staphylococcus aureus, plus silver nitrate cautery if prominent new vessels have formed. Tumours and coagulation disorders should always be considered and excluded.

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Table 1 Summary of randomised controlled trials for recurrent paediatric epistaxis								
Author(s)	Number (N)	NaseptinR alone	75 % AgNO ₃ Cautery	75 % AgNO ₃ and NaseptinR	95 % AgNO ₃ and NaseptinR	Vaseline	No treatment	Results
Ruddy J et al 1991	48	24	24	X	X	X	X	No statistical significance in both groups (p=0.56)
Kubba H et al 2001	103	51	X	X	X	X	52	Statistically significant improvement with the use of Naseptin 55% vs 29 % in the control group (p<0.05)
Calder N et al 2009	109	55	X	54	X	X	X	Improved subjective results with combination treatment of AgNO ₃ and Naseptin 91.3% vs 70.2% receiving Naseptin alone (p=0.01)
Flynn G et al 2011	101	X	X	49	52	X	X	75 % better in short term FU (P = 0.01) Both AgNO ₃ concentration offer similar results long term
Loughran S et al 2004	105	X	X	X	X	52	53	No benefit of Vaseline over simple observation (p = 0.472)

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Rings, slings and other things – anomalies of the trachea

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Abstract

This article reviews the embryology and key anatomical features of the trachea. It describes four important congenital tracheal anomalies; tracheomalacia (primary and secondary, including causes of vascular compression), congenital tracheal stenosis, tracheoesophageal fistula and laryngotracheoesophageal clefts. The epidemiology, common presenting features, diagnosis and management of each condition is discussed with reference to recent literature.

Key words

congenital, tracheal, anomaly

J ENT Masterclass 2014; 7 (1): 14 - 19.

Introduction

Embryology and anatomy of the trachea

The laryngotracheal diverticulum is first identifiable at day 20, appearing between the 4th and 6th branchial arches. By day 22 the primitive pharynx is visible, and at around day 24 the respiratory diverticulum divides into two lung buds. This migrates caudally, ventral to the developing foregut, with independent development of the two systems by the sixth week, separated by the tracheoesophageal septum. The connective tissue, muscle and cartilage is derived from mesenchymal proliferation of the cells which line the coelomic cavity, with cartilage differentiation first evident at 10 weeks gestation.

The most common defect is caused by failure of complete separation of the respiratory and digestive components resulting in a tracheoesophageal fistula. Complete failure of recanalization of the larynx results in laryngeal atresia, where as laryngotracheoesophageal clefts are caused by incomplete formation of a posterior septum. Defects in the development of the distal trachea can result in anomalies including atresia, webs and stenosis.

The trachea originates at the level of the cricoid cartilage extending down into the superior mediastinum to the level of the sternal angle, where at the carina it divides into the two main bronchi. In a neonate the trachea is 4mm in diameter and 4cm long, the adult trachea being approximately 12cm long and an average of 18mm in diameter. The cross-section is D shaped with 16 to 20 C shaped hyaline cartilage rings forming the anterolateral walls. A posterior membranous portion composed of trachealis muscle and connective tissue completes the D, with a normal cartilage to muscle ratio of 4.5:1.

The tracheal mucosa consists of ciliated pseudostratified columnar epithelium. The arterial blood supply is predominantly via the inferior thyroid, bronchial, brachiocephalic and subclavian arteries. Venous drainage is primarily into inferior thyroid veins. Tracheal innervation is derived from the vagus nerve via the laryngeal nerves and pulmonary plexus, and sympathetic fibres from the cervical ganglia.

Due to its small diameter the infantile trachea is vulnerable to compromise by structural abnormalities both intrinsic and extrinsic. During laminar airflow the resistance is inversely proportional to the fourth power of the radius, so that small reductions in airway calibre have dramatic effects on resistance.

Tracheomalacia

Tracheomalacia is the deformation of the normal tracheal lumen during respiration. It is estimated to affect 1:2000 live births. This can be primary i.e. due to an abnormality of the intrinsic cartilage, or reduced cartilage to muscle ratio, leading to collapse during inspiration. This is rarely associated with an underlying cartilage disorder, such as polychondritis or Larsen syndrome. A recent Cochrane review concluded there is currently no good evidence for treatments of any kind for primary tracheomalacia¹.

More commonly the tracheomalacia is secondary, associated with other abnormalities applying external forces upon the trachea. These include vascular compression, tracheoesophageal fistula or extrinsic compression from a neck or mediastinal cyst or neoplasm.

The condition may be self-limiting with significant improvement by age two and not require active management. The presentation depends on the severity of the malacia and may include cough, respiratory distress, stridor (biphasic if extrathoracic, expiratory if intrathoracic) or acute life threatening episodes (ALTE). Mucociliary clearance is impaired which may result in recurrent chest infections and contribute to the cough.

Diagnosis is usually achieved by rigid airway endoscopy with care to ensure the finding is not masked by stenting by the bronchoscope. Flexible bronchoscopy can be complementary and may provide a superior dynamic view. If this examination suggests extrinsic compression by a vascular structure dynamic CT angiography is required to confirm the vascular anatomy and degree of compression.

In patients with severe symptoms treatment is required. This may involve a single modality or combination of tracheostomy, mechanical ventilation, continuous positive airway pressure (CPAP), tracheal stenting or surgery depending on the underlying aetiology.

Vascular Compression

Vascular lesions causing secondary tracheomalacia may be isolated abnormalities or associated with other congenital heart defects or 22q11 deletion.

Vascular rings result from the anomalous configuration of the aortic arch and associated vessels forming a complete ring around the trachea and oesophagus.

The commonest complete rings are double aortic arch and right aortic arch with ligamentum arteriosum, together making up over 85% of cases². Double aortic arch is usually an isolated defect, where as right arch may be associated with other abnormalities including 30% of those with Tetralogy of Fallot. Approximately 10% of cases are due to an anomalous left pulmonary artery known as the pulmonary artery sling, which arises from the 6th branchial arch. This lesion is associated with other tracheobronchial abnormalities including complete tracheal rings and stenosis.

Incomplete rings cause similar symptoms due to compression of the trachea and/or oesophagus. These include an abnormally placed innominate artery and retro-oesophageal right subclavian artery with left sided aorta and right ligamentum arteriosum.

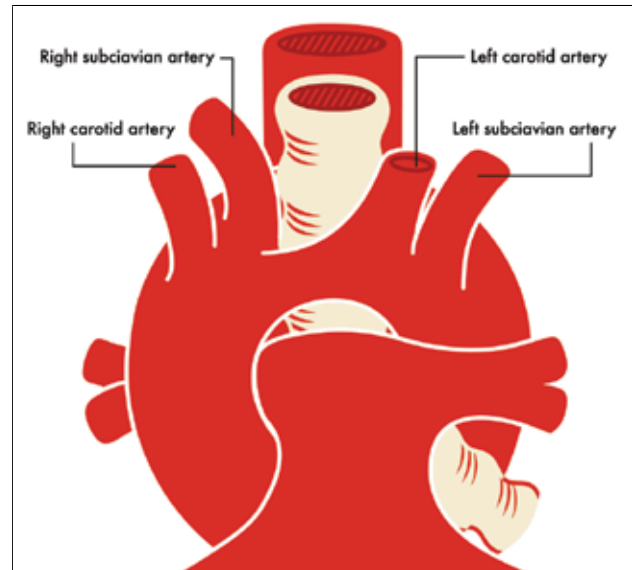


Figure 1: Double aortic arch

Surgical division of a vascular ring is indicated in all patients with significant symptoms. The configuration of the anomaly impacts on the severity of symptoms, for example the double aortic arch usually produces the most significant airway compression in the youngest patients. Other anomalies have a more variable spectrum of symptoms and may not present until adolescence or adulthood, or indeed be discovered incidentally when undergoing an unrelated investigation.

Those patients found to have tracheal compression due to an anomalous innominate artery often have only relatively minor symptoms and a minority of patients require surgical intervention with aortopexy.

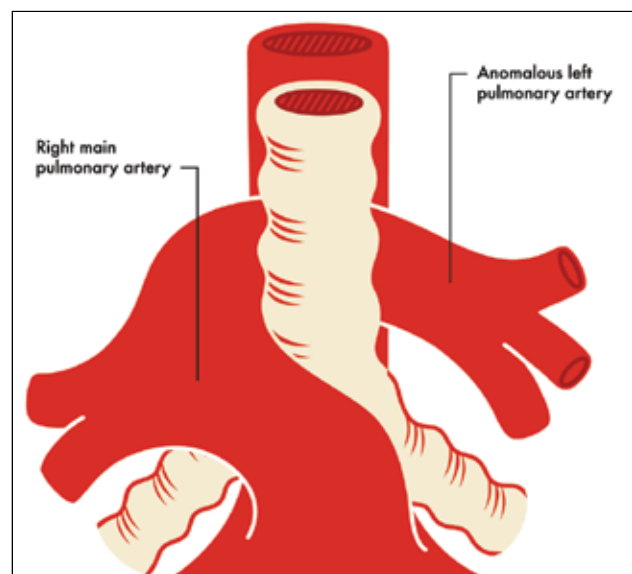


Figure 2: Left pulmonary artery sling

Aortopexy is the commonest surgical procedure used to relieve tracheomalacia. This involves lifting the aortic arch ventrally by suturing it to the underside of the sternum thus suspending the anterior tracheal wall. A recent review of 125 studies included 758 patients with a mean age at surgery 10.4 months³. The most common indication for surgery was secondary tracheomalacia due to oesophageal atresia and vascular anomalies, with a small number of idiopathic cases. A significant improvement in symptoms was reported in 80% of this mixed group of children.

Congenital tracheal stenosis

Congenital tracheal stenosis is a life threatening airway anomaly. It is rare, with an estimated incidence of 1:65,000 live births, though the accuracy of this statistic is compromised by the likelihood of a significant proportion of deaths prior to diagnosis. It is due to an abnormal relationship between the membranous and cartilaginous portion of the trachea. This is associated with complete or near complete cartilaginous rings, and occasionally also vertical fusion of the rings resulting in a cartilage sleeve. Stenosis has been defined as reduction in the luminal diameter by greater than 50%⁴. It can involve a short segment or a longer more generalised stenosis and has been classified into three types; generalised hypoplasia, funnel-like narrowing and segmental stenosis.

In greater than 50% of patients the tracheal stenosis is associated with other anomalies including cardiac and respiratory defects. It is more common in Down syndrome and Pfeiffers syndrome, and as previously discussed has a close association with left pulmonary artery sling known as the “ring, sling complex”.

Presentation depends on severity with diameter more key than length of stenosis. Symptoms are similar to tracheomalacia with stridor, respiratory distress, and ALTEs. The classic symptom of “washing machine breathing” is caused by secretions moving up and down with respiration in a distal stenotic segment⁵. The diagnosis is made by bronchoscopic examination with CT scanning complementary.

Management depends on the configuration of the stenosis and several surgical techniques have been advocated. Tracheal resection and reconstruction is effective for short segment stenosis. Enlargement tracheoplasty using an anterior patch has been described using cartilage or pericardium. This has been associated with significant granulation formation requiring repeated postoperative bronchoscopies and variable outcome⁶⁻⁸.

Slide tracheoplasty is becoming the predominant technique used for long segment stenosis. This involves transverse

division of the trachea at the midpoint of the stenosis. Longitudinal division of the proximal segment posteriorly, and distal segment anteriorly facilitates spatulation of the two tracheal segments to slide over one another, doubling the airway circumference. This reduces tracheal length by exactly half the length of the stenosis and half that which would result from resection and primary anastomosis. The slide may also be taken into a bronchus if the stenosis extends distally to involve the bronchial tree.

A recent review of over one hundred slide tracheoplasties performed in the UK showed very promising results for treatment of long segment tracheal stenosis⁹. Overall mortality was 12% with factors associated with reduced survival including need for pre-operative extra-corporeal membrane oxygenation, presence of malacia and bronchial stenosis.

Tracheoesophageal fistula

Oesophageal atresia (OA) and tracheoesophageal fistula (TOF) are closely linked pathologies occurring in 1:3000 live births¹⁰. In greater than 85% of cases OA will be associated with a fistula, in around half the remainder there will be isolated OA with no fistula and the remaining small proportion with a fistula but no OA^{11,12}. The most common configuration is a blind ending upper oesophageal pouch with distal tracheoesophageal fistula. A proximal fistula, or combination of proximal and distal fistulae do occur, but much less commonly

The condition has over 50% association with other anomalies. This is highest in OA without fistula and lowest in fistula alone, contributing to the frequent late diagnosis of an isolated H type tracheoesophageal fistula. The commonest associated defects are cardiac and may be part of a wider syndrome as in VACTERL association

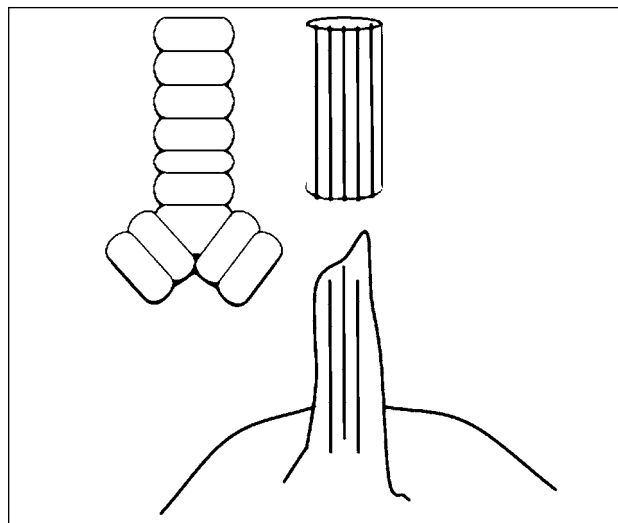


Figure 3: Oesophageal atresia, without fistula (7%)

(Vertebral, Atresia – duodenal, anorectal, Cardiac, Tracheo-oesophageal, Renal, Limb) and CHARGE syndrome (Coloboma, Heart, Atresia –choanal, Retarded growth and development, Genital anomalies, Ear anomalies). It also has a higher incidence in trisomy18 and 21.

It is possible for the diagnosis to be made antenatally on the basis of polyhydramnios and absent stomach; however these are relatively non-specific features, and cannot be accurately identified as early as 20-22 weeks at routine screening scans¹³.

The diagnosis is therefore usually made in the first 24 hours of life. Infants are unable to swallow their saliva, cough and choke on attempted feeding and may show a degree of respiratory distress. Suspicions can be confirmed by the inability to pass a 10F nasogastric tube further than 10cm from the lips. A chest radiograph with this tube in situ often provides confirmation of the diagnosis. The presence of other associated anomalies may prompt the diagnosis of OA, whilst if the OA is identified first, it should prompt cardiac and genetic investigation to assess for other anomalies.

Delay in diagnosis is much more likely of an associated proximal fistula which may be missed or an H type isolated TOF. These patients may present with coughing during feeding, recurrent pneumonia and cyanotic episodes. Diagnosis is usually made by rigid bronchoscopy with careful clearance of secretions to identify the tracheal end of the TOF. A suction catheter can be introduced to confirm it passing distally into the oesophagus. Prone oesophagogram is an alternative diagnostic tool, but is associated with a significant false negative rate.

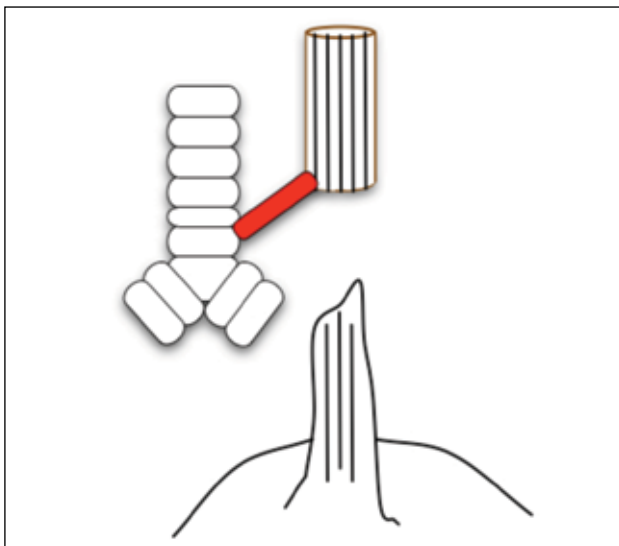


Figure 4: Oesophageal atresia, with proximal fistula (2%)

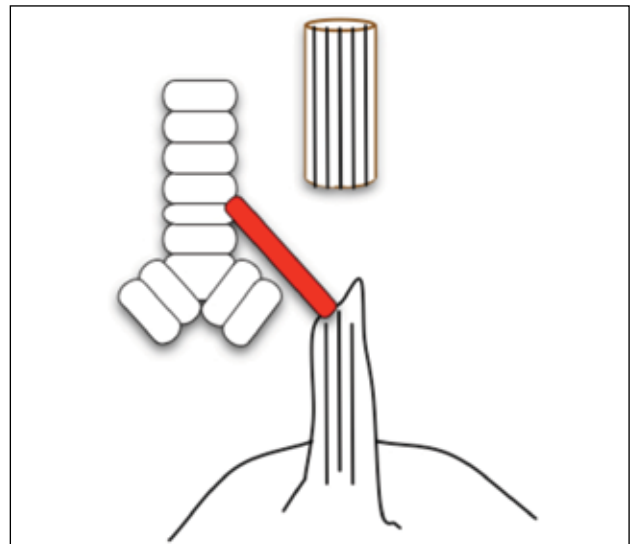


Figure 5: Oesophageal atresia, with distal fistula (82%)

Management depends on the association with OA. Primary repair of OA and TOF is now achievable in the majority of cases and minimally invasive techniques are advocated in some centres. The TOF is identified divided and oversewn. Long gap OA (4 or more vertebral bodies when under tension) requires special consideration, with no clear consensus on management.

Recurrence of the TOF may occur, with a rate of approximately 10% in most series^{14,15}. This usually presents with recurrent LRTI and can be confirmed by bronchoscopic examination.

The majority of patients have some degree of residual tracheomalacia of varying severity, which may require intervention.

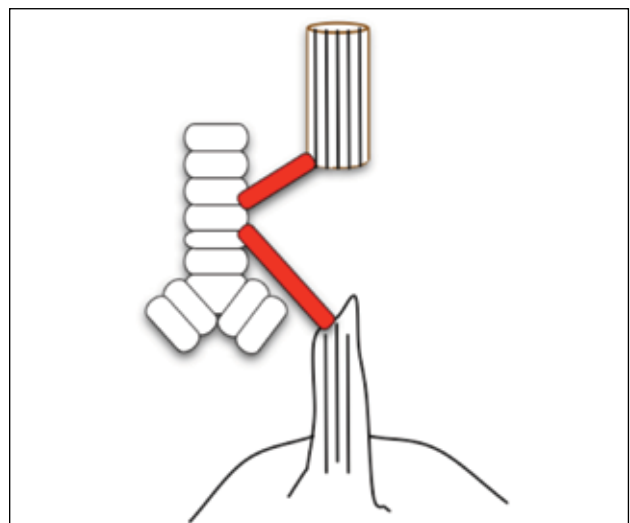


Figure 6: Oesophageal atresia, with proximal and distal fistulae (2%)

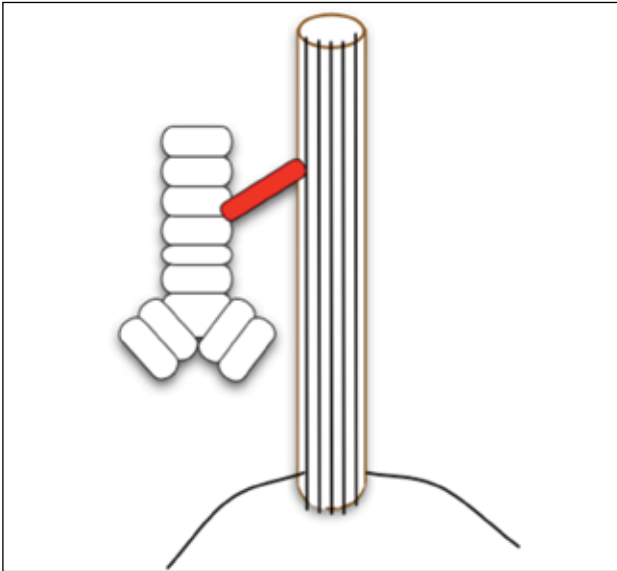


Figure 7: Isolated Tracheoesophageal fistula, without oesophageal atresia (7%)

Laryngotracheoesophageal clefts

This is a congenital malformation caused by an abnormal posterior communication between the larynx and pharynx, which may extend inferiorly to involve the trachea and oesophagus. The incidence is 1:10,000 live births. Laryngotracheoesophageal clefts (LC) are also often associated with other anomalies including laryngomalacia, tracheobronchomalacia and gastro-oesophageal reflux. They are also associated with VACTERL association and CHARGE syndrome as well as Opitz/BBB and Palliser-Hall syndromes and 22q11 deletion, which should be actively excluded in a patient presenting with LC¹⁶.

Depending on the degree of inferior extension of the cleft these have been classified into types I to IV. The most commonly used classification is Benjamin and Inglis 1989¹⁷, which was modified by Sandhu 2006¹⁸ to subdivide grade 3 clefts. Type 0 was also proposed in 1987 by Tucker who described a submucosal cartilage defect¹⁹.

Table 1: Classification of Laryngotracheoesophageal Clefts	
Type 0	Submucosal cleft
Type I	Supraglottic, interarytenoid cleft, above level of vocal folds
Type II	Cleft extends below level of vocal folds into cricoid cartilage
Type IIIa	Cleft extends through cricoid cartilage, but not into trachea
Type IIIb	Cleft extends into cervical trachea
Type IV	Cleft extends into thoracic trachea

Patients may present with stridor, swallowing problems, aspiration pneumonia, cough, dysphonia, respiratory distress and cyanosis. The symptom severity and therefore age at diagnosis is highly variable dependent on the extent of the cleft. Diagnosis is usually confirmed by rigid bronchoscopy. Videofluoroscopy to assess for evidence of posterior laryngeal penetration is very helpful in borderline or grade I clefts.

Management involves maintaining adequate ventilation, prevention of recurrent aspiration with longterm pulmonary complications and adequate feeding. In severe cases endotracheal intubation or tracheostomy are required to establish a safe airway. Maintaining adequate nutrition may require nasogastric feeding, or a longer term gastrostomy, often with Nissen’s fundoplication. The prompt diagnosis and holistic management of these patients has had a significant impact on mortality, which has been reported as 46% in a series in 1983²⁰, and less than 10% in more recent series²¹. Mortality rates for children with Type IV clefts have similarly improved from 93% to less than 50%²².

Type 0-I clefts may be managed conservatively initially with speech and language therapy input, anti-reflux therapy and thickened feeds. If this fails, and for all more extensive clefts, early surgery should be performed to limit long term complications. The classic open technique has recently been replaced by the endoscopic technique for grade I-II and occasionally grade III LCs, due to its lower morbidity and comparable results²³. The remaining grade III and IV clefts and any failed endoscopic cases are still managed via the open approach. The basic principles of surgery are to excise the mucosal edges of the cleft to create a raw surface and to suture the cleft together. There is much debate regarding number of layers of sutures, interrupted versus continuous suture lines and use of interposition grafts.

Other anomalies of the trachea do occur rarely. These include complete agenesis which is almost universally fatal, webs, trachiectasis (abnormally wide trachea), abnormal bronchial configuration, including high take off right upper lobe bronchus above the carina known as porcine bronchus, and congenitally short trachea.

Congenital tracheal anomalies present with similar symptom complexes and require a high degree of suspicion at rigid bronchoscopy to ensure accurate diagnosis and appropriate management of these serious conditions.

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Current management of laryngeal papillomatosis in adults and children

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Abstract

Introduction

Recurrent respiratory papillomatosis (RRP) is a chronic disease. Aim of this review article is to update the reader with current insights in terminology and potential therapeutic pathways.

Material and methods

Seventy-six patients included in the Groningen Papilloma Study were used as own material, and compared to previous publications.

Results

New diagnostic modalities (Narrow Band Imaging, virus typing) have been developed and implemented. There is difference in clinical course between HPV6 and HPV11 infected RRP patients. Confounders of true treatment effect are age of onset, HPV-type, location of the papillomas, gastroesophageal reflux disease, asthma and a disease course that naturally becomes less severe.

Discussion

Treatment modalities have changed significantly in the past decades. New principles of treatment are most likely to emerge.

Conclusion

Currently RRP is an incurable disease. However, scientific knowledge concerning the disease is increasing.

Keywords

Recurrent respiratory papillomatosis; cidofovir; Gardasil®; HPV

J ENT Masterclass 2014; 7 (1): 20 - 25.

Introduction

Laryngeal papillomatosis is a disease affecting both children and adults. It is a debilitating disease which most of the times originates in the larynx. Spread of the disease to trachea, lungs, pharynx and nose may occur – hence the preferred name recurrent respiratory papillomatosis (RRP). It is caused by human papilloma virus (HPV) types 6 and 11, characterized by voice change, sometimes even by airway obstruction. As its name implies, it has a recurrent and unpredictable character. Currently (2014), there is no definitive curative treatment. Goal of treatment is to maintain a patent airway and sufficient voice, with avoidance of a tracheostomy and spread to the lungs. This might need up to more than 100 surgical interventions in a single patient – a heavy burden for the patient.

Epidemiology

RRP occurs in all ages. There are several risk factors, such as being the first child in a family, low age of the mother, duration of delivery, and a mother with condylomata acuminata or HPV-induced genital warts. Traditionally, one distinguishes between juvenile onset RRP (JoRRP) and adult onset RRP (AoRRP).

Characteristics of JoRRP (≤ 17 years old) include an incidence of 0.17 per 100.000/year (1). The male to female ratio is 2.7:1. Its transmission is poorly understood. Literature appoints a more severe disease than AoRRP, with a higher rate of tracheotomy and morbidity.

AoRRP (≥ 18 years old) has a lower incidence of 0.54 per 100.000/year¹. The male to female ratio is comparable with 3.4:1. Transmission of the virus might occur during sexual activity. The clinical course of AoRRP tends to be milder.

A general look at the age distribution of a cohort of 55 patients in the Groningen Papilloma Studies suggests there is a continuum in age in RRP, yielding no difference between separate diseases JoRRP and AoRRP (fig. 1)².

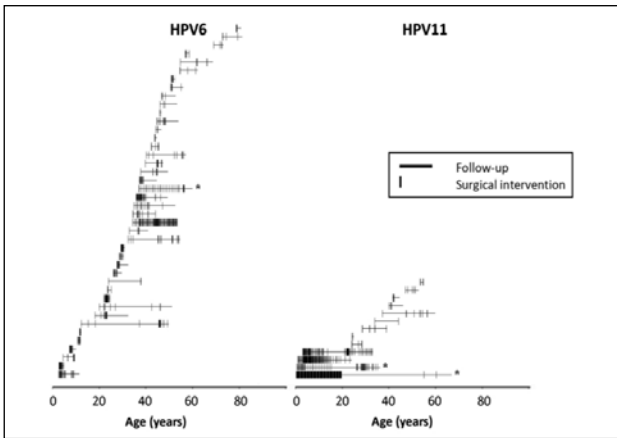


Figure 1: Follow-up of individual cases with recurrent respiratory papillomatosis associated with either HPV6 or HPV11 PCR positivity (2).

Analysis of data of more than 600 patients - acquired in a study in side effects of cidofovir treatment³ - to either support or reject this assumption, is on its way.

The diagnosis RRP should be made on the combination of patient history, symptoms and signs, and confirmation of the clinical suspicion by histopathological examination. It is characterized by exophytic growth. The papilloma is fixed to epithelium with central vascular core. Viral characteristics are present in the epithelial cells.

There is controversy as to whether the disease is currently curable, or if one should speak of ‘clinical remission’

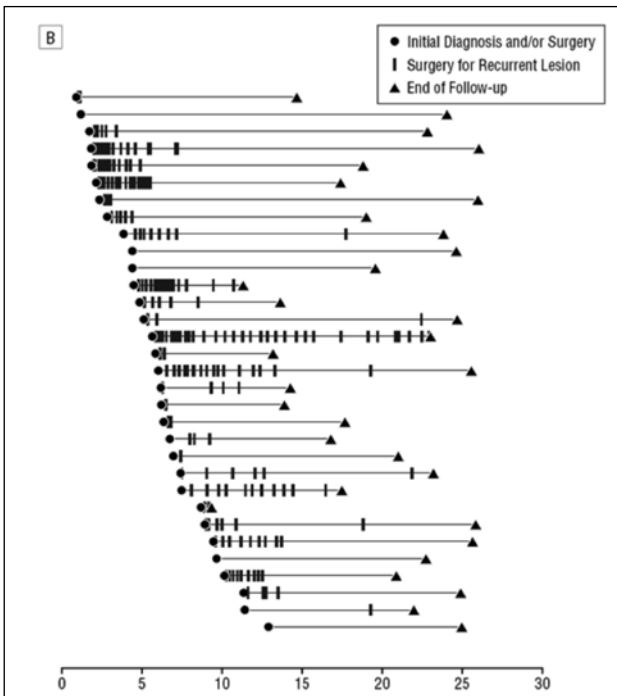


Figure 2: Follow-up of individual cases with JoRRP (4).

rather than ‘cure’ of RRP1. Follow-up of individual cases with JoRRP shows that the disease is highly unpredictable, as shown in fig. 1² and 2⁴. Estimated direct costs add up to €0.083/ person/ year in the UK⁵. In the EU this would lead to an estimate of more than €41 000 000/ year.

There is controversy regarding prevalence of HPV between groups of patients. The best typing method is HPV PCR. A positive result for HPV PCR, however, only demonstrates the presence of HPV and does not necessarily imply its role in infection and eventually carcinogenesis⁶.

Staging

Papillomas originate in the basal layer of epithelium. Predilection site is the transition zone between columnar epithelium, and non-keratinizing planocellular epithelium. Papillomas show exophytic growth. The papillomas are fixed to epithelium with a central vascular core. The epithelium shows characteristics of viral influence. Papillomas are located in the epithelium (the cover, according to Hirano’s body-cover theory). Treatment of RRP should therefore be performed in the cover, and not in deeper layers.

Derkey et al developed a clinical staging system⁷. Its aim is to predict intervals of surgical intervention in RRP patients. It has two sources of input: a clinical score and an anatomical score. The clinical score considers voice, stridor, urgency of intervention and respiratory stress. The anatomical score is a score which needs to be assessed at 25 subsites. Assessment depends on size of the lesion. This score is, therefore, difficult to use in retrospective studies.

Another staging system was developed by Dikkers⁸. It contains three grades. Grade 1 is papilloma with sessile growth, unifocal or multifocal (fig. 3). Grade 2 shows exophytic growth, unifocal (fig. 4). Grade 3, finally, shows exophytic growth, multifocal (fig. 5). To describe the amount of papillomata, we advocate to use the Derkey score in future studies². The Dikkers score is aimed at surgical need and modality.

Staging papilloma is, of course, dependent on the way it is looked at. Indirect laryngoscopy is still being used by lots of laryngologists as first way of examination. Small papillomas are likely to be missed. Flexible laryngoscopy shows the larynx in a more natural position. Laryngostroboscopy has the advantage of understanding the impact of the papilloma on the patient’s voice. Suspension microlaryngoscopy has the advantage of being able to touch the larynx in hidden corners, such as the ventricle and the subglottic area. Narrow band imaging (NBI) as additional tool shows more histopathologically

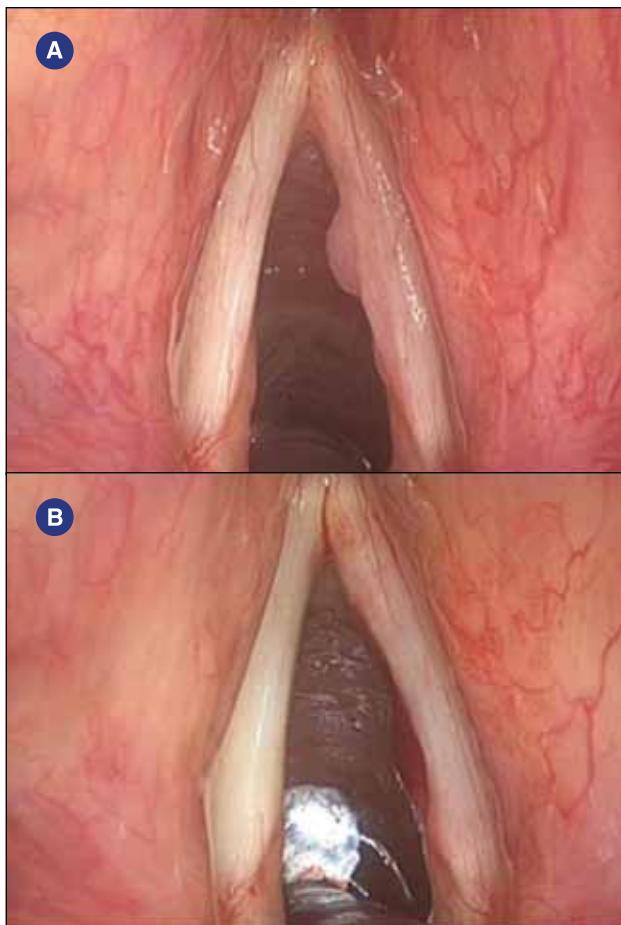


Figure 3: Grade 1 papilloma in a 43-year-old male, according to Dikkers scale. A. Preoperatively. B. Postoperatively.

confirmed RRP lesions than examination with conventional white light alone. This occurs due to the fact that capillary vessels in RRP absorb the narrow band light and show typical brown or increased intraepithelial papillary capillary pattern within a lobular shimmering pale wart-like mass. NBI clearly provides added value to visualize RRP, which can lead to better removal of the papillomata. NBI can therefore be considered a simple, safe, quick and useful additional diagnostic tool in the visualization of RRP⁹. As all respiratory epithelium should be inspected, in new patients laryngeal examination should be expanded with nasal endoscopy and tracheobronchoscopy.

Clinic

In a recent survey among 76 patients in the Groningen Papilloma Studies, a cohort of patients with RRP in the University Medical Center Groningen, the Netherlands, the associated virus was analyzed using PCR². Forty-two patients were positive for HPV6, thirteen patients for HPV11. Fourteen patients were negative for any HPV, and in 7 cases PCR was not possible due to poor DNA quality of the samples. Median follow-up in both groups was

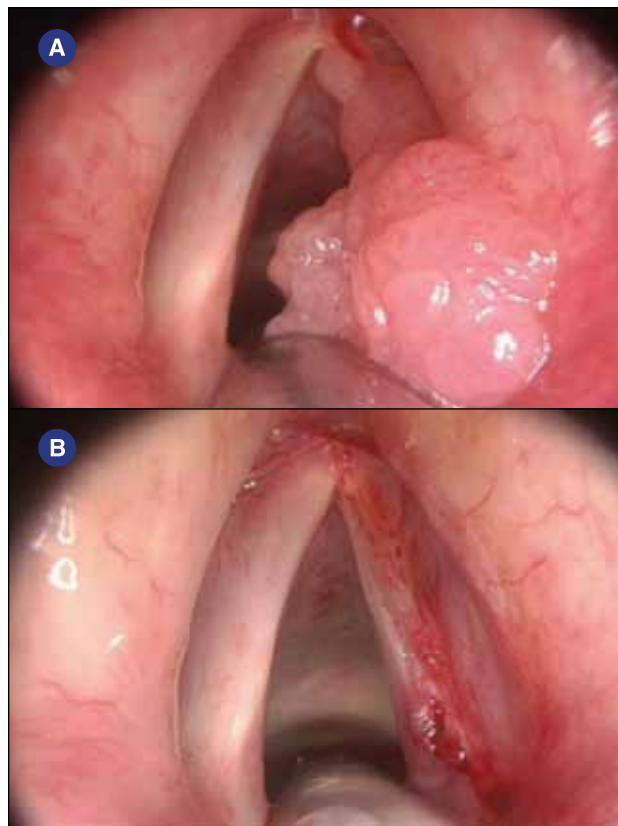


Figure 4: Grade 2 papilloma in a 37-year-old female, according to Dikkers scale. A. Preoperatively. B. Postoperatively.

9 years (mean resp. 8.5 and 13.5 years, no statistically significant difference). Male to female ratio was 3.2-1 in the HPV6, and 5.5-1 in the HPV11 group. Mean age at diagnosis was similar (resp. 35 vs. 28).

The course over time per patient shows a wide variety in the number of surgical interventions, range 1-152. Surgical intervals vary from 4 days to 34 years. At the start of the disease the surgical frequency is high in both HPV groups. The frequency of surgical interventions on average is reducing with follow-up time. Although the mean number of surgical interventions is much higher, the median number of surgical interventions per patient was 6 (range 2-78) for HPV6 patients and 5 (range 1-152) for HPV11 patients, yielding no statistically significant difference ($p=0.889$). No statistically significant differences were found in surgical frequency in the first year per patient or in peak surgical frequency per year per patient. HPV11 patients had a higher number of anatomical locations of the papillomata (by the Derkay score) in the respiratory tract than HPV6 patients ($p<0.01$). Patients infected with HPV11 had statistically significant more extralaryngeal spread of the papillomata (for instance in the nose, pharynx or the trachea) than HPV6 infected patients.

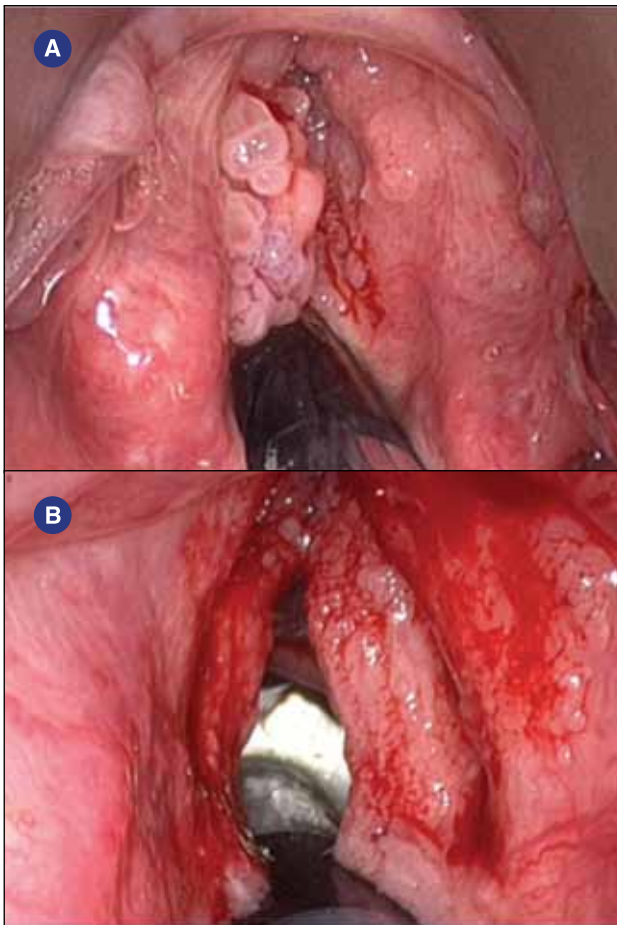


Figure 5: Grade 3 papilloma in a 44-year-old male, according to Dikkers scale. A. Preoperatively. B. Postoperatively.

Consequently HPV11 patients did have more distal involvement of papillomata (trachea)².

The same study concluded that patients with a young age of onset are likely to run a more relapsing and longstanding course of the disease with a higher surgical frequency. Irrespective of age of onset, the surgical frequency is the highest in the first years, decreasing each year after diagnosis. A model was developed predicting the expected number of surgeries per age, and per HPV2. At age of diagnosis of 1 year and 5 years the predicted number of surgeries is higher for HPV11 patients (resp. $p < 0.001$ and $p < 0.001$). At age of diagnosis of 40 years and 60 years the predicted number of surgical interventions is higher for HPV6 patients. All results displayed above clearly show the need for virus typing in cases with RRP, irrespective of their age of onset².

In the same cohort, we made observations concerning development of malignancy. None of 42 patients with HPV6 as associated virus developed a malignancy. One of 13 HPV11 patients developed testis carcinoma. No patients

in our group were HPV16 or HPV18 positive. Strikingly enough, of 21 patients where all HPV tests were negative, 4 developed a malignancy (3 in larynx, 1 in nasopharynx). Recent literature shows comparable outcomes¹⁰. This is a sign that should be explored.

Treatment

Many types of treatment have been tried in RRP. In literature it is often unclear if decrease of the severity is attributable to the described treatment modality. Confounders of true treatment effect are age of onset, HPV-type, location of the papillomas, gastroesophageal reflux disease, asthma and a disease course that naturally becomes less severe. Furthermore extremely long intervals are not uncommon. The above mentioned factors should be included in the analysis of the treatment response of RRP. Treatment results without mentioning these factors have to be used with caution. Case reports can therefore not be considered as proof of effective treatment².

Goal of treatment is to obtain a good functional voice with a patent airway. Traditionally, surgical treatment can be performed using classic instruments (cold steel), microdebrider or laser (CO₂ laser, KTP, PDL). Own observations show that in the 80's and 90's of the 20th century, CO₂ laser was used in approximately 80% of cases. The past 10 years, however, the surgical instruments are cold steel in 80%, and microdebrider and CO₂ laser both in some 10%². Whatever surgical technique is used, scarification and webbing of the anterior commissure might deteriorate the voice. Adjuvant drug therapy has been tried with several (groups of) agents, such as bevacizumab (Avastin[®]), celecoxib (Celebrex[®]), cidofovir (Vistide[®]), quadrivalent papillomavirus vaccine (Gardasil[®]), PPI's, interferon (Intron-A[®]), propranolol (Inderal[®]). Unfortunately, no curative drug has been established as yet.

Cidofovir ((S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)-cytosine) is a cytosine nucleotide analogue. It has a broad spectrum antiviral activity against papilloma-, herpes-, and pox viruses. The first application in RRP was reported in 1998¹¹. Use of cidofovir for adjuvant treatment of RRP became widely advocated.

Early 2011, the manufacturing company of cidofovir stated that off-label use of cidofovir was no longer permitted, because it was said to induce nephrotoxicity, neutropenia, oncogenicity. However, no specifications about severe side effects after intralesional cidofovir in RRP patients were provided¹². This led to a multicenter retrospective case study whether nephrotoxic, neutropenic, or oncogenic side effects did occur after intralesional use of cidofovir in a large cohort of patients with RRP.

However, no significant differences in severe side effects between the cidofovir and non cidofovir group were shown³. Therefore there was no support for the alarming newsletter from the manufacturing company. However, to date (July 2014), use of cidofovir for treatment of RRP is still impossible in Europe. Strangely enough, its use is allowed again in the USA.

A totally new line of treatment might be obtained in immune modulation. To illuminate why patients with RRP fail to effectively control their disease, the suppressive cellular microenvironment in papillomas was further investigated. The majority of papilloma-derived CD4(+) T cells expressed the CD4(+)CD25(-)CD127(low/-)Foxp3(-)PD1(+)CD69(+) phenotype and failed to suppress PBMC proliferation, suggesting that these T cells are chronically activated and exhausted. The PD-1/PDL-1 pathway may represent an additional immunosuppressive mechanism that contributes to defective HPV6/11 clearance in RRP¹³. Currently unpublished results from an international collaboration on genetic proneness of RRP show three candidate regions in trios (patient, father and mother), suggesting an underlying genetic susceptibility. This discovery might induce growth of a potential new branch for treatment.

Another principally different line of treatment is present in HPV vaccination. HPV16 and HPV18 cause 70% of all cervical cancers. Gardasil® is a quadrivalent vaccine aimed at diseases caused by HPV6, 11, 16 and 18. It was introduced in Austria, Canada, France, Italy, Germany and Greece in 2007, and is currently approved in more than 140 countries worldwide. Out of principle, a vaccine cannot be used as a therapeutic agent. However, there are reports in favor of using the vaccine therapeutically. A retrospective, double blind, placebo controlled randomized study of over 17000 women was performed in women who had surgical treatment for HPV related disease¹⁴. A total of 587 vaccine and 763 placebo recipients underwent cervical surgery. The incidence of any subsequent HPV related disease was reduced 46.2% in the vaccination group. Vaccination was associated with a significant reduction in risk of any subsequent high grade disease of the cervix by 64.9%. The incidence of any subsequent HPV related disease was reduced 35.2% by vaccination. Previous vaccination with quadrivalent HPV vaccine among women who had surgical treatment for HPV related disease thus significantly reduced the incidence of subsequent HPV related disease, including high grade disease¹⁴.

The effect of Gardasil® was tested in RRP as well¹⁵. The authors propose the hypothesis that HPV vaccination could have a therapeutic effect in RRP by preventing new

papilloma formation at additional sites. Patients showed an increase of antibodies against HPV after Gardasil®. Clinical improvement was present in two patients. Own unpublished results corroborate these findings: 9 patients were treated with Gardasil®, where 7 patients showed clinical improvement. However, in the light of the spontaneous course of the disease, one needs to wonder whether we have seen the effect of vaccine, or the disease's natural course. Our data show that even after 34 years the symptoms can relapse².

Conclusion

RRP is an invalidating disease, in which NBI is a useful and helpful tool is diagnostics. HPV analysis can help in individual prognosis. The current optimal treatment is surgical excision. The expected surgical frequency in patients with RRP is highest in the first years after diagnosis. In the future, immune modulation might be the treatment of choice. The disease cannot be cured, but the patient's symptoms can be suppressed.

Acknowledgment

Michel RM San Giorgi, MD, is gratefully acknowledged for his valuable input in an earlier version of the manuscript.

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The future of paediatric cochlear implants

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Abstract:

Cochlear implantation is one of the most dramatic and life changing medical innovations of the 20th century. The use of paediatric hearing implants has become a routine component of the rehabilitation of the profoundly deaf children. Developments in the field are driven by three main forces; technological progress, greater surgical confidence, and psycho-physiological understanding of early language development. This paper reviews the current boundaries of clinical use of neural stimulators (cochlear and auditory brainstem implants) to establish hearing in deaf children.

Keywords

Paediatric Cochlear Implant; Deafness; Auditory Brainstem Implants; Bone Anchored Hearing Aids; Auditory Neuropathy

J ENT Masterclass 2014; 7 (1): 26 - 31.

Introduction

The auditory rehabilitation of prelingually deaf children has been revolutionized by cochlear implantation^{1, 2}. To date, more than 60,000 children have received cochlear implants, with often spectacular results. Cochlear implants provide access to sound that enables development of speech, language and literacy as well as attendance in mainstream education for many deaf children and is established as an effective and cost-effective intervention³⁻⁷.

Implantable hearing aids for children include two broad groups, 'electric hearing' with cochlear implants and 'acoustic hearing' with bone conduction implants (of which there are several types). For profound SNHL the implant of choice is a cochlear implant. This article discusses cochlear implants and auditory brainstem implants.

Cochlear implants are auditory implantable prostheses that electrically stimulate the spiral ganglion cells of the

cochlear nerve directly in circumstances when the cochlear hair cells themselves do not function effectively to give adequate speech intelligibility. It consists of an external device with a microphone/ processor and an internal device to stimulate the cochlear nerve. With improving technology, the indications for cochlear implantation are continually widening.

The first attempt to implant a cochlear implant (CI) was made in 1957 by Djourno and Eyries in Paris using a single channel device⁸. These devices established that hearing could be achieved but these early recipients used their implants largely to lip read. In 1961, William House (otologist), John Doyle (neurosurgeon) and James Doyle (physicist) began work to implant a single channel device. House's work continued into the 1970s leading to the production of a 3M manufactured single channel device which was the first Food Drug Administration (FDA) approved model in 1984.

Paralleling the developments in California during this period, there were significant advancements made in Vienna, Austria by Professor Kurt Burian and in Melbourne, Australia, by Professor Graeme Clark. Professor Burian implanted a multichannel cochlear implant in 1977. Similarly, Professor Clarke developed the Australian prototype of the bionic ear, which was a multichannel device first implanted in 1978 on a patient named Rod Saunders. The device on Rod Saunders was replaced in 1983 due to failure with a Nucleus 22, which was the world's first commercial multi-channel CI with FDA approval.

The technology continued to improve with more widespread application of the product and greater confidence in its use. It was finally FDA approved for use in children in 1990. At this stage it was only approved for use for above 2 year of age, but the age limit was reduced to 18 months in 1998 and then further to 12 months in

2000. Since then cochlear implants are routinely placed in children as young as 6 months, although in an anomaly the licence has never been amended to children below 12 months.

Recent developments in candidacy for children:

Prior to 2009, public funding in the UK allowed access for children to unilateral CI. However, in 2009, NICE published new guidelines, which established that all eligible children were to receive bilateral simultaneous CI. These guidelines were reviewed in 2011 after a multicentre audit and left unchanged⁶.

Given that binaural hearing skills are acquired early, there has been a preference for early implantation. This allows children rapid development of hearing and speech understanding by reducing duration of deafness and maximise the opportunity of early plasticity of the auditory system⁹.

With the recognition of the benefits of bilateral cochlear implantation for children, a further consensus was reached in 2010 by the Working group of European surgeons who released the European Bilateral Paediatric Cochlear Implant consensus statement stating that any infant or child who is an unambiguous CI candidate, should receive bilateral simultaneous cochlear implants as soon as possible after the definitive diagnosis is made and that surgery should be atraumatic to preserve cochlear function^{10,11}. Currently more than 25% of children implanted before age of 3 have received bilateral implants worldwide whereas in children older than 3 years it is most likely that bilateral implants are inserted in a sequential manner^{9,12}.

Nevertheless, there are still many children around the world who receive a single implant or a sequential implant. The main reason for this is financial. A number of children have residual hearing in the un-implanted ear and can benefit from bimodal (CI & hearing aid) amplification. There are also surgical concerns about bilateral simultaneous implantation (although there is no evidence to suggest a higher complication rate^{13,14}), and possible vestibular dysfunction.

Future areas of Development

Earlier

Children implanted earlier have quicker language acquisition, earlier binaural skills, better language skills and can even develop along the normal path for language development¹⁵. Furthermore, data exists that early implantation increases the proportion of children in mainstream school, and increases the cost utility of cochlear implants significantly¹⁶.

Surgery in these young children is safe^{13,17,18}, but barriers exist to early implantation. These include delays in scanning children, protracted behavioural audiology, parental concerns, and waiting for surgery, but usually the greatest delay is in referral from audiology / paediatric services for cochlear implantation. Newborn hearing screening, which exists in the majority of developed countries, identifies almost all of the children with congenital severe / profound hearing loss, but there is sometimes a reluctance to refer to cochlear implant centres without extended hearing aid trials and reassessment, which causes significant delays¹⁹.

Evidence does not yet exist that implantation below six months of age continues to improve outcomes further, and there is surgical concern that simultaneous implantation in very young infants carries a risk of bleeding which may be significant. Very early implantation (less than six months of age) is not yet a standard in paediatric implant surgery.

Bilateral

Bilateral cochlear implants improve hearing for children with bilateral deafness beyond what can be realized with a unilateral cochlear implant²⁰. The aim in children is to promote important auditory processing that normally occurs when listening with 2 ears. Binaural hearing skills are normally acquired very early on; by 6 months of age, children with normal hearing show consistent lateralization of sounds by turning their heads. This means that small differences in interaural timing and level differences are detected and perceived by the auditory pathways. Speech comprehension in noise and localization are compromised when sound is only heard from one side or through only 1 cochlear implant but can be improved with bilateral cochlear implants in both adults and children²¹⁻²⁴.

Children receiving a sequential bilateral implant with an interval of several years have demonstrated significant asymmetries in brainstem and cortical function compared with those with a delay of less than 1 year or implanted simultaneously¹⁰. These children have demonstrated poorer speech scores in the second ear compared to the first, stronger ear²⁵.

A most telling outcome of bilateral cochlear implantation is that children with 2 implants almost universally wear both devices and demand to have any equipment breakdowns (depleted batteries, broken components, or device failures) repaired. Children and families also report improved hearing in the “real world” even when outcomes measured in the audiologic sound booth are minimal, which probably reflects the increased complexity of most listening situations beyond the quiet test environment^{26,27}.

Partial Deafness

An increasing number of studies have confirmed that partial deafness, most commonly high frequency hearing loss with residual low frequency natural hearing, is effectively treated in children with cochlear implantation²⁸. These children are hard to aid with conventional hearing aids because of the ‘ski-slope’ nature of the hearing loss. It is possible to implant with an approximately 90% chance of preserving useful hearing using a variety of electrodes²⁹. There is an incidence of late loss of hearing a few months after the surgery, and it is usual to lose around 10-20dB of hearing. There are speech processors that are designed to stimulate the high-frequency hearing using the electrical implant, and can boost low frequency hearing with an acoustic hearing aid – combined in a single processor. This approach still allows access to inter-aural level and timing differences which facilitates localisation of sound and binaural effects to increase speech understanding in background noise, compared to a conventional cochlear implant without low frequency residual hearing. Once the residual hearing is below 80dB this approach is ineffective as the residual hearing is no longer aidable – so assuming a hearing loss due to the implant, it means that this ‘hybrid’ strategy is not attempted if the pre-operative low frequency hearing is less than 60dB HL.

A concern in children is that they will lose the residual hearing eventually during the natural process of aging in the cochlear; a process which often occurs early in individuals with hearing loss. However, the modern hearing preservation electrodes are full or near full length, and will function well even if the residual hearing is lost.

Extended candidacy

Different criteria for candidacy have been adopted in different health economies. In the UK the NICE (National Institute for Health and Care Excellence) guidelines determine candidacy – for children this is 90dB hearing loss at 2 & 4 kHz, with evidence of delayed speech and language development. However, children with hearing above these thresholds benefit from cochlear implantation under certain circumstances. There are numerous reports of children with asymmetric hearing loss benefiting more from the implanted side than the hearing aid side^{30, 31}. Furthermore, the outcomes after cochlear implantation in ~ 80% of children with hearing thresholds between 80 and 90dB are better than can be achieved with hearing aids. This raises the possibility that current guidelines are too restrictive, and that a wider range of severely deaf children could be offered cochlear implants, especially as residual hearing can usually be preserved allowing hybrid electro-acoustic stimulation in both ears³¹.

Single Sided Deafness

Although the concept of cochlear implantation to restore bilateral hearing in adults is quite well established³², the value of using CROS (Contralateral Routing of Sound) aids, bone conducting aids or cochlear implants is much less clear in children. However, unilateral hearing loss in children results in educational deficits. Children with unilateral hearing loss are at increased risk of grade failures (24 - 35% vs. 3% in normal hearing children) and are more likely to require educational assistance (12 - 41%). Compared to normal hearing siblings, these children have lower oral language scores, 4.4 times risk of requiring an educational plan and 2.5 times risk of speech therapy³³. Functional MRI scans have demonstrated neuro-anatomical differences in auditory regions between single sided deaf children and normal hearing controls, but also in attention and executive control areas, and these children have a much higher incidence of behavioural problems³⁴.

CROS hearing aids are very poorly tolerated in children. Bone conducting hearing aids (BCHA) are more accepted, but the majority of children with single sided deafness do not use them. A bone conducting aid corrects the head shadow effect but does not give interaural level or timing differences to allow binaural hearing. Consequently, there are only modest improvements with a BCHA in localisation or speech in noise comprehension. A cochlear implant will allow access to interaural level differences and will improve localisation and speech in noise compared with BCHA especially in situations where noise is presented to the normal hearing ear and speech to the implanted ear. Interestingly, adults with unilateral cochlear implants report a reduction in tinnitus – in children with hearing loss tinnitus is often present but is rarely a major clinical problem.

There are only a few published reports of unilateral cochlear implantation in children³⁵. However, it appears that this is as well tolerated by children as in adults who have had a sudden sensorineural hearing loss^{32, 36}, and studies of pre-lingually unilaterally deaf children are underway – early results are promising and this may be a viable treatment in the very near future. As with bilaterally deaf children, minimising the duration of deafness and early implantation will probably be very important in achieving good outcomes. However, significant questions remain about the cost-effectiveness of this treatment, and the acceptability of a unilateral cochlear implant in older children and teenagers who may not wish to wear a hearing device for a unilateral disability.

ANSD

Auditory neuropathy is recognised in newborn hearing screen children with an absent brainstem auditory response

(ABR) and a detectable otoacoustic emissions. It is a spectrum from children who have delayed maturation and who will develop normal hearing to a group of children who are profoundly deaf. In the middle, are children with measurable hearing on pure tone audiogram who are ‘functionally deaf’ with very poor speech discrimination. The majority of these children can be managed with hearing aids, but if there is a profound loss or poor speech and language development then cochlear implants give generally good outcomes³⁷.

Future technologies

The technological advancement of auditory implants continues apace – in fact, it is likely that any report on this will be out of date within a few months, and certainly within several years. Current areas of development which look to be fruitful include:

Electrode design & insertion – there are a number of electrodes developed by commercial implant companies which allow hearing preservation, deep insertion into the cochlea for ‘complete cochlea coverage’, and custom electrodes for anomalies in cochlea anatomy. Insertion forces appear to be crucial to maintain a healthy cochlea for long-term health of the inner ear, as well as hearing preservation. Robotic insertion to reduce these forces further is an active area of research interest with promising early studies.

Neurotrophins & gene therapy – a cochlear implant is a promising conduit for delivering growth factors directly or by gene therapy techniques, as well as electrical stimulation to prolong and increase neural response. Recent animal studies have shown great promise in animal models, but these have not yet been translated to human trials³⁸.

Totally implantable implants – adults implanted with totally implantable devices have found outcomes limited by the subcutaneous microphone³⁹. Newer devices may use the ossicular chain as a microphone for middle ear stimulation, and the translation of this technology to cochlear implants is inevitable⁴⁰. However, at this point, no totally implantable cochlear implants have been used in children.

Improved processing strategies – sound processing strategies to improve the appreciation of music and to allow speech discrimination in background noise are actively being developed and released. Bidirectional microphones to determine sound direction, and communication between bilateral cochlea implants, along with automatic programmes that especially suit children, give better outcomes and are often retrospectively available to previous versions of cochlear implants.

Improved User Experience – already cochlear implant processors are routinely available which are compatible with add-on devices by Bluetooth™, or wi-fi signals. The processors are water resistant, and in some cases waterproof, to allow swimming and showering while hearing. Off the ear solutions to minimise the visibility and improve the comfort of the processors are also helpful to some patients, although cochlear implants still use significant power and so battery size can limit the size of devices. Finally, data logging and feedback to audiologists to help with tuning and remote management of devices to save on clinic visits can make life easier for patients and their families.

Auditory Brainstem Implants (ABI)

Auditory Brainstem Implants are auditory prosthesis designed to provide electrical stimulation directly to the cochlear nucleus in the absence of a functional cochlear nerve. First used in 1979 by William House and William Hitselberger after removal of an acoustic neuroma, its use has been mainly reserved in the setting of neurofibromatosis 2 (NF2)⁴¹. Colletti et al. first reported its use in a paediatric setting in 2000^{42, 43}. Candidates suitable for an ABI can largely be divided into 2 groups: prelingual and post lingual deafness in the paediatric setting. Its use in prelingually deaf children remains primarily those children in whom CI is contraindicated, for example complete labyrinthine aplasia or congenital malformations with cochlear nerve hypoplasia or aplasia⁴⁴. In postlingual deafness, an ABI may be indicated in tumours of the acoustic nerve or non tumour patients. Tumour patients include patients affected with NF2 or bilateral Vestibular Schwannomas whereas non-tumour patients include those with bilateral severe cochlear ossification (which may be secondary to meningitis), gross cochlear destruction from otosclerosis, other surgical conditions precluding CI, fractures through the internal auditory meatus causing cochlear nerve avulsion or unmanageable facial nerve stimulation post CI^{45, 46}.

Long term results are still pending but audiological outcomes are generally much poorer than cochlear implants and rarely give open set speech discrimination and therefore a cochlear implant, where possible, should always be the first option^{45, 47}. Furthermore, a CI is easier and safer to implant, with a much lower risk of life threatening complications. In the setting of prelingual deafness, outcome will depend on early intervention and therefore it is important to identify candidates through newborn screening and subsequent medical and radiological assessment and assess them for ABI early.

The optimal age for elective intracranial surgery is 18m – 24 months, but in some experienced centres the minimum age for an ABI can be as low as 1 year. Earlier intervention carries the risk of hypovolemia through CSF and blood loss, poorly developed lateral recess anatomy, and higher risk of post-operative brain swelling, but delayed intervention loses the benefit of cortical plasticity. Parents and carers need to be counselled that for prelingual recipients programming and rehabilitation is a lot more intensive than for CI and the results are not as good.

Conclusions

The frontiers of paediatric cochlear implantation are rapidly changing. In a few years paediatric implantation has become the standard treatment for profound hearing loss in children, providing impetus for national newborn screening programmes. Implantation is now usually bilateral, simultaneous and performed in infants less than a year old. Cochlear implants are a viable treatment for children with less-than-profound hearing loss, auditory neuropathy and (perhaps) single sided deafness. Auditory brainstem implants provide options for children who are not suitable for cochlear implants. The future holds the promise of totally implantable implants, which may also stimulate hearing recovery or increased neural responses, utilising techniques such as gene therapy.

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Current management of vascular malformations of the head and neck

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Abstract

The field of vascular anomalies of the head and neck region has gained important improvements in terms of therapeutic opportunities. In contrast to hemangiomas of the infancy, a spontaneous regression of vascular malformations of the head and neck may never be expected. Thus, all symptomatic vascular malformations require treatment. The classification by ISSVA (International Society for the Study of Vascular Anomalies) is the base for clinical management of vascular malformations. Low flow malformations are represented mainly by lymphatic, capillary and venous malformations. Conventional surgical approach, sclerotherapy, and laser treatment display today's invasive therapeutic options for lymphatic malformations. The treatment of choice for capillary malformation is the pulsed dye laser but this is limited to responders. Venous malformations are the most common type of vascular malformations of the head and neck. Treatment with the Nd:YAG laser is effective for those lesions involving the mucosa of the upper aerodigestive tract. Significant improvements are observed in terms of safety of new alcohol based sclerosing agents for venous malformations. Arterio-venous malformations are considered as the most dangerous subtype of vascular malformations. These are the main representatives of high-flow lesions with the tendency of uncontrollable growth to a point of incurability.

Keyword

Vascular malformations; Head and neck; Venous malformations; Arteriovenous malformations; Lymphatic malformations; Capillary malformations

J ENT Masterclass 2014; 7 (1):32 - 37.

Introduction

During the last three decades, the field of vascular anomalies especially of the head and neck region has rapidly grown. Important improvements of the therapeutic strategies for the management of vascular malformations of the head and neck region could be achieved. Beside the intensified multidisciplinary and international exchange¹, preconditions for this development were the strict application of an accurate classification of hemangiomas and vascular malformations. Nowadays, the classification as presented by the ISSVA (International Society for the Study of Vascular Anomalies) is the base for clinical management and scientific exchange with regard to vascular anomalies. In particular the fact must be emphasized that the term of “*hemangiomas*” is exclusively used for the benign vascular tumor of infancy, namely the *infantile hemangioma*. So today it can no longer be accepted to use the term of hemangioma for several kinds of vascular anomalies. This article focuses on vascular malformations which in contrast to most hemangiomas are by definition already present at birth but in the majority of the cases show a proportional growth behavior to the body growth. The classical infantile hemangioma which is nowadays treated in large series with propranolol is not the subject of this article.

As mentioned before, the vascular malformations of the head and neck are per definition present at birth but also this simple rule-of-thumb is not true for all vascular malformations. Only a certain part of vascular malformations is exposed to potentially accelerated growth during body growth. In contrast to hemangiomas, however, one fact can be considered as sure: While spontaneous regression can be expected in hemangiomas of the infancy,

especially in the first three years, a spontaneous regression of vascular malformations of the head and neck may never be expected. So the rule may be stated that all symptomatic vascular malformations showing an aesthetic or functional impairment or even a combination of both require treatment.

The management of vascular malformations is multimodal. This is the special background of the heterogeneity of this large group of congenital vessel disorders. This review focuses on therapeutic modalities that are applied to vascular malformations of the head and neck region and that are considered today as state of the art for the treatment of those anomalies. However, comparable to any other field with increasing knowledge, a further improvement and modification of the treatment options mentioned in this manuscript can be expected.

As stated above, the correct terminology and classification are essential to choose the accurate therapeutic management. The ISSVA classification has been recently updated (in April 2014 during the 20th Workshop in Melbourne, Australia). The current classification can be uploaded from the website of the ISSVA (www.issva.org).

The differentiation between vascular tumors and vascular malformations is of highest clinical relevance. Vascular malformations are the focus of the present article and so they are subdivided according to their primarily affected channel morphology. In summary, the differentiation between capillary, lymphatic, venous and arterio-venous malformations has a clinical relevance while mixed or combined types are classified as e.g. capillary-venous, capillary-lymphatico-venous, lymphatico-venous, and capillary-arterio-venous malformations. In order to keep the overview, this article only focuses on the treatment of capillary, lymphatic, venous and arterio-venous malformations that are the main appearances of vascular malformations of the head and neck.

Another essential aspect is the distinction of vascular malformations regarding the haemo-dynamic properties beside the above-mentioned morphologic features. Low-flow malformations consist of lymphatic, capillary or venous and high-flow malformations consist of arterio-venous malformations as their main representative of these two categories.

Low-flow malformations

Lymphatic malformations

Lymphatic malformations of the head and neck are usually in the vast majority of the cases already present at birth. Especially advanced lymphatic malformations are still a

major therapeutic challenge. Huge disfiguring lesions are still not accessible to complete cure. Their therapy is necessary for a lot of patients since the lymphatic malformation may cause functional compromises like obstruction of the upper aerodigestive tract, restriction of visual acuity or severe dysgnathia. Invasive therapeutic options for lymphatic malformations can be divided into three approaches, namely the conventional surgical approach, sclerotherapy, and the treatment by laser assistance².

The surgical treatment of large lesions especially with a significant microcystic component is still frustrating in advanced cases. These lesions are not available for complete resection, especially those that involve both the infra- and suprahyoidal neck and the facial area. As a rule-of-thumb, infrahyoidal affection is mostly macrocystic. These lesions are well available for surgical resection and also for sclerotherapy^{3, 4}. The sclerotherapy agent which has been established during the last years in Europe is in first line Picibanil® (OK-432) which is the most frequently used sclerosing agent beside doxycycline. But doxycycline is especially restricted for pediatric cases because of the side-effects which are known during dentition. The main principle of both sclerosing agents is the fibrosis induction. The effect of Picibanil® is the artificially induced inflammation in the lesion while an inhibition of angiogenesis is attributed to doxycycline⁵.

The laser treatment is usually performed with CO₂ laser. This CO₂ laser is mainly used in a defocused mode to vaporize microcystic lesions of the mucosa. This therapeutic approach is preferred for laser treatment of the oral cavity, especially of the tongue. In some cases, Nd:YAG laser is combined with the CO₂ laser in order to benefit from the depth effect of the Nd:YAG laser aiming at the superficial vaporization and also the fibrosis more in the depth of the tissue. Laser treatment is appropriate for a mid-term symptom relief of weeks or months because on the one hand the potential effect is classified as low and on the other hand because of the very low or even negligible risk of side-effects and the possibility to repeat this therapy in several sessions^{6, 7}. Laser – if used with CO₂ laser alone or in combination with Nd:YAG laser – is an important tool for the management of lymphatic malformations.

Extensive cervico-facial lymphatic malformations need an interdisciplinary approach. Sometimes they might be accompanied by thoracic and mediastinal involvement [Fig. 1a-b], thus a close cooperation be insured between head and neck surgeons and thoracic surgeons. These large lesions are in most cases already diagnosed during the



Figure 1a: Large cervico-thoracic lymphatic malformation of a 5-year old boy

prenatal period by prenatal sonography so that also obstetricians should be aware of those lesions and refer to a specialized consultation already before birth⁸. Because of the complex form of possible manifestations such as secondary deformities of the facial skeleton [Fig. 2], a close cooperation should be ensured between all involved medical subspecialties. Beside the prenatal diagnosis, this includes obstetricians, head and neck specialists, radiologists, maxilla-facial surgeons, thoracic or pediatric surgeons, orthodontists, and also speech pathologists. The role of medical treatment of lymphatic malformations is still in a premature stage. Some recent reports include rapamycin (sirolimus) to treat large lymphatic malformations as this immune-modulatory agent has shown positive impact on the treatment of lymphangiomatosis⁹. Acute inflammatory based volume increases and symptom exacerbations of lymphatic malformations are usually treated with systemic antibiotics (e.g. cephalosporines or ampicillin-sulbactam) and steroids (up to 5 mg per kg body weight Prednisolone as initial dose). The antibiotic and steroid treatment is applied with the background to possibly reduce at least in the acute phases the symptoms caused by inflammation-triggered expansion of lymphatic malformations.

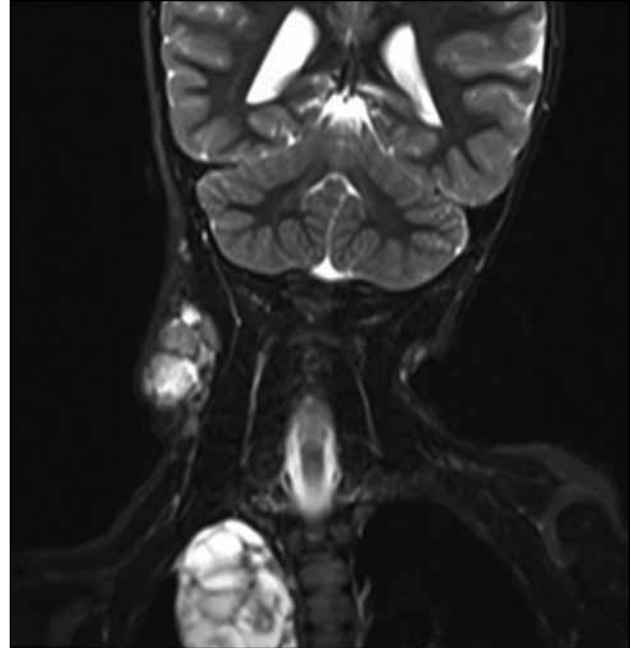


Figure 1b: Note the intrathoracic extension which is implied on the MRI

Capillary malformations

The typical representative of capillary malformations of the head and neck region is the so-called port wine stain (PWS) or naevus flammeus. Usually they affect the head and neck area in a characteristic segmental pattern. Primarily, these lesions are seen as diseases of the skin but especially due to expansion during life, more and more subcutaneous and mucosal affections become evident and cause symptoms. Even if at the beginning the major handicap of the patient may be the aesthetic affection, a large portion of the patients suffer from the affection of the upper aerodigestive tract and the cervical soft tissue, that



Figure 2: Malocclusion caused by a lymphatic malformation of the neck involving the suprahyoidal neck, oral cavity and the tongue in a 5-year old girl despite multiple treatments by surgery and laser therapy. Note the residual microcystic affection of the tongue



Figure 3a: Severe lower lip hypertrophy of a 38-year old female caused by a deep capillary malformation of "port-wine stain"- type



Figure 3b: Status 1 year after conventional surgical volume reduction

gives rise to relevant clinical symptoms by involving the oral cavity, the lips, the tongue, the nasal, the pharyngeal, or the laryngeal mucosa or even the soft tissue of the neck and the parotid gland¹⁰.

Even though the treatment of choice of the cutaneous affection and the gold standard today is still the pulsed dye laser¹¹, macrocheilia or the manifestation in the soft tissue may make a conventional surgical approach for these lesions necessary [Fig. 3a-b]. Today's recommendation for responders to pulse dye laser is to consequently perform the dye laser treatment in the childhood and to regularly follow-up the patients, with the background to avoid the expected increase of nodularity and deep tissue affection during the years¹².

Venous malformations

Venous malformations have a special role in the head and neck area. The reason for this is simply the fact that venous malformations are the most common type of vascular malformations of the head and neck¹³. Depending on the size and extension and location of the venous malformations, a multimodal approach is required to manage venous malformations. Laser treatment, and this especially with the Nd:YAG laser, is the method of choice to treat venous malformations involving the mucosa of the

upper aerodigestive tract¹⁴. If the soft tissue of the head and neck area is involved, the laser treatment will face limitations. Thus, in cases of severe disfigurement or dysfunctional problems, the conventional surgical approach is still the treatment of choice [Fig. 4a-b]. Since venous malformations are low-flow malformations, angiography and embolization in a transarterial classical form are of no value for these lesions. The conventional surgical approach to these lesions bears the severe risk of bleeding. The bleeding risk is based not only on the vascular nature of the lesion but also on the very often observed local intravascular coagulopathy of larger venous malformations which can also be present in the head and neck area¹⁵. Significant local intravascular coagulopathy which is pathognomonic for large venous malformations is identified by elevated d-dimers and lowered fibrinogen levels¹⁶. Optimization of the local intravascular coagulopathy can be performed preoperatively by application of low-molecular weight heparin derivatives and controlled by d-dimers and fibrinogen level stabilization.

The classical surgical approach necessitates continuous local hemostatic procedures, predominantly performed with electrocoagulation which is an effective tool to control bleedings during resection. The most potential sclerosing agent is ethanol which can be applied on the fluoroscopic control but pure ethanol is hazardous especially because of potential nephrotoxic side effects and also potential tissue destruction and necrosis. Thus nowadays ethanol-based gels are introduced to perform the sclerotherapy by improving the viscosity and the local diffusion control of the sclerosing agent. Ethanol gel or ethyl-cellulose-ethanol agents have significantly contributed to the safety of sclerosing therapy of venous malformations based on alcohol^{17, 18}. Another known worthy agent is bleomycin which has been rediscovered



Figure 4A: Venous malformation affecting the cervical soft tissue and the external ear in a 21-year old male. **Figure 4B:** Status 7 months after conventional surgical therapy

after promising experiences from China^{19, 20}. Bleomycin treatment should be performed with strict monitoring of the renal and pulmonary functions and it is contraindicated in cases of renal or pulmonary impairments.

High-flow malformations

Arterio-venous malformations

Arterio-venous malformations (AVM) of the head and neck are the main representatives of high-flow vascular malformations. They are considered as the most dangerous subtype of vascular malformations not only because of their hemodynamic property but also because of the tendency of uncontrollable growth and expansion to a point of incurability²¹. AVM are in the childhood mostly misdiagnosed as harmless port-wine stains or “hemangiomas”. In case of uncontrollable growth, the AVM which can be present as a simple form with a single AV nidus or a complex form with several AV nidi is associated with destructions and life-threatening bleedings [Fig. 5].



Figure 5: Arteriovenous malformation of the face of a 41-year-old female with a history of multiple embolizations, partial resections and even bilateral ligation of the external carotid artery at another institution

Conventional surgery is still the treatment of choice for resectable AVM. Intravascular embolization alone cannot replace the surgical excision because of the potential re-growth and the possible risk of iatrogenic growth stimulation after embolization. It is assumed that local hypoxemia which is induced in the lesion after embolization or even after surgical resection of supplying arterial vessels would provoke a potential growth of the AVM analogous to intracranial AVM²². Thus the embolization alone as a sole treatment is reserved only for advanced cases to achieve temporary relief such as reduction or cessation of arterial bleedings. This is especially performed when a surgical resection which should include the resection of the AV nidus is not possible. The liquid embolization agent Onyx® (an ethylene-vinyl alcohol copolymer) has become popular also for embolization of AVM of the head and neck. This agent is able to embolize even smallest vessels but its application especially in the facial area is accompanied commonly with a post-interventional local inflammation²³. Beside this, a black tattooing of the overlying skin is may occur²⁴. Thus an Onyx® embolization of AVM should preferably offered in combination with post-embolization surgical resection.

As stated before, large facial AVM with multiple AV nidi are incurable. So the efforts to find a pharmaco-therapeutic alternative treatment of AVM are very high. Still medical therapy with curative intention of AVM is in an experimental stage. Examples are application of marimastat²⁵ or doxycycline²⁶, both acting as matrix metalloproteinase inhibitors, to control AVM of the upper extremity or intracranial AVM, respectively.

Conclusion

Vascular malformations are a heterogenous group of diseases that are distinctive from hemangiomas. The main representatives of low-flow malformations are lymphatic, capillary, and venous malformations. Advanced lymphatic malformations display a severe multidisciplinary challenge. Therapeutic options for lymphatic malformations are sclerotherapy, laser therapy and conventional surgery. The most frequently applied sclerosing agents is Picibanil® which sufficient in macrocystic disease only. Inflammatory induced symptom exacerbations of lymphatic malformations of the head and neck are usually managed with systemic antibiotics and steroids in the acute phase. Multi-organic involvement and a spectrum of possible symptoms make a close interdisciplinary approach to lymphatic malformations necessary. The main representative of capillary malformations is the port wine stain as cutaneous manifestation; established treatment is the pulsed dye laser. Soft tissue and mucosal involvement are possible

which would potentially give rise to symptoms in the head and neck/ENT fields. Thus also capillary inflammations might make a conventionally surgical treatment necessary as it is commonly performed on the macrocheilia which is caused by deep penetration of capillary malformations.

The treatment of choice for mucosal affection of venous malformations is the laser. The Nd:YAG laser seems to be the most reliable tool for laser treatment of mucosal venous malformations. Sclerotherapy for venous malformations can be performed with ethanol-based embolic agents preferably those with modified and improved viscosity. The treatment of choice for thrombophlebitis induced swelling conditions of venous malformations is the application of low molecular weight heparin which can be combined with antibiotics. Low molecular weight heparin can also be applied to the patients to optimize the intravascular coagulopathy in large lesions before surgical treatment.

The arterio-venous malformations are the most challenging type that can only be cured if the lesion in toto including the arterio-venous nidus is excised. Embolization as monotherapy is not sufficient to cure AVM. Incomplete embolization and ligation of supplying arteries may result in an iatrogenic expansion of AVM and cause incurability in otherwise curable lesions. Large multifocal lesions with multiple AV nidi are with today's tools incurable. In those cases limited surgery or embolization alone are justified to control the complications such as severe bleedings. A pharmaco-therapeutic approach to AVM is still not established.

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Complications of acute otitis media

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Abstract

Acute otitis media is one of the commonest disease affecting children. The highest incidence is in the first 6 years. In a small proportion of patients, intracranial (meningitis, intracerebral abscess, venous sinus thrombosis) and extracranial (labyrinthitis, mastoiditis, facial palsy) complications can occur. The spread of infection to these areas is due to the close proximity of these structures to the middle ear. These complications can be life threatening and therefore require prompt diagnosis and management.

Key Words

Otitis media; acute; complications

J ENT Masterclass 2014; 7 (1): 38 - 44.

Introduction

Acute otitis media (AOM) is one of the commonest ear diseases affecting children^{1,2,3,4}. The highest incidence is in the first 6 years of life⁵.

Treatment guidelines vary. However there is a consensus that all children are prescribed analgesia. Routine antibiotics are to be avoided in cases where there is diagnostic uncertainty or in mild to moderate cases in children aged two years or more^{1,2,6}. Amoxicillin is the most recommended first line antibiotic agent¹. A small proportion (1-5%) present with complications of AOM^{7,8}.

Despite the widespread use of antibiotics complications of AOM continue to occur⁹. These may be intracranial (meningitis, intracerebral abscess, venous sinus thrombosis) or extracranial (labyrinthitis, mastoiditis, facial palsy, gradenigos). The mortality rate for these complications is still 8-26.3%⁵. Risk factors for developing complications of AOM include; less than 6 months age; anatomic defects in the ear; and immunosuppression¹⁰.

Pathophysiology of AOM

An immature immune system and structurally immature Eustachian tube (ET) are important factors related to otitis media in children¹¹. Pathogens enter the middle ear through the ET¹². Following an upper respiratory tract infection ET blockage leads to negative middle ear pressure and subsequent effusion¹². There is purulent inflammation of the middle ear causing mucosal oedema and hence blockage of the aditus and antrum. This leads to a purulent effusion and tympanic membrane (TM) perforation in the majority of patients. However in some patients this process leads to infection in key structures in this area (i.e. mastoid, labyrinth, facial nerve). The middle ear infection prevents mastoid air cells from draining and initiates a cascade of osteitis, and necrosis resulting in mastoiditis⁵. The infection can spread via the osteitic bone to the middle and posterior fossa dura matter; by haematogenous spread or thrombophlebitis; or by infectious spread through the labyrinth via the round and oval window or congenital malformations¹³. The extracranial system enters the sigmoid sinus via the mastoid emissary vein¹³. Direct extension along the petromastoid canal or petrosquamous suture as well as haematogenous spread can cause meningitis in complicated otomastoiditis¹³.

Extracranial complications

Tympanic membrane (TM)

The clinical spectrum of AOM may vary from an early stage when there are clear signs of TM inflammation and middle ear fluid accumulation, to more severe AOM when purulent middle ear fluid under pressure causes bulging of the TM, to spontaneous rupture of TM with otorrhea¹². In a longitudinal study of 294 cases of AOM 6% were found to have TM perforation/ottorheo¹². In a Cochrane review it was found that antibiotics led to a significant reduction in TM perforation³. However, 33 children (95% CI 17-100) needed to be treated with antibiotics to prevent one child experiencing TM perforation³.

In recurrent AOM there may in some instances be progression to chronic suppurative otitis media (CSOM)¹⁴. The use of antibiotics is an area of contention and there is insufficient evidence to know if antibiotics reduce AOM and perforation or prevent progression to CSOM or improve long-term outcomes¹⁴. National Institute for Clinical Excellence (NICE) guidelines state that children with otorrhoea (irrespective of laterality or age) benefit most from antibiotics¹⁵. They recommend immediate antibiotic prescription depending on severity in these patients¹⁵.

Mastoiditis

Acute mastoiditis (AM) is a suppurative condition which remains a serious complication of AOM⁷. It affects 1.4 people per 10,000 per year in the UK¹⁵. Presentation includes otalgia, post-auricular inflammation, and auricular protrusion. It is estimated that 5000 children with AOM would need to be treated with antibiotics to prevent one episode of mastoiditis¹⁵.

AM should be treated effectively as delay may lead to severe intratemporal and potentially lethal intracranial complications¹⁶. The most common intracranial complication of mastoiditis is meningitis⁷. High resolution temporal bone CT is crucial for better characterisation of the intratemporal findings⁷.

Alternatively in certain cases silent mastoiditis may be present. This occurs when antibiotic treatment leads to transient relief of clinical mastoid symptoms whilst middle ear inflammation continues¹⁷.

A ten year retrospective European multicentre study found that the incidence of mastoiditis was stable⁶. Out of 214 children 32% had a postauricular abscess and subsequent mastoidectomy⁶. In this study myringotomy was performed in 183 patients and 66 of these children received ventilation tubes⁶. All patients were treated with antibiotics and analgesia. The complication rate in this set of patients was 1.9%.

Psaromatis et al. retrospectively reviewed notes for children presenting with AM at their institution in Greece. The mean age of the patients was 36.7 (range 2-120) months¹⁶. Of these 155 patients 68% had been treated for AOM prior to presentation. Fourteen children presented with neurological signs and 4 had facial nerve palsy. All patients underwent myringotomy and ventilation tubes were placed in 23 cases.

Bakhos et al.¹⁸ retrospectively reviewed notes of patients presenting with AM secondary to AOM between 1994-2008 in South Africa. All patients received broad spectrum IV

antibiotics. This was ceftriaxone in combination with fosfomycin or metronidazole. The mean duration of treatment was 18 and 24 days in the conservatively and surgically managed patients respectively. Those with subperiosteal abscess (SA) (Image 1) or suspected intracranial complications, or no improvement after 48 hours of treatment underwent high resolution CT. Fifty patients (mean age 32 months) were included of which 43 had a CT scan. Findings included SA (31), sigmoid sinus thrombosis (3), and subdural empyema (1). Conservative treatment without mastoidectomy was adopted in 16 patients with SA. This involved postauricular aspiration of abscess or insertion of ventilation tube; the numbers for these procedures were not specified. This method failed in one patient who went on to have cortical mastoidectomy. The main finding was shorter hospital stay with no adverse affects in the conservatively managed group; 9 days versus 15 days.

There is a wide variation in the approach to AM. Mastoidectomy rates can range from 9-88%¹⁶. In uncomplicated cases of AM antibiotics are commenced followed by myringotomy if response to antibiotics is poor. Mastoiditis in combination with lateral sinus thrombosis and acute petrositis requires surgical treatment as well as intravenous antibiotics and anticoagulants^{8,19,20}. Our recommendation for management of AM is shown in Figure 1.

Gradenigos syndrome

Gradenigo syndrome is a rare but life threatening complication of AOM²¹. In 1907 Gradenigo described a

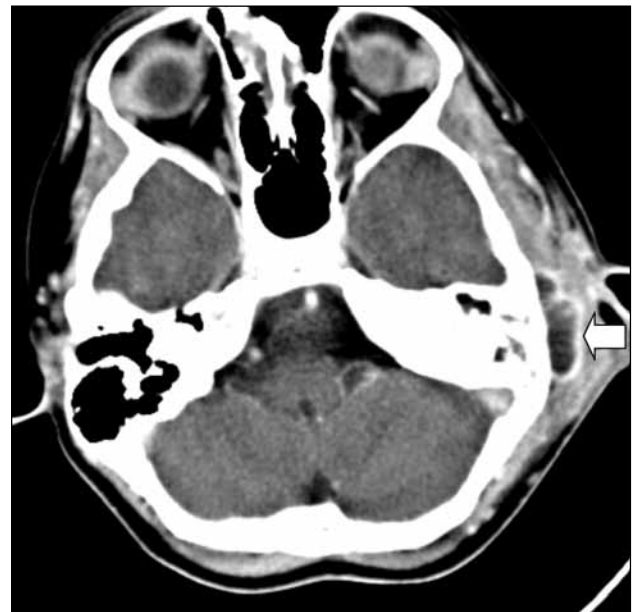


Figure 1: Axial CT demonstrating subperiosteal abscess (white arrow).

condition consisting of abducens nerve palsy; deep pain along the trigeminal nerve; and purulent otorrhoea resulting from petrous apicitis^{7,21,22,23}. The deep pain is due to involvement of dura over the petrous apex or direct irritation of the gasserian ganglion⁷. It is caused by spread of infection from mastoid air cells to the petrous apex²¹. Patients usually presented with headaches, tinnitus and abducens nerve palsy²². CT and MR are useful in distinguishing petrous apicitis from other conditions.

In a case of an 11 year old with gradenigos syndrome secondary to AOM treatment with high dose IV ceftriaxone and dexamethasone was effective. Magnetic resonance venography (MRV) was performed to rule out lateral sinus thrombosis which can often be found in this context. Treatment was continued for 8 weeks. At this stage lateral rectus palsy was continuing to improve²³.

Colpaert et al.⁵ presented a case which was treated with mastoidectomy, drainage of epidural empyema and intravenous antibiotics. The patient also had venous sinus thrombosis. This was treated with low molecular weight heparin (LMWH) which was commenced on the first day post operatively and continued for 12 weeks. The outcome was bilateral mild conductive hearing loss.

Gradenigos syndrome without other complications of AOM can be treated conservatively with intravenous antibiotics^{5,22}. Antibiotics are recommended for 2-3 weeks but osteomyelitis may require up to 6 weeks antibiotics²².

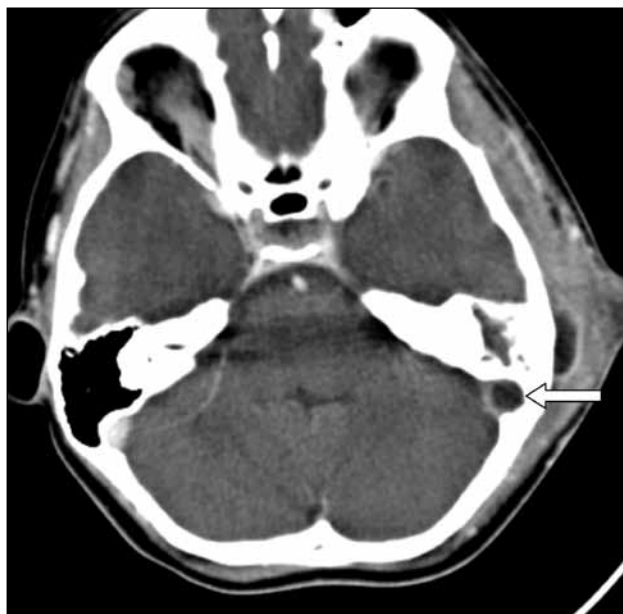


Figure 2: Axial CT showing venous sinus thrombosis (white arrow)

Facial Nerve Palsy

The most common detectable cause of facial palsy in children is otomastoiditis¹⁷. Tsai et al¹⁷. presented two cases of facial palsy following AOM. They presented with otalgia, otorrhoea, and fever. Despite treatment with antibiotics both developed facial nerve (FN) palsy. Subsequently they required cortical mastoidectomy and insertion of ventilation tube. The facial palsies improved after 3 months. In Anthonsens series of 214 patients only one child had facial palsy associated with a retroauricular abscess which improved significantly following cortical mastoidectomy⁶.

In a retrospective review of 113 patients admitted with AOM; 22 had facial palsy. This was partial in 17 and complete in 5²⁴. Two patients had simultaneous AM and one had AM and petrocitis²⁴. The mean duration of facial weakness was 3.7 days. All patients received broad spectrum antibiotics. CT highlighted a dehiscent FN canal in one patient. Seventeen patients had myringotomy and 4 also had mastoidectomy. One patient required FN decompression. Follow up data was only available for 19 patients of which 15 had full facial nerve recovery at a mean duration of 133.5 days (10-365 days)²⁴. Two of the patients who presented with complete palsy achieved House Brackmen grade 2 and 5 respectively. Twelve of the patients who recovered full FN function had myringotomy and insertion of ventilation tube.

IV antibiotics and myringotomy with or without ventilation tube insertion is recommended²⁴. If function is not regained rapidly then CT imaging is essential to exclude other causes. The role of mastoidectomy and/or facial nerve decompression is still controversial.

Suppurative labyrinthitis

Wu et al²⁵. performed a retrospective review of patients presenting with complications over a 22 year period. Labyrinthitis was the commonest extracranial complication. Suppurative labyrinthitis is life threatening as infection can spread from the inner ear into the subarachnoid space leading to meningitis²⁴. Patients present with otalgia, otorrhoea, fever, nausea, dizziness, and vomiting. In a series of 113 children admitted with AOM; two had suppurative labyrinthitis. Both had profound sensorineural hearing loss²⁴. CT imaging was non-specific. They were treated with IV antibiotics for a mean duration of 8 days. One patient had myringotomy with insertion of ventilation tube. The other patient had mastoidectomy. Except for hearing loss recovery was complete²⁴.

Intracranial complications

Intracranial complications represent the most life threatening conditions, therefore require immediate and precise

intervention²⁶. The incidence of intracranial complications is 0.36% and this is on the increase which may be due organism resistance due to availability of antibiotics and vaccinal influence^{5,27}. CT scan is the first line investigation as it is more readily available⁵. Lateral sinus thrombosis (LST) accounts for 2-20% of intracranial complications.⁸ In Psarromatis et al. series of 10 patients all had intracranial complications. Myringotomy and simple mastoidectomy were performed in 9 patients and the epidural and perisinus abscesses were located and drained.

Intracranial Abscess

Otogenic brain abscess and meningitis are the most common central complications of otitis media²⁶. In a retrospective case series of 40 patients the most common site for intracranial abscess was epidural followed by petrous apex and intraparenchymal²⁸. Twenty five patients underwent incision and drainage whereas 5 had mastoidectomy and 3 were treated conservatively with IV antibiotics²⁸.

Meningitis

Meningitis is a medical emergency. Diagnosis is made through a combination of lumbar puncture alongside classic meningitic physical findings such as fever, altered mental state, photophobia and nuchal rigidity²⁹. However, in the context of AOM it is common for more than one intracranial complication to occur simultaneously. The presence raised intracranial pressure (ICP) due to other intracranial complications would potentially cause encephalic herniation therefore lumbar puncture for a diagnosis needs to be considered carefully²⁶. These patients should be managed with the paediatricians and treatment



Figure 3: MRV demonstrating flow void secondary to LST

with high dose IV antibiotics which cross the blood brain barrier should be commenced immediately.

Venous sinus thrombosis

Lateral sinus thrombosis (LST) is a known but increasingly rare complication of otitis media^{19,30,31}. Although the incidence of LST has declined since the advent of antibiotics the mortality of up to 10% remains unchanged^{20,31,32}. Thrombosis or thrombophlebitis can occur as a direct extension from the middle ear or through haematogenous spread^{19,20,30,33}. The sinus on the right side is more commonly affected than that on the left side for unknown reasons^{9,33}. The main symptoms of LST are; headache, otalgia, and swinging fever. If other complications of AOM are also present the patients may also complain of; vomiting, vertigo, diplopia, chills, and neck pain^{8,9,19,20,25}.

In a review of 16 studies fever was the symptom reported with the highest frequency (40-100%)³². Diagnosis is made with thin slice contrast enhanced CT or MRI imaging^{8,19,33}. (Images 2 & 3) CT may show high attenuation within the sinus on unenhanced images and level of enhancement on post contrast images. In MRI there may be increased signal intensity in T1 and T2. The thrombus may extend from the sigmoid sinus to the lateral and superior sagittal sinus interfering with the arachnoid plexus and thus creating an otitis hydrocephalus^{20,33}. The thrombotic process can also extend to the cavernous sinus which is life threatening²⁰.

There are a number of case series reporting on the management of LST in the literature; these are highlighted in Table 1.

Bales et al³¹. presented a retrospective series of 13 patients with LST, AOM, and mastoiditis. Eleven children had a history of AOM and with abnormal otoscopic findings³¹. LST was detected in all patients with extension into the transverse sinus and IJV in 11 and 8 patients respectively. All patients underwent mastoidectomy with myringotomy and insertion of ventilation tube. Two patients had sinus aspiration which yielded blood. Six patients had normal hearing post treatment whereas 5 had a conductive hearing loss. Eleven patients had serial MRI which demonstrated recanalisation of the sinus in 3 patients, partial canalisation in 8 and no resolution in 3 patients.

Management of the thrombus can be medical only, simple aspiration of the thrombus, or formal evacuation of the clot and packing the lumen¹⁹. There is a lot of debate as to whether anti-coagulation should be carried out and if so the length of treatment^{10,20,32}. Anticoagulation has been

Table 1: Summary of LST in literature									
Study	No of patients	Study type	Signs or symptoms	LST	Other intracranial complications	Treatment	Antibiotics	Anticoagulation	Complications
Bales ³¹	13 (mean age 9 years)	Retrospective case series (1997-2007)	Headache 7 AN palsy 1 FN palsy	Yes	Raised ICP AM	All had mastoidectomy, myringotomy, insertion of ventilation tube 2 sinus aspiration	IV (mean 15 days) PO (mean 22.6 days)	Yes 12 patients	4 post op bleeding 1 raised ICP requiring mastoidectomy
Funamura ³⁰	5 (age range 13 months to 15 years)	Retrospective case series (1996-2012)	fever	Yes	4 AM	1 ventilation tube 4 mastoidectomy + sinus aspiration	IV (ceftriaxone, ceftazidime, clindamycin, CA)	No	
Novoa ³²	9 (mean age 6.1 years)	Retrospective case series (2000-2009)	4 vomiting, apathy, headache 1 AN palsy	Yes	9 AM	9 Mastoidectomy + ventilation tube Sigmoid sinus de-roofed	IV (6 ceftriaxone + CA; 2 ceftriaxone + metronidazole; 1 CA+ metronidazole (mean 21.5 days)	Yes (mean 4.2 months)	2 patients thrombocytopenia with LMWH
Shah ¹⁹	2 (5 years and 14 years)	Case series	Diplopia, raised ICP	Yes	AM	Mastoidectomy + ventilation tube	IV (1 ceftriaxone, vancomycin, metronidazole, 1 ceftriaxone)	Yes LMWH 1 & 2 months followed by warfarin 3 months	Bleeding from wound site
Ropposch ²⁰	6 (mean age 7 years)	Retrospective Case series (2005-2010)	1 AN palsy 1 purulent otorrhoea fever	Yes	AM	1 conservative 5 mastoidectomy + exploration of sigmoid sinus 3 thrombectomy (2 of these had IJV ligation)	IV (mean 11.3 days)	Yes 3 days unfractionated heparin then 3 months LMWH	
Christenson ⁸	7 (mean age 7.4 years)	Retrospective Case series (1997-2008)	5 – fever (2 spiking temperature) 4- recurrent AOM	Yes	AM	5 Mastoidectomy + de-roofing and aspiration sigmoid sinus 4 of 5 ventilation tube	IV ceftriaxone (mean 13 days)	1 LMWH followed by warfarin	2 re-admitted otitic hydrocephalus 1 long-term lateral gaze diplopia
Van Munster ¹⁰	1	Case report	2 week AOM developed Left AN palsy, unsteady gait	Yes	AM, LST, Cerebellar empyema	Mastoidectomy, thrombectomy, drainage of empyema, dexamethasone	IV ceftriaxone	Yes LMWH	
Ooi ³³	1	Case report	Mastoiditis, purulent otorrhoea	Yes	AM	Mastoidectomy + skeletonisation sigmoid sinus	IV ceftriaxone, metronidazole, gentamicin, benzylpenicillin	No	
Au ⁹	1	Case report	Purulent otorrhoea, otalgia, fever, neurological signs	Yes	AM	Mastoidectomy + ventilation tube	IV ceftriaxone + clindamycin	No	

AN – Abducens nerve; FN – Facial nerve; AM – Acute mastoiditis; LST – Lateral sinus thrombosis; LMWH – Low molecular weight heparin; ICP – Intracranial pressure; PO – Oral, IV – Intravenous; CA – Co amoxiclav

reported to be safe in children³². Anticoagulation limits clot propagation and improves intracranial venous drainage and reduces intracranial pressure thereby leading to improved neurological outcomes^{19,20}. There is however

evidence that following mastoidectomy and 6 weeks of antibiotics the venous sinus recanalises¹⁹. Intra or postoperative bleeding, thrombocytopenia, drug interaction, and release of septic emboli from dissipation

of the thrombus are potential complications if anticoagulants are used²⁰.

A retrospective study by Novoa et al. reported use of anticoagulation for an average of 4.2 (range 3-11) months in 9 children³². Treatment was stopped after resolution of symptoms or when recanalisation had occurred. Following aspiration complete thrombosis was confirmed in 4 (44%) of patients. Recanalisation occurred in 7 children by 2 years. This was confirmed by serial MRV. One child was left with residual sensorineural hearing loss; all other children made a full recovery.

Numerous studies recommend interval MRIs to assess thrombus progression^{8,20,30,32,33}. This can be problematic in children as they may require a general anaesthetic.

Ropposch et al. presented 6 cases of LST. Thrombus extended to the lateral sinus in 3 cases and internal jugular vein in 3. One patient was managed completely conservatively with 10 days of IV antibiotics and anticoagulation. Subsequent MRI demonstrated normal venous flow through the sigmoid and lateral sinus²⁰. The remaining 5 patients all had mastoidectomy with exploration of the sigmoid sinus wall. Thrombectomy was performed in 3 patients and internal jugular vein (IJV) ligation in 2 of the three patients. There were no anticoagulation related complications. At 3 months MRI scan demonstrated recanalisation in the two patients who did not have thrombectomy or IJV ligation. There is no evidence to suggest that thrombectomy improves prognosis³³. Ropposch et al. concluded that thrombectomy and ligation of the IJV did not show a beneficial effect on treatment of LST²⁰. In the pre antibiotic era IJV ligation was carried out to prevent septic emboli, however this was associated with a risk to the vagus and hypoglossal nerves³³. This procedure is not recommended unless there is thrombosis of the IJV, ongoing septicaemia despite treatment, and when the clot extends beyond the mastoid area³³.

In a review of 16 studies 124 children with LST were identified³². Of these 111(89%) underwent surgical intervention and of these 68 (58%) were anticoagulated. The mortality in this pool of patients was 3%. There were no anticoagulation related complications. The remaining 13 had antibiotics only (n=4) or a combination of antibiotics and anticoagulation (n=9). Anticoagulation was recommended to improve recanalisation of the sinus which is thought to reduce neurological sequelae³². A less invasive approach (sinus aspiration with sigmoid decompression) yielded a rate of recanalisation of 75% in the non anticoagulated group and 79% in the anticoagulated group³².

In a review of 104 patients from the literature (1993-2011) the average age of presentation was 7.7 years. There was an average time period of 11 days between onset of symptoms and presentation to hospital⁹. The average length of stay in hospital was 14.5 days. There was a single mortality in this cohort. Mastoidectomy was performed in 94.2%⁹. Approximately half of these patients also had myringotomy and ventilation tube insertion. Manipulation of the sinus was performed in 51 patients. Of those needle aspiration was performed in 54.9% and thrombectomy in 47.1% and IJV ligation in 7.8% of cases⁹. Over half of these patients received anticoagulation and partial or complete recanalisation occurred in 84%. There were 3 complications in the anticoagulated group; one case of incisional bleed and 2 cases of post operative haematoma. Of the patients who did not receive anticoagulation partial or complete recanalisation occurred in 75%. Anticoagulation may be useful in preventing clot propagation, promoting intracranial drainage and limiting increased intracranial pressure. Anticoagulated patients with LST are more likely to have better cognitive outcome and minor neurological sequelae in comparison to non treated patients²². Morbidity was 10% and included cranial nerve palsy, sensorineural hearing loss, stroke, septic hip and papilloedema.

Treatment comprises intravenous antibiotics and surgical intervention with or without anticoagulation^{19,20,30,32,33}. There is controversy with regards to the most appropriate management. Antibiotics for at least six weeks are recommended¹⁹. In certain cases of LST treatment with IV antibiotics alone may be successful³³. Surgery allows removal of the source of infection, middle ear ventilation, and removal of the clot and prevention of further propagation¹⁹. Surgical treatment is mastoidectomy with or without placement of a myringotomy tube and sinus aspiration^{30,32}. The appropriate management of the thrombus in the sinus is uncertain³³. Aspiration is performed to confirm diagnosis. The prognosis does not seem to improve by exploring the sinus or thrombectomy³³.

Microbiology

AOM is the most frequent reason for children to take antibiotics³⁴. Guidelines recommend selective use of antibiotics in children particularly if they are 2 years or older³⁴. The NICE guidelines recommend withholding antibiotics unless the child is younger than 2 years of age; has purulent otorrhoea; bilateral AOM; or congenital abnormality or immunosuppression¹⁵. A retrospective study carried out by Anthonsen et al. found that out of 202 ear canal and middle ear cultures 'no growth' was the commonest finding⁶. In AOM group A beta haemolytic

streptococci, streptococcus pneumonia, pseudomonas aurigenosa, haemophilus influenzae, and streptococcus pyogenes are most frequently isolated^{6,9,16,31}. Early broad coverage is recommended in light of the numerous organisms which may be the causative agent⁸. In uncomplicated AOM amoxicillin is the first line antibiotic². In complicated AOM ceftriaxone seems to be the antibiotic of choice in the literature due to its broad spectrum cover and penetration in the central nervous system^{8,9,16,19,32}.

Conclusions

We present a comprehensive review of complications of AOM and their management. Although the incidence of these complications has reduced significantly since the advent of antibiotics in the cases where complications do occur consequences can be dire. The evidence presented allows a systematic approach to identifying and managing these complex patients.

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Non-vestibular causes of dizziness

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Abstract

As ENT surgeons treating balance disorders, a broad overview of the causes of dizziness is essential. Identifying and treating the vestibular causes are occasionally made difficult by the presence of non-vestibular causes. This is especially so in the elderly. Though not exhaustive, we have listed some of the common causes of non-vestibular dizziness and their management, as seen at our balance centre.

Keywords

Dizziness, non-vestibular causes, diagnosis, management.

J ENT Masterclass 2014; 7 (1): 45 - 50.

Introduction

Dizziness is a non-specific term and a common cause for seeking medical advice. More than 30% of the population see their GP with dizziness before the age of 65. With the expansion of “balance clinics” offering a centralised referral point for dizzy patients, an ever broader range of non-vestibular disorders will be encountered by ENT surgeons and at an early stage of the disease process when symptoms and signs may still be subtle. A broad understanding of the medical conditions relevant to the dizzy patients is therefore required. It is helpful to distinguish between patients with chronic imbalance and episodic vertigo (Table 1). An introductory RSM presentation on the subject is available on the web with videos¹.

Aetiologies

Physiological

- **Height vertigo²** - In order to maintain a static posture, 2cm of normal sway of the head is allowed to produce visual cues to aid balance. When looking out from a

high building the head moves beyond 2cm as part of normal sway and this is perceived as motion in those who are visually dominant.

- **Motion sickness/Sea sickness** – Central sensory conflict results when visual input (looking at the fixed floor of the boat) is in conflict with vestibular input (the bobbing boat). Hence the advice to fixate on the horizon.
- **Purely visual:** New spectacles or cataract surgery lead to changes in refractive requirements. This requires adaptation of the vestibulo-ocular reflex (VOR) in order to re-calibrate eye movements to head movements.

Table 1: Key questions for Paroxysmal dizziness (13 P's of Paroxysmal dizziness)

1.	Positional	Arnold-Chiari Malformation, BPPV
2.	Postural	Hypotension / Syncope
3.	Phono/photophobia	Migraine
4.	Pressure	Perilymph Fistula, Superior Semi-Circular Canal Dehiscence
5.	Psychological	Hyperventilation
6.	Palpitations	Cardiac, panic attacks
7.	Paroxysmia	Episodic ataxia 2, vestibular paroxysmia
8.	Pills	eg Anti-hypertensives
9.	Periods	Migraine
10.	Peripheral sensation	Neuropathies/DM
11.	Preference (visual)	Vestibulopathy with Visual preference
12.	Posterior circulation	Transient Ischaemic Attacks
13.	Poor hearing	Meniere's Disease

Ocular dizziness occurs when refractive change exceeds the individual's ability to adapt their VOR. With aging, VOR adaptation slows and becomes less effective. In children, strabismus can cause ocular dizziness³.

Neurological: Peripheral

The peripheral neuropathies described will emphasize the importance of examining the feet of patients with chronic unsteadiness. Listen for the slapping steps of Charcot-Marie-Tooth, and test for the loss of proprioception in diabetes.

Peripheral neuropathy results from sensory, motor or autonomic nerve impairments. Sensory impairment gives rise to poor proprioception and influences gait and balance. This results in chronic imbalance. There are more than 100 causes of peripheral neuropathy. Some of the common causes are:

- Diabetes Mellitus is by far the commonest cause. 10 – 20% of newly diagnosed diabetics have diabetic polyneuropathy. The likelihood of developing diabetic polyneuropathy increases with the duration of having diabetes. Loss of distal sensation and postural hypotension are the commonest problems. Other risk factors for diabetic polyneuropathy include: smoking, hypertension, heavy consumption of alcohol, increasing age and poor diabetic control.
- Other causes of metabolic peripheral neuropathy include Vitamin B1, B6, B12, E deficiencies, alcoholism, hypothyroidism, chronic liver disease and chronic renal disease.
- Autoimmune disorders such as SLE, Sjögren's Disease and Guillain-Barré Syndrome may cause peripheral neuropathy.
- Infective neuropathies such as Lyme disease, HIV, diphtheria and leprosy may require appropriate investigation.
- Charcot-Marie Tooth Disease: This is a hereditary motor and sensory neuropathy. It usually presents in early adulthood with foot drop and tripping. Whilst classically associated with inverted champagne bottle legs, in clinic we commonly note pes cavus, clawing of toes, slapping gait, numb feet and areflexia.
- Malignancy related neuropathies are observed with lymphoma, multiple myeloma and paraneoplastic syndrome. Paraneoplastic syndrome may present with tremor and ataxia of gait and limb months or years before tumours manifest. They are typically related to

bronchial, breast and ovarian tumours. It is thought to be an auto-immune reaction and emphasizes the need for a multidisciplinary approach to such patients.

- Arsenic, lead or mercury poisoning are other potential causes.

Neurological – central

Central causes of dizziness are very common and may form part of a multi-system presentation in older patients. In the balance clinic we are often the first to identify these disorders and appropriate onward referrals should be sought.

- Migraine associated vertigo (MAV)⁴ is a very common cause of vertigo and can be difficult to distinguish from Ménière's disease in some patients. Indeed, up to 40% of Ménière's patients also have migraine. It presents with either episodic or persistent vertigo and is often associated with photophobia and/or phonophobia. It may present as travel sickness in children and is the most common cause of vertigo in them. Migrainous headache and visual migraine with aura may be absent. It is more common in women and may be related to their menstrual cycle, so ask for a diary of events. The primary treatment is explanation, dietary modification and lifestyle changes. We usually use a low dose amitriptyline initially, but beware of fatigue even at 10mg nocte, as well as weight gain. We use propranolol and topiramate at times, but liaise with our neurologists in more resistant cases. Botox has also been tried.
- Diffuse vascular disease affecting the brain parenchyma is a common cause of chronic unsteadiness in the elderly. Community-dwelling older adults with even mild degrees of cerebral atrophy have more balance problems than people without cerebral changes⁵. As problems with balance induce a fear of falling, consequent hesitation to move may result in marked disability and reduced quality of life as it is very difficult to overcome the significant loss of confidence. The input of a "Falls" (Prevention) Clinic" may be helpful. Figure 1 shows diffuse cortical atrophy and a "Dawson's finger" in this case caused by diffuse cerebral atrophy and leading to gait changes with short steps (marché a petit pas).
- Arnold-Chiari malformation – Displacement of the cerebellar tonsils (>5mm) through the foramen magnum gives rise to positional dizziness and ataxia. Other features include headache, oscillopsia, downbeat nystagmus on Hallpike's testing, sensori-neural hearing loss and reduced response on caloric test.

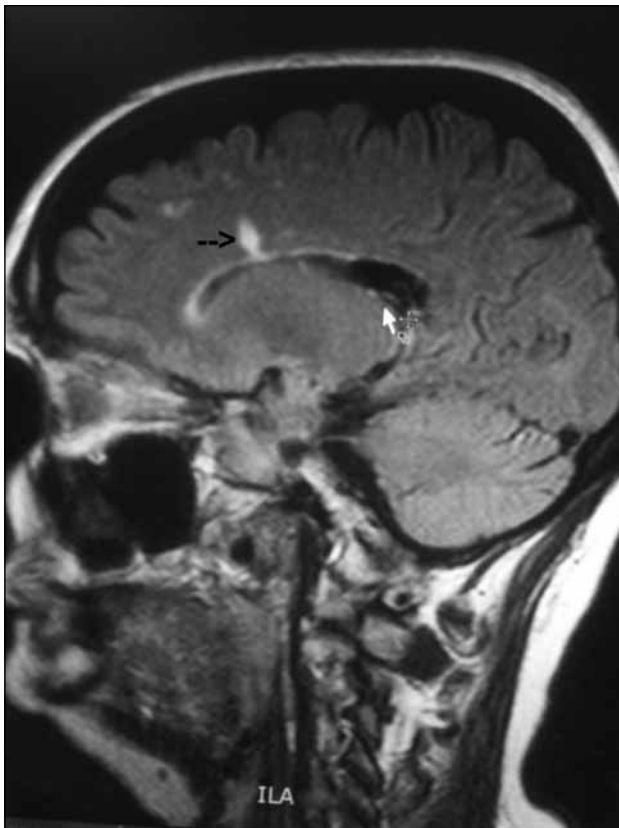


Figure 1: Sagittal MRI Scan showing Diffuse Cortical Atrophy with Dawson's Finger (black arrow) and enlarged ventricle (white arrow).

- Local ischaemia
 - Unexplained dizziness in older adults results, much more commonly than we might realise, from central ischaemic events. As these may herald further strokes which might be preventable we should seek them where indicated.
 - Posterior Inferior Cerebellar Artery (PICA) stroke (Lateral Medullary Syndrome) is the commonest “dizzy” stroke. Vestibular nuclei infarction gives rise to vertigo & tilt sensations, whilst infarction of the inferior cerebellar peduncle causes ataxia. Other symptoms may include dysarthria, dysphonia, dysphagia, loss of pain and temperature sensation and Horner's Syndrome.
 - Anterior Inferior Cerebellar Artery (AICA) strokes give rise to a mixed central and peripheral syndrome as it supplies the pons, cerebellum and the labyrinth. The labyrinthine involvement may lead to sudden onset of vertigo, tinnitus and sensorineural hearing loss (SNHL) and lower motor neurone facial palsy. Other features include ataxia and loss of motor and sensory function. Care must be taken, as a peripheral
- labyrinthine abnormality (eg BPPV, caloric weakness) may mask a central cause.
- Vertebro-basilar insufficiency (VBI) is a rare cause of episodic vertigo associated with head movement. As opposed to BPPV, the patients are dizzy while holding the neck position and there is no fatiguing. A history of whiplash injury or atherosclerosis in the posterior circulation should be explored. VBI is a transient posterior fossa ischaemia leading to a transient vertigo, dysarthria, diplopia or drop attacks. The latter can cause sudden falls leading to injury. A full cardiovascular work up to exclude cardiac syncope and MRI & MRA are indicated.
- Multiple Sclerosis (MS) presents with vertigo in 5%, whilst 20% eventually develop vertigo and it is commonly first diagnosed in the balance clinic. Look for inter-nuclear ophthalmoplegia, brisk reflexes, upgoing plantar reflex and cerebellar signs routinely. If the plaque is at the root entry zone of the VIIIth nerve, it can mimic vestibular neuritis. BPPV is often associated with MS so undertaking Dix-Hallpike's test in MS patients is sensible. We have seen a number of patients who have done well with vestibular rehabilitation too.
- Degenerative – These patients are often seen in the early stages in the balance clinic before their diagnosis is made. A high index of suspicion and exploring soft signs are essential. Neurological referral is required.
 - Basal Ganglia – See Table 2
 - Ataxias are a heterogeneous collection of diseases affecting cerebellar function and causing postural instability and inability to perform smooth movement. They may be episodic or chronic. The ataxias are best assessed at specialized neurology centres. Table 3 lists examples seen in the balance clinic.
 - Epilepsy – This very rarely presents to the balance clinic. The patients may complain of an “Alice in wonderland” syndrome – like falling down a hole. This occurs in temporal lobe epilepsy. Epilepsy may rarely be associated with “quick spin” type dizziness.
- Drugs – There are a number of drugs, which produce dizziness as a side-effect.
 - Centrally Acting: Phenytoin, barbiturates, carbamazepine, lithium and 5fluoro-uracil may cause ataxia and dysmetric arm movements while prochlorperazine may cause Parkinsonian symptoms. Aspirin, in high doses, cause dizziness.

Diagnosis	Demographics	Clinical Features	Management
Parkinson's Disease (PD)	Incidence of 1%>60yrs Falls – late	Resting Tremor Rigidity Bradykinesia Dysequilibrium Shuffling stooped gait with no arm swing	Treat PD 10% secondary BPPV – Needs Dix-Hallpike
Progressive Supra-nuclear Palsy (PSP)	Rare – sixth decade Postural instability and falls – early	Fatigue, Headaches, Arthralgia, Dizziness, Depression Ocular - slow vertical saccades, square wave jerks and supra-nuclear ophthalmoplegia (down gaze before up gaze), lid lag, poor convergence – diplopia Dysarthria, Dysphagia Apathy Axial rigidity without cog-wheeling or tremor	No known treatment 6 yr survival from diagnosis
Multi-System Atrophy (MSA)	Rare - Age of onset ~ 60 yrs	Parkinsonian -Rigidity – Slowness to initiate movement Cerebellar – Ataxia Autonomic – Genito-urinary, orthostatic hypotension	5 yrs – disability 7 yrs – mean survival

- Vestibulo-toxic: Aminoglycosides and chemotherapeutic agents like platinum drugs, taxanes, plant alkaloids and thalidomide are known to cause dizziness by damaging the vestibular apparatus and cochlea.

tinnitus, blurred vision with a reduction of visual fields, papilloedema and raised intra-cranial pressure. Dizziness or pulsatile tinnitus is the presenting symptom in the ENT clinic.

Idiopathic intra-cranial hypertension and normal pressure hydrocephalus (NPH)

- Idiopathic intra-cranial hypertension (Benign intra-cranial hypertension) – The patients are typically obese young women, who present with headache, pulsatile

- NPH is a condition where there is excess CSF in the brain causing a ventriculomegaly and the classical triad of symptoms: 1) gait disturbance - broad based, ataxic, and “magnetic” (usually the presenting complaint); 2) urinary incontinence and 3) memory decline. About

Diagnosis	Demography	Clinical Features	Management
Episodic Ataxia Type 2 (EA2)	Mutation in the CACNA1A gene for voltage-gated Ca ²⁺ channel in Purkinje Cells of the cerebellum	Dizziness (hours to days) Triggers - coffee, alcohol, stress, cerebellar signs	Acetazolamide Genetic testing of the CACNA1A gene
Spino-Cerebellar Ataxia	>60 types Most Autosomal Dominant	Progressive Ataxia in early adult life	Symptomatic & supportive
Friedreich's Ataxia	Autosomal Recessive Replication of CAG codon – excess glutamine FA gene deficit Reduced frataxin	Early age Ataxia, areflexia, dysarthria	As above + Trial drugs like Anti-oxidants, recombinant human erythropoietin and Gene therapy
Idiopathic Late Onset Cerebellar Ataxia	Unknown Cause 1:10000	50s Insidious gait & limb ataxia	Symptomatic & supportive

0.5% over 65's have NPH. Diagnosis is difficult as the symptoms overlap with Alzheimer's or Parkinson's Disease.

Trauma

- Post-concussion syndrome - Headache along with dizziness form the main physical components of post-concussion syndrome. There is associated cognitive loss and increased irritability and these symptoms are worsened by underlying depression. Most resolve spontaneously, whilst some need behavioural therapy.
- Intra-Cranial Haemorrhage – Acute intracranial haemorrhage is usually not seen by a “dizzy” doctor. However, chronic subdural haematoma may present with dizziness and ataxia. It is more common in the elderly and a history of head trauma should be explored. Anticoagulant use or alcohol abuse can predispose to such problems. (Figure 2)
- Benign Paroxysmal Positional Vertigo (BPPV) – Post-traumatic BPPV is more persistent than spontaneous BPPV and many need repeated particle repositioning manoeuvres or even posterior canal occlusion to correct it⁶.

Musculo-skeletal

- Joint replacements often contribute to multi-system balance disorder.

Cardiovascular

- The common presentation is syncope - a transitory, self-limiting loss of consciousness with no sequelae. Milder forms result in lightheadedness (as opposed to vertigo) which is relieved by sitting/ lying down, pallor/ sweating and blackouts (loss of vision). Exertional onset, chest pain, dyspnoea, low back pain, palpitations, severe headache, focal neurologic deficits, diplopia,

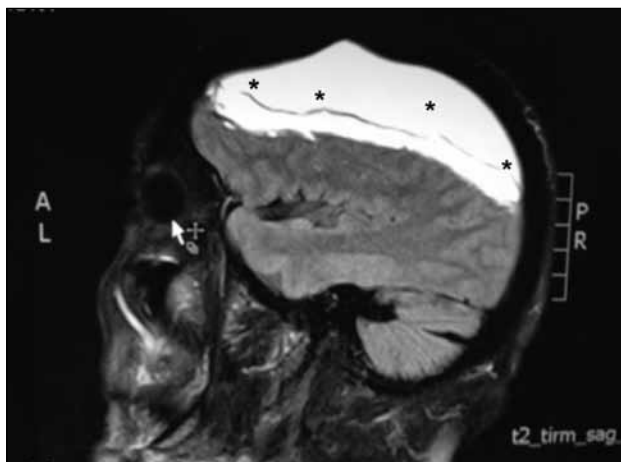


Figure 2: Sagittal t2-weighted MRI Scan showing a large Chronic Subdural Haematoma (black asterisk), following a fall from a tree three months ago. White arrow in the orbit.

ataxia or dysarthria are red flag symptoms and should alert one to the possibility of serious underlying disease.

- Pulse, heart sounds and lying/ standing blood pressure (at 0, 1, and 3 minutes) along with an ECG are basic assessments, while 48 hour ECG, blood test, echocardiogram and tilt table testing are required for some.
- The aetiology of syncope is discussed below⁷:
 - Reflex syncope is the most common cause of syncope. This can be 1) Vasovagal which can be initiated by emotional distress or prolonged standing; 2) Situational which can be caused by cough, GI disturbance (visceral pain), micturition and 3) Carotid sinus syndrome which can be caused by a tight collar or head rotation.
 - Syncope due to Orthostatic hypotension which may be due to
 - 1) Primary autonomic failure which is also seen in Parkinson's Disease;
 - 2) Secondary autonomic failure following DM, amyloidosis, spinal cord injury;
 - 3) Drug induced e.g. Diuretics, vasodilators, tricyclics;
 - 4) Volume depletion after Diarrhoea & Vomiting and
 - 5) Unknown Cause - POTS (Primary Orthostatic Tachycardia Syndrome) – Tilt table test is required.
 - Cardiac syncope can result from
 - 1) Arrhythmia,
 - 2) Structural Heart Disease or
 - 3) Channelopathies.

Psychological

- Most patients with a vestibular cause for their dizziness have a psychological component to their disorder. This may manifest as a loss of confidence, anxiety or panic attacks. Treatment should be aimed at correcting the underlying vestibular disorder, although specific psychological treatment may ultimately be required.
- However, as many as 5-10% of patients may present with primary chronic anxiety states or panic attacks with dizziness as their main symptom.
- Psychogenic Pseudosyncope/ Pseudoseizure is very similar to syncope, except that it brought about by stress and more common in young women. It may be an attention seeking behaviour but a history of abuse must be explored.

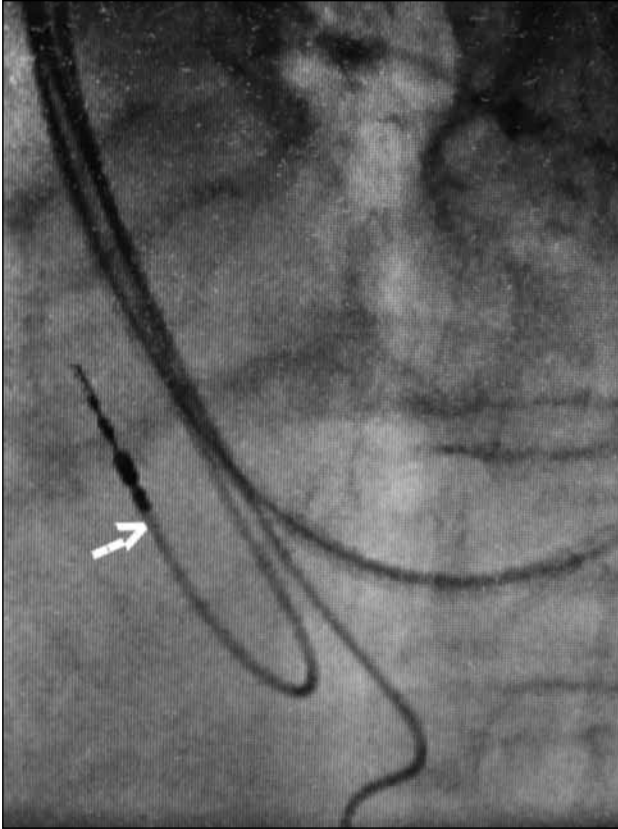


Figure 3: Pacemaker inserted in an 84-year old patient who presented with dizziness on extending head after lying flat. Though the other features were like BPPV the pulse was very slow and the patient was found to have a complete heart block. This was treated with urgent admission and replacement of his pacemaker (white arrow).

Malingering – A mild head trauma is exaggerated in the hope of compensation. The mainstay of diagnosis is consistency. Computerised dynamic posturography may show typical changes.

Obstructive Sleep Apnoea – OSA causes dizziness because of hypoxic damage to the central vestibular systems or fatigue. Lack of continuous sleep can cause lightheadedness^{8,9}.

Sinusitis – A ‘heavy’ head is a common complaint of people suffering with sinusitis. The associated nasal blockage along with mouth breathing may cause a sensation of dizziness.

Mass lesions – The most common mass lesion causing vertigo is a Cerebello-Pontine Angle (CPA) lesion. The commonest CPA lesion is a vestibular schwannoma. As it is a slow growing tumour, vestibular hypo-function and central compensation happen simultaneously. Acute vertigo can happen if there is a sudden expansion like a

haemorrhage into the tumour. Thus disequilibrium rather than true vertigo is the norm, although it is not inevitable. Other tumours large enough to cause dizziness will usually show central signs. Malignant brain tumours are rare in a balance clinic.

Endocrine/ Systemic

Anaemia, diabetes mellitus, hypo- and hyper-thyroidism and pituitary disorders are all known to cause dizziness. Addison’s Disease results in adrenal insufficiency causing postural hypotension.

Multi-sensory – In the elderly multiple pathologies may co-exist.

- Deafferentation in the elderly
- Vision e.g. macular degeneration
- Proprioceptive
- Musculoskeletal / joint replacements
- Peripheral neuropathy
- Vestibular hypofunction
- Depression, anxiety and isolation

A broad medical knowledge is helpful in seeking early diagnosis and appropriate referral, reducing time for diagnosis and treatment.

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Middle ear implant: classic and extended indications

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Abstract

Hearing implant technology is evolving at a rapid rate and more than ever patients with hearing loss are benefiting from these emerging hearing devices. Middle ear implants are alternatives to hearing aids and bone conducting aids, offering patients an expanded range in improving their hearing. This article discusses one such middle ear implant, the Vibrant Soundbridge (Med-El, Austria). Indications for its 'classical' and extended uses are discussed.

Keywords

Middle ear implant; hearing loss; aural atresia; Vibrant Soundbridge

Acknowledgement:

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J ENT Masterclass 2014; 7 (1): 50 -53.

Introduction:

The past decade has seen significant advancement in hearing implant technology. Patients with hearing loss now have a wider range of treatment options to rehabilitate their hearing. Those who have previously been unable to benefit from conventional hearing aids now have the possibility of having a hearing implant.

A middle ear implant (MEI) is a surgically implanted hearing device that is directly coupled to the ossicles or the inner ear. Sound is converted to electrical energy and then transduced to mechanical energy to vibrate the ossicles or directly drive the cochlea via the round or oval windows¹. An advantage of the middle ear implant is that it bypasses the external auditory canal and potentially eliminates the occlusion effect and feedback associated with conventional hearing aids. These implants are suitable for patients with a stable sensorineural hearing loss or a mixed hearing loss

who are unable to benefit from conventional hearing aids. Patient groups include those with chronic stenosing otitis externa, external ear malformation and chronic dermatitis². Patients with a potentially suitable hearing loss are assessed by a multidisciplinary team to determine their candidacy and the potential benefits from hearing implants.

There are two classes of middle ear implant, piezoelectric and electromagnetic. Both types of device transduce sound energy into mechanical energy by directly vibrating the middle ear structures¹. The most commonly studied and implanted device in the United Kingdom is the electromagnetic Vibrant Sound-Bridge (VSB) device (MED-EL, Austria) and will be the focus of this article. The device consists of two parts, an external speech processor and an implanted receiver stimulator connecting to a vibrating ossicular prosthesis (VORP) also known as a floating mass transducer (FMT). Figure 1. The FMT is

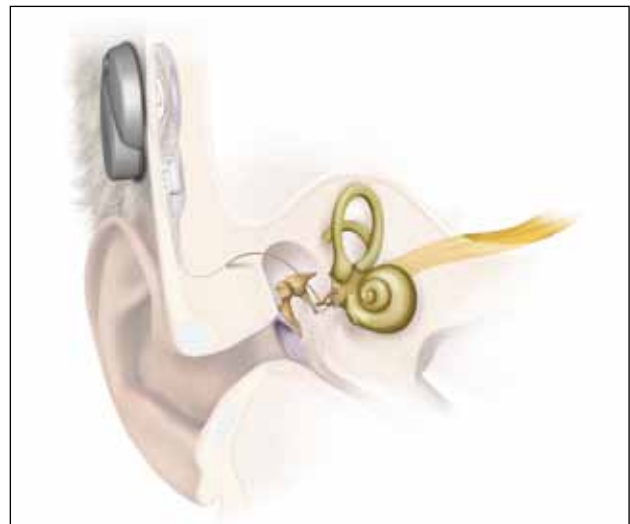


Figure 1: Vibrant Soundbridge active middle ear implant, showing external processor and implantable vibrating ossicular prosthesis.



Figure 2: Magnified view of the floating mass transducer (FMT).

an electromagnetic transducer, which augments the natural movement of the ossicles (by attachment to the incus or stapes), or directly stimulates the inner ear via the round or oval windows². Figure 2.

This provides a direct drive for the sound waves compared to the indirect drive of a hearing aid. This has the following advantages over the conventional hearing aid.

- Eliminates occlusion effect
- Better sound quality with reduction of feedback
- Improved sound fidelity of high frequency

Indications

There are typically two patient groups who can benefit from middle ear implant. The first group is those with a sensorineural hearing loss that meet the following criteria⁵. Figure 3.

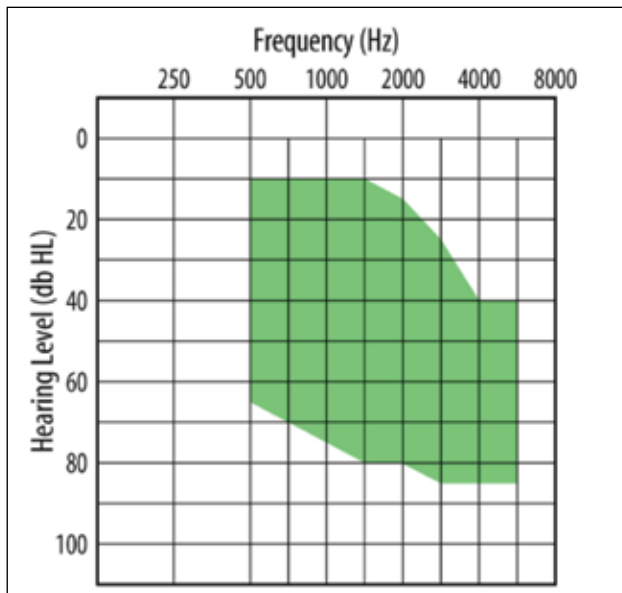


Figure 3: Audiogram showing candidacy criteria for sensorineural hearing loss.

- Air-bone gap less than 10dB
- Stable, non-progressive hearing loss
- Speech understanding score of 50% or better on recorded monosyllabic word test at 65 SPL in free-field using hearing aids.
- Normal middle ear anatomy and function, including acoustic reflexes.
- Absence of retrocochlear pathology.

The second group is those with conductive or mixed hearing loss that meet the following criteria⁵. Figure 4.

- A healthy middle ear space (no active infection or chronic effusion).
- Stable bone conduction thresholds.
- Middle ear anatomy that permits the position of the FMT in contact with middle ear structure.
- Absence of retrocochlear pathology or central auditory disorders.
- Absence of skin conditions that may prevent the attachment of the external processor to the scalp.

The indications for middle ear implantation have expanded over time with surgical innovation and the development of new transducer coupling techniques. This has been driven by an increase in the clinician and patient hearing outcome expectations following temporal bone surgery. Previously hearing rehabilitation options in patients undergoing complex temporal bone surgery for eradication of middle

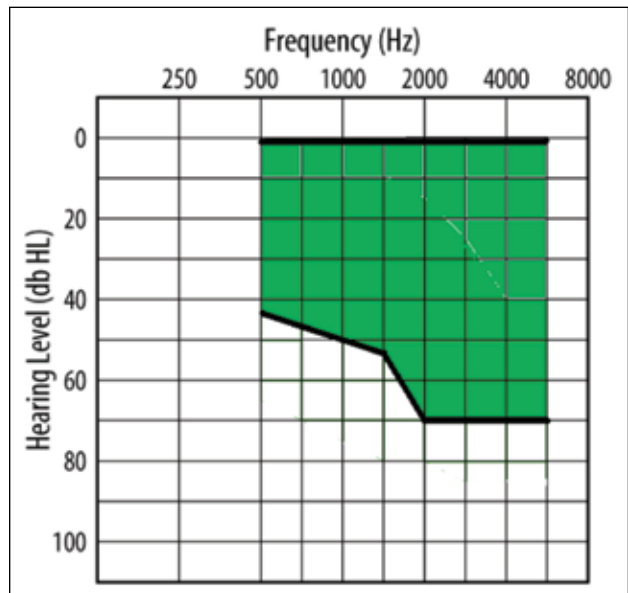


Figure 4: Audiogram showing candidacy criteria for conductive and mixed hearing loss.

ear diseases such as chronic otitis media (with or without cholesteatoma), was limited to conventional hearing aids, passive prostheses such as partial or total ossicular chain replacements or bone conducting hearing aids⁶. However, recent studies have validated the use of middle ear implant for hearing rehabilitation in patients who have had subtotal petrosectomy or open cavity mastoid surgery. Most patients achieved a good functional hearing outcome at 6 months. The long-term outcome is subject to further investigation⁷.

Patients with congenital aural atresia are another group where the VSB may be of a benefit. Reconstruction of an atretic ear often require multiple procedures and the hearing outcome is variable due to pre-existing anatomical factors such as lack of middle ear cleft, missing stapes superstructure, and surgical factors such as multiple tympanoplasties due to reconstruction failure⁸. Whilst BAHA is indicated in a number of these patients but middle ear implant has advantages over it of offering an intact skin solution, acceptable aesthetic and sound localization^{9,10}. The data suggest an improvement in word recognition score from 15% in unaided condition to 94% in aided condition for those patients with congenital aural atresia with middle ear implants. Furthermore, there is an argument that bilateral middle ear implants should be offered to those patients with bilateral aural atresia for better sound localization and understanding of speech in noise⁴.

The surgical approach for placement of the VORP is similar to that required for cochlear implantation; typically via a cortical mastoidectomy and posterior tympanotomy. For the classic application, the device is attached to the long process of the incus; this requires a wide posterior tympanotomy with skeletonisation of the facial nerve and chorda tympani. This facilitates a view of the entire length of the long process of the incus and provides enough access for the instrumentation required to attach the FMT clip to the incus³. If the incus is absent or abnormal, the FMT can be attached to the stapes superstructure. For round window placement a wide tympanotomy is also required but additional bone removal in the hypotympanum anterior to the facial nerve is required to allow space for the FMT to be placed perpendicular to the round window. There are a variety of techniques and couplers used to connect or couple the FMT to round window, stapes or footplate⁴. The device receiver stimulator is then secured in a bony well under the scalp.

Conclusion:

The VSB middle ear implant is an excellent alternative for hearing rehabilitation in those individuals who do not

receive adequate benefit from conventional hearing aids. Its application and indications continue to broaden. The long-term efficacy is still under investigation but most preliminary studies suggest good functional and audiological outcomes.

The classical and most common indication for a VSB middle ear implant is in those patients with a sensorineural hearing loss. However, the use of the VSB has expanded with surgical innovation to include those with a conductive or mixed hearing loss. Patients with a history of previous middle ear disease who were previously perceived as being unsuitable for a VSB middle implant, are now able to be considered for this intervention.

Advances in hearing rehabilitation means that there is a greater responsibility placed upon the otologist to consider hearing rehabilitation as an integral aspect of the management of ear disease and hearing loss. The imperative is to provide a hearing solution such that an ear not only 'hears to the best of it's ability' but that also maximizes sound quality, directionality and signal to noise ratio.

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Cochlear implants

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Abstract

The cochlear implant (CI) is the first true bionic organ and arguably the greatest success story of twentieth century otology. Since their initial conception, the refinement of technology, surgical technique and rehabilitation have led to widened indications and greatly improved outcomes.

Patients who require a CI should be managed in a setting where a multi-disciplinary team (MDT) is available for assessment, treatment and follow up. Pre-lingual deafness, variations in cochlear anatomy, extremes of age, and residual hearing all provide different challenges to the clinician. This article provides an up-to-date overview of cochlear implants and current controversies in management.

Keywords

Cochlear implant, hearing loss, CI.

The authors declare no conflicts of interest

J ENT Masterclass 2014; 7 (1): 54 - 58.

Introduction

Unlike hearing aids which amplify the normal transmission of sound, CIs use an electrical signal to directly stimulate spiral ganglion cells. As a result they are unique in their ability to aid hearing. Attempts at directly stimulating the cochlear nerve were first carried out by Djourno and Eyries in 1957¹. Three years later, Von Bekesy described the tonotopic organisation of the cochlea². Based on these principles CIs produce electrical signals that stimulate frequency specific spiral ganglion cells allowing some sensation of auditory perception. As few as 10% of the spiral ganglion cells need to be functioning to allow successful cochlear implantation³.

Currently, CIs all have an external microphone to receive sound. The microphone relays information to the speech

processor which converts the signal from analogue to digital. This information is then relayed via an external induction coil transmitter to the internal components consisting of a hermetically sealed electronics package, a telemetry coil and a magnet. An electrode array exits the electronics package and is placed in the cochlea (Figure 1).

Current controversies revolve around unilateral vs. bilateral vs. sequential implantation, and when to implant in extremes of age. Some centers are now implanting hybrid or electrode acoustic stimulation (EAS) implants and patient selection for this also needs careful consideration.

History

Early work in cochlear implantation was carried out simultaneously in Australia, Austria, and America. As a result there are now three main companies; CochlearTM, MedElTM, and OtologicsTM based in the three countries respectively. Early models of CIs included body worn aids and large parts, which were cumbersome and unsightly. Equally, the early electrode arrays were simple with only two electrodes, allowing perception of sound but not speech. Current models are of a high specification with their names and number of channels outlined in Table 1. All are now MRI safe up to 1.5 Tesla.

CIs are licensed for patients with severe to profound hearing loss. There are approximately 800,000 people in

Table 1: The number of channels in different Cochlear implants.

	Advanced Bionics	Cochlear	MedEl
Product name	HiRes90k	Nucleus	Concerto Flex
Number of channels	16	22	12



Figure 1: Components of a cochlear implant. Image reproduced with the kind permission of Cochlear Ltd.

the UK alone classified as severe to profoundly deaf^f. The British Cochlear Implant Group released figures last year showing a steady rise in the numbers of CIs with 1361 patients being implanted between 2011 and 2012⁵. According to the Food and Drug Administration (FDA), up until December 2012, approximately 324,000 people world-wide had received CIs. A NICE appraisal document, 2008, estimated the cost effectiveness of single-sided CIs in post-lingually deaf adults at £14,200 per incremental QALY gained. For pre-lingually deaf children implanted at 1 year of age this figure fell to £13,400⁶.

The ultimate goal of hearing rehabilitation is to be able to understand open-set speech in everyday environments. Predicting individual outcomes from Cochlear implantation is difficult due to the heterogeneity of implant candidates. It is now widely accepted that in pre-lingual children, earlier implantation results in better outcomes. Implanting pre-lingually deaf children before the age of two will result in almost normal language development⁷. A number of factors influence outcomes, however, including aetiology of the hearing loss, the level of residual hearing, the mode of communication, rehabilitation (speech therapy, education), and device type⁸. Over the next few years, further advances in technology will result in the likely distinct possibility of achieving the ultimate goal of a fully implantable device.

Indications

The guidelines for implantation in the UK have broadened over the years. People in extremes of age, with auditory neuropathy spectrum disorder (ANSD) and those with residual low-frequency hearing are now accepted as suitable candidates in some centers.

The National Institute of Clinical Excellence (NICE) issued guidelines in 2009 which form the basis for practice in the UK (Table 2). The exact audiological criteria are discussed later.

Patient assessment

CI centers in the UK are reliant on effective multi-disciplinary teams. Possible CI candidates will be assessed by a team as discussed below, and patients receiving an implant will require long-term input from many professionals to optimise their ongoing hearing needs.

Audiological

Audiological assessment is a key component of patient selection. The current UK guidelines produced by the British Cochlear Implant Group have been incorporated into the NICE guidelines. Specifically, people who do not hear sounds at 90dB at 2 and 4 kHz without hearing aids in either ear are deemed eligible for

Table 2: NICE guidelines for cochlear implantation.

Implantation Process	Recommendation
1. Unilateral implantation	Recommended for people with severe to profound hearing loss not receiving adequate benefit from hearing aids (3 month trial)
2. Simultaneous implantation	Recommended for all children meeting criteria in 1. Recommended for adults meeting criteria in 1 who are blind or disabled leading to greater dependence on auditory stimuli.
3. Sequential implantation	Not recommended unless unilaterally implanted already and meet criteria in 1 & 2 for simultaneous implantation.

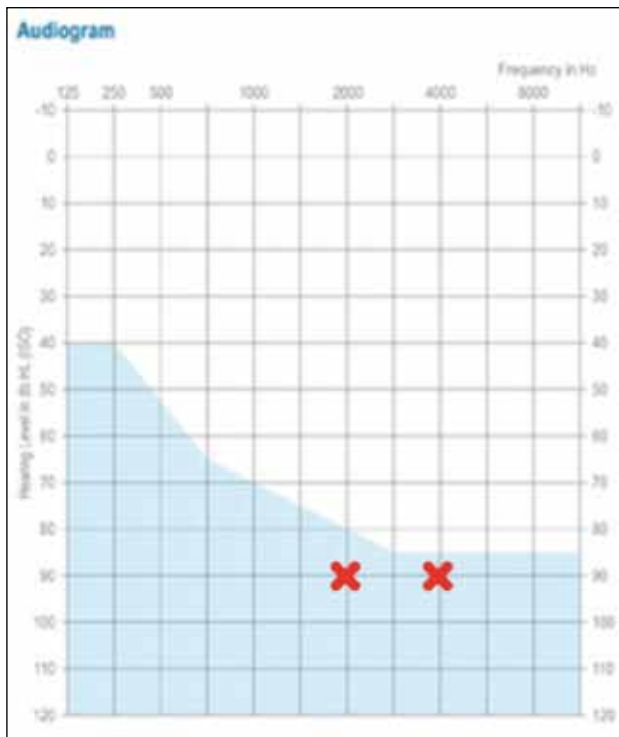


Figure 2: An audiogram showing the level of hearing loss set as the audiometric criteria for cochlear implantation. Image reproduced with the kind permission of the Ear Science Institute of Australia.

implantation if they do not receive adequate benefit from acoustic hearing aids (Figure 2). This benefit is assessed by testing the patient's ability to perceive speech. For adults, Bamford-Kowal-Bench (BKB) sentences are used. Adults who perceive 50% or fewer words presented at 70dB SPL in a quiet environment are considered to be gaining inadequate benefit and are audio logically suitable for a CI. For children there is no single set of tests, and a battery of assessments looking at the child's development and maintenance of speech, language, communication and listening skills are used.

After switching the device on (usually four weeks post operatively), audiologists will see patients regularly to optimise the programming for the patients' needs.

Otological

Ideally the ear to be implanted would have a healthy middle ear and mastoid. An ear with active chronic suppurative otitis media, for example, would need appropriate treatment either simultaneously with implantation, or sequential implantation if eradication of disease or infection is not compatible with implantation at the same sitting.

Medical

As with all middle ear surgery, a thorough medical history should be taken so that any co-morbidities can be taken into account when considering surgery.

Expectations

A key aspect in assessment, and indeed, successful implantation is appropriate patient expectations. Full and detailed discussions regarding the initial results after switch on and the progressive improvements in speech perception are explained. It is explicitly stated that their hearing will not be normal, as many patients think this is the case!

Radiological

The cochlea should be imaged with CT, MRI or both to exclude cochlear malformations e.g. a Mondini malformation. This provides further information when discussing the potential outcomes and allows appropriate planning for surgery and the type of implant array.

Surgical technique

The most commonly performed surgical technique for CIs involves a post-auricular incision followed by a mastoidectomy with posterior tympanotomy approach (MPTA). This incision preserves the blood supply to the skin, and gives excellent access without flap compromise⁹. Unfortunately, with this technique there is still a low risk associated with damaging the facial nerve and chorda tympani. In addition, there is a minority of patients for whom the MPTA is not possible due to access. As a result a variety of other techniques have been trialed including non-mastoidectomy techniques such as the suprameatal approach and endaural approach. Incisions are decreasing in size, with some surgeons using minimal access techniques. Variation also exists with where best to insert the electrode into the inner ear. The cochleostomy has become the standard approach but involves drilling a hole through the promontory antero-inferior to the round window using a 1-1.5mm drill. An alternative is the round window approach which avoids the associated risk of acoustic trauma from drilling through the promontory (equivalent to 130dB).

Programming

At the end of the surgical procedure CIs are tested using electrically evoked compound action potentials (ECAP) from the auditory nerve and impedance testing. ECAP is essentially the electrical version of wave I of the auditory brainstem response (ABR). Because there is artefact generated by the stimulus, each manufacture has developed its own software to reduce this. All three companies use telemetry as part of this software. ECAP readings allow

objective verification of the implant and auditory nerve function. For those patients who are unable to provide reliable behavioural responses once the implanted is switched on, ECAP also allows programming of the speech processor. Impedance testing assesses whether the array is in fluid (intra cochlea) or in air (extra-cochlea).

Special considerations

Types of cochlea – dysplasia/ ossificans/aplasia

Variation in cochlea anatomy has obvious implications when considering electrode array type and placement. Cochlear ossification is a problem primarily seen post meningitis (meningogenic ossification), however tympanogenic and haematogenic cases are also seen. All result in entry into the basal cochlear first, and most commonly affect the scala tympani¹⁰. MRI imaging demonstrates attenuation of the intra-cochlear fluid signal on T2 weighted images. Approximately 20% of all children with sensorineural hearing loss will have abnormalities detected on imaging of the temporal bone¹¹. All types other than a Michel deformity (complete inner ear aplasia) can be implanted, and surgical technique is determined by the type of dysplasia. For the majority, the MPTA is preferable, however the common cavity is best approached by a trans-mastoid labyrinthotomy.

Which ear to implant?

While ultimately the choice of ear to implant rests with the patient, it is accepted that the ear with better speech recognition leads to the best audio metric result in that ear. This fact needs to be taken in consideration with the evidence that patients do best with bimodal hearing, CI in one ear, HA in the other. This can leave the CI team and patient with difficult decisions as to which ear to implant. Typically, if there is marked asymmetry between the ears, patients opt for their worse ear and continue using a hearing aid in their better ear. If both ears are equally impaired it is generally the ear with the shorter duration of deafness which is implanted.

Bilateral vs unilateral vs bimodal

Although single-sided implants have been very successful for many years, many centres will now aim for simultaneous bilateral cochlear implantation. Bilateral cochlear implantation has benefits in many areas including reducing the head shadow effect, better speech recognition scores in background noise, and better sound localisation¹².

CIs in old age

The upper age limit for patients considered for cochlear implantation is now rising. In 2004 the UK Cochlear Implant Study Group (UKCISG) established that cochlear

implantation is effective in patients over 70 years¹³. Studies supporting this suggest no difference in hearing outcomes between older and younger patients, and that quality of life is significantly improved in older patients¹⁴. It is now commonplace for patients in their 80's and 90's to receive CIs.

Electro acoustic stimulation (EAS) implants

Many people have severe-to-profound hearing loss in the high frequencies, but some preservation of low-frequency hearing (Figure 3). Due to this preservation, they often will not meet the criteria for implantation. High frequency hearing loss is associated with poor speech discrimination due to the inability to discriminate between consonants. Hodges showed that some patients with CIs had preserved residual hearing post implantation¹⁵. As a result, many patients are now being implanted utilising Lenhardt's concepts of soft surgery (cochleostomy with slow turning burr, preservation of underlying endosteal membrane - subsequently opening with a needle, and slow insertion of the electrode array)¹⁶. This attempts to preserve residual hearing allowing stimulation of high frequencies electrically and acoustic amplification of the preserved residual hearing in the low frequencies.

Pre-lingual deafness

Implantation of pre-lingually deafened adults with CIs is increasing in frequency. The goal in these patients is to provide an aid to lip reading and appreciation of environmental sounds. It should only be considered in patients who are active hearing aid (HA) users, to ensure there has been ongoing stimulation of their auditory cortex. Outcomes are assessed in changes in quality of life.



Figure 3: An audiogram highlighting the audiometric criteria associated with EAS implant candidates. Image reproduced with the kind permission of MedEl.

Outcomes and quality of life

Complications of cochlear implantation are rare. In a study of 505 implants, Hansen et al¹⁷ found the major complication rate to be 1.8%. Vertigo is the most common complaint, and cholesteatoma and electrode migration the most common major complications.

What the future holds!

There are currently many exciting areas being targeted in CI research. The ultimate aim would be a CI that allows hearing identical to the normal hearing population. Additional benefits would include a fully implantable device with no external components that lasts the life-time of the patient. It should be simple to implant and have minimal risks associated with surgery. Although this goal may be elusive, the evolution of CI technology is rapidly progressing. New software will continue to improve speech processing in challenging environments. The ability to appreciate music more is already being investigated – with developments focusing on improving the perception of pitch and timbre of music. New techniques including implantable microphones and wireless battery charging are also currently being tested.

Conclusions

CI technology has progressed rapidly over the last twenty years. Perhaps due to their success, implant centers are relaxing their criteria for patient selection whilst maintaining excellent results. Despite this, however, only 1.25% of potential UK candidates by 2012 had received an implant and world-wide this fraction is likely to be significantly lower. Healthcare professionals have an important role in identifying and referring appropriate patients to implant centers for further assessment.

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Assessment for rhinoplasty

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Abstract

Rhinoplasty is a technically challenging surgical procedure carried out on one of the most prominent parts of the face. The achievement of consistent successful surgical outcome is based on accurate planning which requires a detailed assessment of patient expectations and clinical examination. The surgeon performing rhinoplasty must take into consideration both aesthetic and functional factors.

Keywords

Facial, nasal, examination, assessment, rhinoplasty.

J ENT Masterclass 2014; 7 (1): 59 -64.

Introduction

A systematic approach to the assessment of patients for rhinoplasty/septorhinoplasty facilitates appropriate patient selection and surgical planning. This paper aims to provide a comprehensive yet practical method for rhinoplasty assessment that can be incorporated into clinical practice. Successful surgical outcomes require realistic patient expectation, careful consideration of facial aesthetics and a detailed examination of the nose.

Analysis of the patient

Obtaining a clear history of the patient's complaint and their specific request is critical, however it is just as important to clearly communicate to patients the underlying anatomical variations that is causing their problem with a discussion of what results surgery can achieve. This permits an assessment of whether a patient's expectations are realistic or not. A preoperative psychological assessment may be required before further surgical planning is undertaken in those patients in whom body dysmorphic disorder (BDD) is suspected^{1,2}. BDD describes a subjective feeling of ugliness or physical defect which the patient feels is noticeable to others, although the appearance is within normal limits¹. Patients with this condition are unlikely to be satisfied with surgical results.

The rhinoplasty improvement scale is a useful descriptive method of explaining a realistic magnitude of post-operative improvement (Fig 1). Patients should be cautioned that an improvement from one point on the scale to an adjacent point is accepted as realistic, anything more than that would be unlikely. Establishing preoperative expectations is important as poor results are often based on emotional dissatisfaction rather than technical failure³.

Surgeons undertaking rhinoplasty procedures must be vigilant of unsuitable personality attributes in this patient population. Many of these attributes have been described. Examples such as BDD, unreasonably demanding, insisting on secrecy, surgiholic, obsessive, perfectionist, impolite and flattering patients are commonly referred to in the literature. The simplified acronyms SIMON (single, immature, male, overly expectant/obsessive, narcissistic)

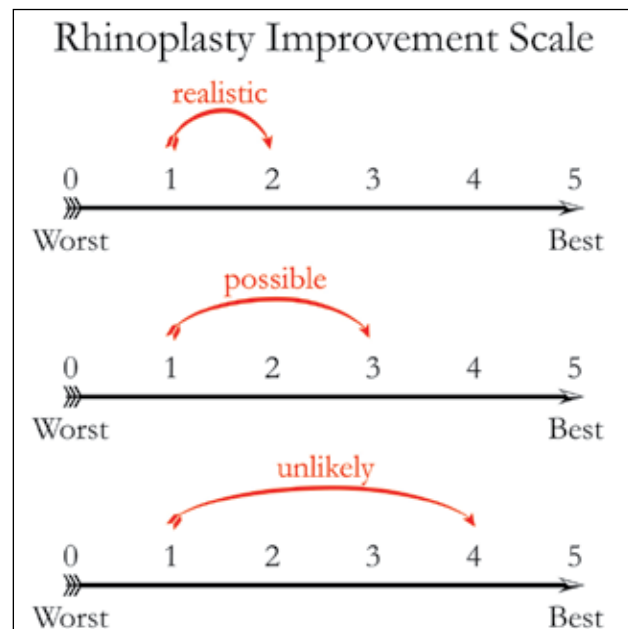


Figure 1: Rhinoplasty improvement scale used by the senior author.

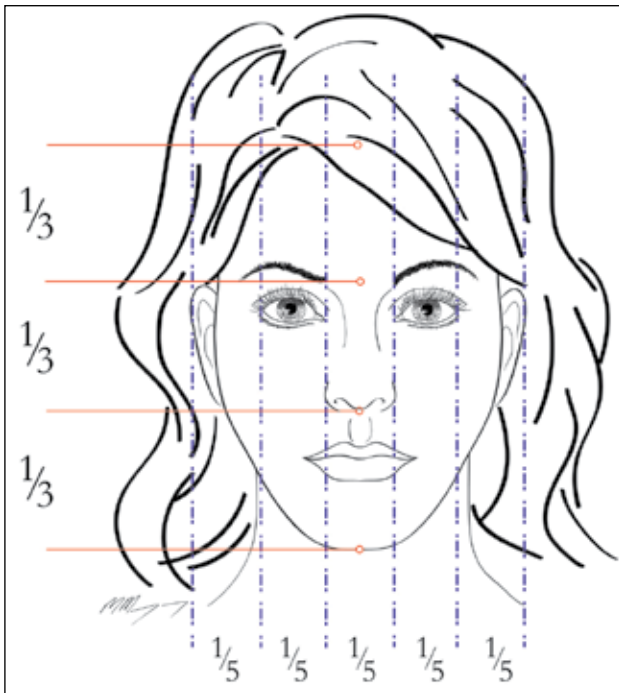


Figure 2: The concept of dividing the symmetric face into thirds and fifths.

and SYLVIA (secure, young, listens, verbal, intelligent, attractive) describe the characteristics of the high risk and the ideal patient respectively^{4,6}.

Analysis of the face

Facial assessment commences as a patient enters the consultation room and is formally assessed prior to a detailed assessment of the nose. Attractive faces are deemed to have ideal measurements and angles, which are reportedly based on the dimensions first described by Leonardo da Vinci^{7,8}.

Facial symmetry is reported to be the basis for a beautiful face, although minor asymmetry may be associated with the perception of beauty⁹. Facial asymmetry may have a significant impact on the perception of post-operative results and therefore it must be assessed pre-operatively, communicated with the patient and documented. Symmetry is assessed using midline facial landmarks; a line running through the mid-philtrum of the upper lip, the midpoint of the glabella and the midpoint of the chin indicates a symmetrical face. Asymmetry of the nose has been reported to be a significant contributing factor in the perception of overall facial asymmetry, therefore rhinoplasty performed to correct asymmetry of the nose may well improve the overall perception of facial symmetry in the absence of any other surgical procedures^{10,11}.

Analysis of facial proportions is performed using the ‘rule of thirds’ and the ‘rule of fifths’ to assess the face from a frontal view (figure 2)⁸. Horizontal facial thirds should be approximately equal, the landmarks defining each third are the trichion to glabella, glabella to subnasale and the subnasale to soft tissue menton. The rule of fifths describes the ideal transverse proportions of the face vertically divided into equal fifths, each fifth is approximately equal to the width of one eye; the alar base is equal to the intercanthal distance. The nose ideally occupies one-third of the length of the face and one-fifth of its width.

Powell and Humphrey expanded this approach to include the angles of the aesthetic triangle¹². The accepted dimensions of each of the ideal facial angles are: nasofrontal angle 115-135°; nasofacial angle 30-40°; nasomental angle 120-132° and the mento-cervical angles 80-95° (Figure 3). Specific terminology is used to describe the constant landmarks of facial anatomy; these are listed in Table 1.

Table 1 Terminology of facial landmarks	
Landmark	Definition
Trichion	Anterior hairline in the midline
Glabella	Most prominent point of forehead in mid-sagittal plane
Nasion	Deepest point of frontonasal angle
Rhinion	Midline point of junction of nasal bones and upper lateral cartilages
Pogonion	Deepest point on outer cortex of mandible
Gnathion	Most inferior point of the chin
Gonion	Most inferior/posterior point of mandible
Menton	Lowest point of mandibular symphysis
Subnasale	Junction of columella and upper lip in mid-sagittal plane

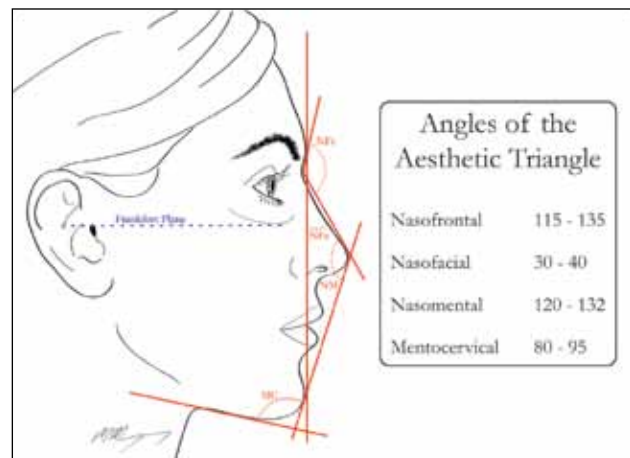


Figure 3: Triangles of Powell and Humphrey.

Analysis of the nose

Inspection of the external nose

Detailed inspection of the external aspects of the nose provides information about the individual nose as well as a comparison to accepted ideal measurements.

- **Skin Quality:** this is variable and an assessment of whether the skin is thick and sebaceous or thin is required. This provides a measure of how forgiving the skin will be to the presence of minor irregularities and the effects of post-operative swelling and bruising. Thick skin can increase the difficulty of refining and narrowing the nasal tip.
- **Deviations:** the nose is divided into upper, middle and lower thirds. The upper third corresponds to the bony vault, the middle third to the upper lateral cartilages and dorsal septum and the lower third to the lower lateral cartilages, caudal septum and alar base. Deviated noses are described on the basis of direction of the deviation of each third. For example classically described C-shaped, one-sided or S-shaped deviations are described starting from the upper third as right/right/left, left/left/left and left/right/left respectively (Figure 4). This provides an anatomical assessment of the aetiology of nasal deviation, which is key to surgical planning.
- **Length of the Nose:** nasal length is measured from the nasion to the tip which is equal to the distance between the stomium and the menton. This can also be calculated mathematically as the distance from the nasal tip to the stomium multiplied by a constant of 1.6. Nasal Length, $NT = TS \times 1.6$ (Figure 5).
- **Tip Projection:** this is a measure of how far the nasal tip lies anterior to the face. Ideal projection is determined using Goode's ratio, where a line drawn from the alar-facial groove to the nasal tip measures 0.55-0.60 of the distance from the nasion to the nasal tip. A ratio less than this equates to an underprojected nose and greater than this corresponds to overprojection (Figures 3 and 6).

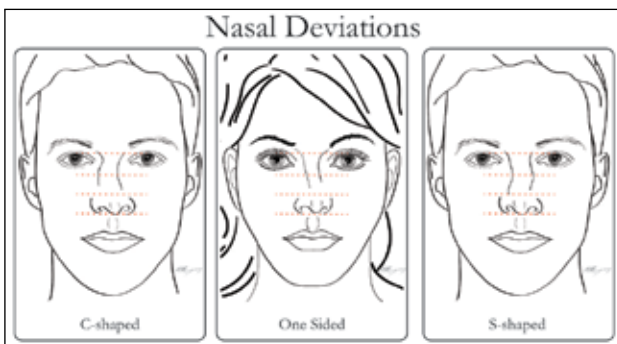


Figure 4: Classifying classic nasal deviations using thirds.

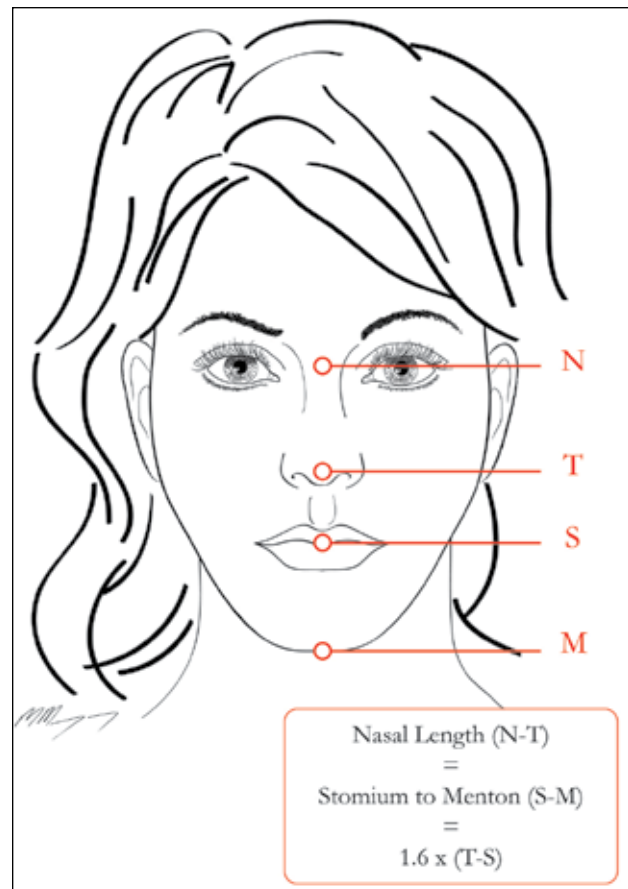


Figure 5: The assessment of nasal length.

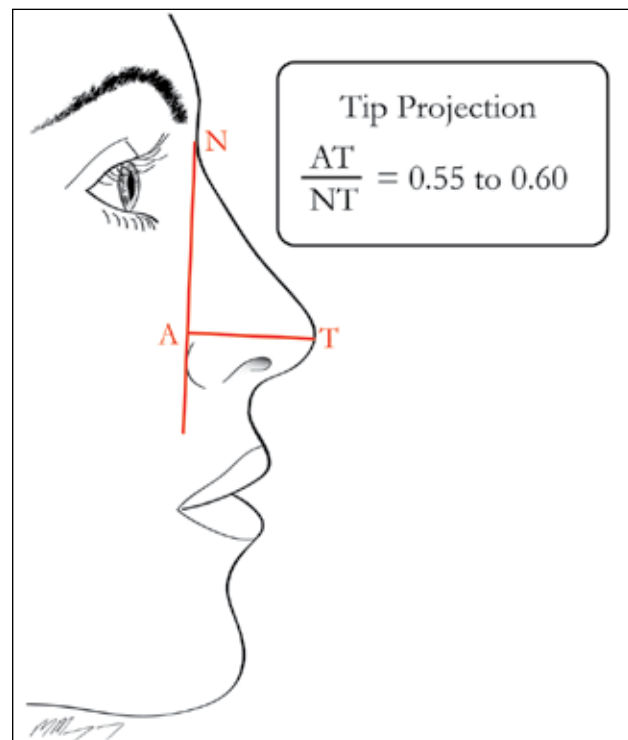


Figure 6: Determining tip projection by using Goode's ratio.

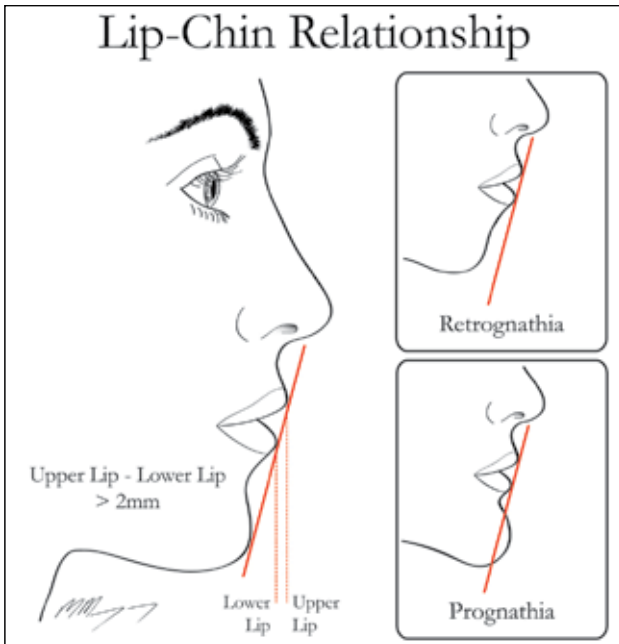


Figure 7: Lip-chin relationship.

- Lip-Chin relationship: the horizontal distance from the surface of the upper lip to that of lower lip is normally around 2mm. The anterior surface of the upper and lower lips rest on the nasomental line in an aesthetic face (Figure 7)¹³. When the chin lies posterior to this line, it is described as retrognathic, when it lies anterior to this line it is described as prognathic. A retrognathic chin can give the illusion of an overprojected nose and the reverse applies to a prognathic chin. Genioplasty or chin implant procedures are therefore often used in conjunction with rhinoplasty¹⁴.
- Dorsum: the dorsum is inspected from both frontal and lateral views. Tracing the lateral aesthetic lines (also known as the brow-tip line) should reveal a smooth

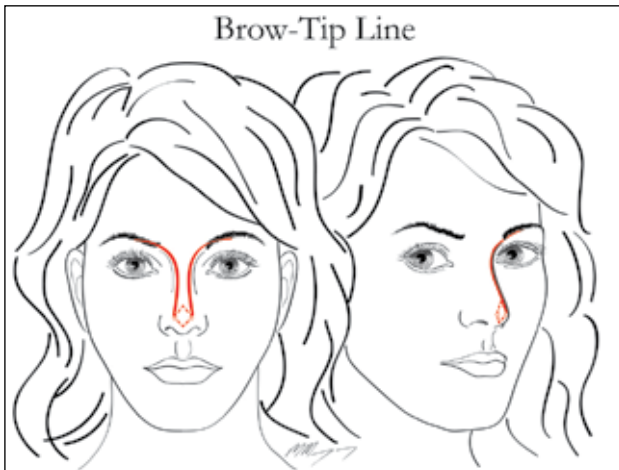


Figure 8: Front and right oblique views showing the brow-tip line – note the four tip defining points.

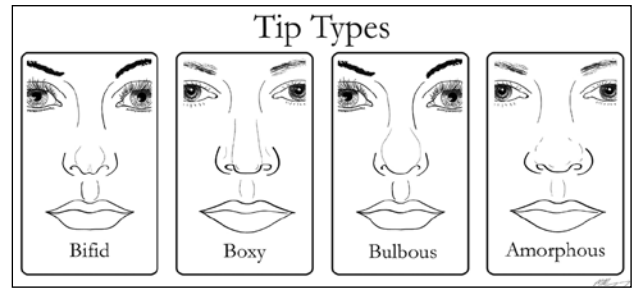


Figure 9: Common nasal tip morphology.

curvilinear line connecting the eyebrow superiorly to the nasal tip inferiorly. Identification of any irregularities in this smooth curve highlights sources of nasal deformity. In the lateral view, the height of the dorsum is assessed; the dorsum is a straight line in men and in women gently curves with a supratip break delineating the dorsum from the nasal (Figure 8). A wide array of variations of dorsum height exists and often characterises different ethnicities.

- Tip configuration: there are 4 tip-defining points identified by light reflection (Figure 8). These represent the domes, the supratip and infratip. The size and shape of the lower lateral cartilages are assessed, as well as assessing for asymmetry, bifidity and rotation. Various tip configurations are generally related to these characteristics and to the skin thickness. Figure 9 depicts a commonly encountered selection of tip appearances - normal, boxy, bifid, bulbous, amorphous.
- Tip rotation: describes the position of the tip along an arc with its radius centred on the nasolabial angle. The ideal dimension of the nasolabial angle in a man is 90-95° and in women is 95-105° (Figure 10)¹⁵.
- Columellar show: the relationship between the ala and the columella is assessed in the lateral view. The amount of visible caudal septum is ideally limited to

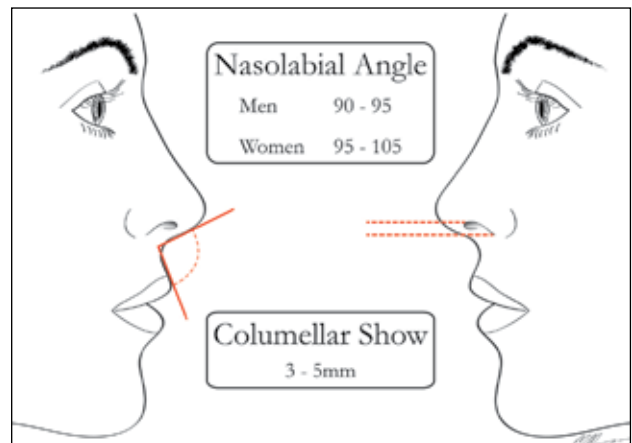


Figure 10: Left - nasolabial angle in men and women. Right - normal columellar show.

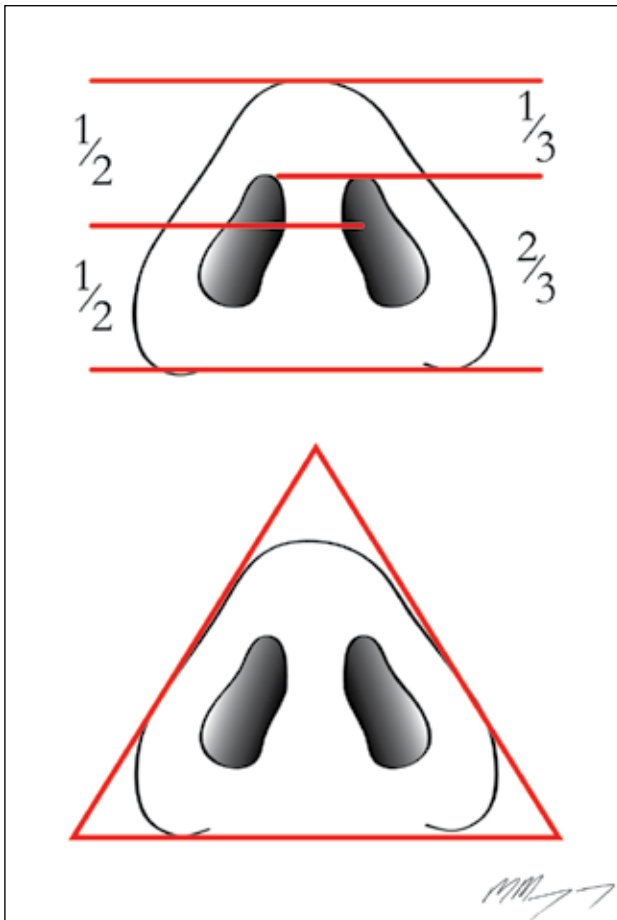


Figure 11: Basal view

3-5mm (Figure 10). This is the distance between two parallel lines drawn from the anterior most and the posterior most parts of the nasal vestibule. If the degree of columellar show is greater than this, then it may be due to either a hanging columella or alar retraction.

- Basal view: the width of the alar base approximates to the intercanthal distance. The ratio of the width of the dorsum of the nose relative to the alar base should be equal to 80% (Figure 2). From the basal view, the nose can also be divided into thirds. The upper third corresponds to the lobule and the lower two-thirds corresponds to the columella. A line that transects the columella at the area of medial crural footplate diversion divides the base into two halves (Figure 11). The overall basal view outline conforms to an isosceles triangle with pear-shaped nostrils lying at an angle of 45° to the vertical¹⁵. Multiple ethnic variations exist in alar base configuration.

Inspection of the internal nose

Examination of the internal nasal cavity is an essential component of assessment of rhinoplasty in identification

of abnormalities and in the assessment of donor cartilage sites.

- Septum: inspect for deviation, spurs, perforation, or the presence of a septal button.
- Lateral nasal wall and turbinates: inspect for congestion, hypertrophy and asymmetry.
- Internal nasal valve: this must be assessed during normal quiet respiration at rest, as exaggerated effortful breathing is likely to precipitate transient internal nasal valve collapse in the normal individual. Cottle's manoeuvre of opening the internal nasal valve by pulling on the soft tissues of the cheek is non-specific. A better test is to place a Jobson-Horne probe in the internal nasal valve to prevent the collapse of the upper lateral cartilage and detect its effect on inspiration.
- Alar collapse: must be identified pre-operatively, it is a measure of external nasal valve collapse. The external nasal valve is not a true valve and is identified by the area bounded by alar cartilages, septum and columella.

Palpation

- Skin: palpate for an assessment of skin texture and elasticity.
- Irregularities: palpate for underlying irregularities that may be due to skin, soft tissue, cartilage, bone or previous graft material.
- Nasal bones: assess the size, position and presence of palpable steps.
- Tip recoil: this is an assessment of the strength of the lower third of the nose and provides a palpable measure of the degree of underlying tip support¹⁷.
- Alar caridges: palpate for thickness, strength and shape.
- Spine and Septum: tip support, confirm presence and quantity of septal cartilage.

Photograph Review

Standardised photographs are essential for pre-operative planning. They are also useful during discussion of proposed surgery with the patient, as an intraoperative reference and essential for comparison with post-operative results. The reproducible patient position used in rhinoplasty photography is one where the Frankfurt plane is parallel to the floor; the Frankfurt plane is a line that runs from the cephalic tragus to lower orbital margin (Figure 3). Standard photographic views obtained are frontal, left and right lateral, left and right oblique and basal. Additional views which are of use are the close-up frontal view, superior view, base-radix view and the bird's eye view¹⁸⁻²⁰. Computer morphing of the patients

photographs has been found to be improve communication with the patient and is associated with higher patient satisfaction²¹. It is essential to clarify to the patient that image manipulation is only a means of communication and does not imply a specific guaranteed outcome.

Conclusion

Once the systematic clinical assessment and examination of the patient has taken place, the proposed surgery can be effectively planned with clear surgical steps. It is good practice to commit the surgical steps to a written plan (Table 2).

Table 2 Summary of rhinoplasty assessment		
Patient Analysis	What does the patient want? Is it realistic?	
Facial Analysis	Symmetry Rule of thirds Rule of fifths	
Nasal Analysis	Inspect: External	Skin Deviations Nasal length Tip projection Lip-Chin relationship Dorsum – Brow-tip line Dorsum - Lateral view Nasal tip configuration Tip rotation Columellar show Basal view
	Inspect: Internal	Septum Lateral nasal walls Internal nasal valve External nasal valve
	Palpate	Skin Irregularities Nasal bones Tip recoil Alar cartridges Spine Septum
Clinical photographs	Anterior Lateral: Left & Right Lateral Oblique: Left & Right Basal view	
Computer morphing		
Surgical plan		

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The relationship between the upper and lower airway - an ENT perspective

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Abstract

The association of upper and lower airway disease together has been recognised for centuries. Often the upper airway is the site of initial disease manifestation before any bronchopulmonary involvement or any systemic manifestation occurs. Early recognition and intervention can often prevent disease progression, severity and improve long term prognosis. ENT surgeons are in a unique position to not only be the first to rapidly intervene in relation to upper airway disease but integrate early on a multidisciplinary team (MDT) approach via involvement of other specialists and thus improve patient care and outcomes. This article outlines why upper and lower airway disease may occur together and why treating the upper airway may improve lower airway outcomes and quality of life in patients. We have chosen three broad upper airway conditions of rhinitis, chronic sinusitis and vasculitis to illustrate the one airway system.

Keywords

Airway Disease, Rhinitis, Vasculitis, One Airway Hypothesis.

J ENT Masterclass 2014; 7 (1): 65 - 69.

The One Airway Model

STRUCTURE

Whilst it is helpful to divide the airway into upper and lower airway components in terms of anatomical study modules and training focus, it must be remembered such an arbitrary division cannot apply to medical diseases that have an airway predisposition. The airway is a continuous structure that begins at the nasal vestibule and terminates

with the terminal bronchioles. Whilst regional anatomical and physiological differences exist, the airway mucosa is in fact a continuous structure lined by pseudostratified ciliated columnar epithelium and a rich vascular submucosa. The mucosal regulatory and protective mechanisms in the upper and lower airway are similar or identical.

FUNCTION

Over 10 000 litres of air is cleaned and warmed daily before delivery to the lungs. The upper airway is thus highly adapted in its role of protecting the lower airway from environmental insults, irritants, microbes and allergens via effective mucociliary clearance and arms of a highly efficient innate and adaptive immune system. Although the mechanisms by which the upper and lower airways coexist and possibly interact with disease processes are not completely understood, it is possible to speculate from airway allergen challenge studies in allergic rhinitis that the upper and lower airway immune system is integrated and there is bidirectional disease activity with clinical manifestations that can occur together. Overlapping pathological findings probably reflect a manifestation of the same process but in relation to the different airway locations in individuals having a genetic predisposition to disease.

Rhinitis

Rhinitis is a broad term to cover any nasal inflammatory process that presents with a set of symptoms characterised by nasal obstruction or congestion, rhinorrhoea (anterior and/or posterior), sneezing and nasal itch. Rhinitis is further defined as allergic or non-allergic on the ability to demonstrate IgE sensitisation to an aeroallergen that is consistent with the patient's environmental exposure

history. Robust epidemiological studies confirm that both forms of rhinitis are associated with a markedly increased risk of developing allergic or non-allergic asthma with an odds ratio as high as three^{1,2}. Rhinitis is a strong predictor of future asthma risk.

Further detailed epidemiological studies confirm that rhinitis and asthma coexist such as the prevalence data on 463,801 teenagers from the landmark International Study of Asthma and Allergies in Childhood (ISAAC)³. The airway inflammation process in the nose and bronchus is identical in terms of immunopathology. Paired nasal and bronchial biopsies from individuals with allergic rhinitis and asthma demonstrated similar numbers and distribution of mast cells, eosinophils, neutrophils and CD3+ T cells, supporting a single immunological unit concept for the airway⁴.

Overall up to 80% of asthmatics report symptoms of allergic rhinitis⁵. The latter is the basis of the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines⁵. This document emphasises the importance of correct diagnosis of rhinitis as allergic or non-allergic along with classification of disease as mild, moderate or severe based on the patient's perception of effects on daily function such as sleep or time off work. Treatment is initiated based on severity defined according to this classification in ARIA. The recognition of asthma can often be made on the basis of a history of cough, variable shortness of breath with or without chest tightness or wheeze, which are attributed to increased airway hyper-responsiveness (AHR). Demonstration of airway function reversibility with a peak flow chart over time or improvement following inhalation of a B2 agonist in clinic is then undertaken, although asthma with fixed airway obstruction (presumed to be as a result of airway remodelling) is still recognised⁶. ENT clinics should ask about lower airway symptoms and document peak flow and spirometry with a low threshold for a respiratory opinion.

Untreated rhinitis is associated with poor asthma control and increased risk of exacerbation. In a UK general practice population with 3916 asthmatics, severe rhinitis was associated with an odd ratio (OR) of 4.62 for having poor asthma control, worse than not treating asthma with an OR of 1.35 and as bad as concurrently smoking (OR=4.33)⁷.

Studies as far back as 25 years demonstrate the efficacy of intranasal steroids on allergic rhinitis in improving asthma control and the most recent meta-analysis confirms such findings^{8,9}. Indeed it has been shown in a study setting that a dose of corticosteroid when given intranasally is more

effective in treating AHR than the same dose given to the lower airway via the orally inhaled route^{10,11}.

We now have insight into immunological mechanisms that may explain such clinical observations. For example allergen challenge in the nose of allergic rhinitis patients leads to rapid induction of allergic inflammation in the bronchial tree¹². The converse is also true with instillation of allergen into the bronchus stimulating allergic nasal inflammation¹³. Figure 1 illustrates how allergen instillation into the lower airway induces rapid recruitment and degranulation of eosinophils. Such studies confirm the airway as one immunological unit with ability to respond to activation anywhere along its route. Another outstanding finding was that local upper airway mucosal allergen challenge up-regulated markers of cell trafficking such as intercellular adhesion molecule 1(ICAM-1) in lower airway vessel walls. This confirms that nasal immune activation by allergen not only leads to a ripple of inflammation along the entire airway but also systemic immunological activation. Figure 2 summarises the potential ways the upper and lower airway may interact in disease.

Asthma exacerbations confer significant morbidity and many asthma deaths still occur. The most common cause of asthma exacerbation is rhinovirus infection that begins in the upper airway. Whether upper airway immune response can prime the lower airway as shown with allergen studies is unknown. When virus and allergen exposure occur together in an allergic airway, the risk of hospitalisation in children is 20 fold more than for normal individuals¹⁴.

In patients treated for allergic rhinitis there was a 50% reduction in asthma related events, including halving of asthma hospital emergency visits and admissions over a one year period compared to patients untreated for rhinitis¹⁵.

Asthma prevention remains a goal. Both decreasing allergen exposure and desensitisation in allergic rhinitis may decrease the incidence of future asthma in children^{16,17}. With the emerging availability of safe and easy to administer immunotherapy products, such airway disease modifying intervention has the potential to be delivered more broadly and so it is imperative that ENT surgeons appreciate that these patients can benefit from early intervention with immunotherapy and so refer on for further consideration to allergists¹⁸.

Chronic Rhinosinusitis

Chronic rhinosinusitis (CRS) is an umbrella term for a group of heterogeneous diseases featuring inflammation of the nose and sinuses. CRS is grossly subdivided into with and without nasal polyps¹⁹. This approach is too

simplistic as it does not allow any interpretation of aetiology or immunopathogenesis. Once a CRS subtype is defined then prediction of lower airway manifestations become more obvious since the disease mechanism that promotes rhinosinusitis often has a pan airway impact.

The first population based survey to definitely show the strong association of CRS with asthma in Europe, particularly in relation to late onset difficult to treat asthma phenotypes, was recently published²⁰. CRS with nasal polyps (CRSwNP) and asthma is strongly co-associated²¹. Lower airway dysfunction or AHR consistent with an underlying asthma phenotype is present in CRSwNP even when patients fail to declare clinical asthma symptoms²².

Such strong epidemiological studies suggest overlapping disease mechanisms and indeed emerging genetic and molecular studies support shared immunological and pathophysiological pathways²³. CRSwNP and associated asthma demonstrate in the broadest sense a common immune signature predominated by a so-called Th2 T-cell predominance and interleukin (IL)-5 driven eosinophil recruitment and IL-4 driven mucosal IgE synthesis. IL-13 promotes mucus synthesis and augments Th2 inflammation. Emerging therapies for asthma such as blocking IgE-driven allergic inflammation²⁴ and IL-5 airway eosinophil recruitment²⁵, preventing asthma exacerbation, show clinical impact in CRSwNP. Such findings are encouraging as they not only support the one airway hypothesis, but also give hope that one treatment will achieve airway control not just asthma control. It is therefore essential that ENT colleagues in training adapt to the idea of an MDT approach to upper airway disease.

Bronchiectasis is an anatomical term to describe abnormal dilation of the bronchial lumen due to destruction of the airway wall, often by inflammation. The clinical manifestations are characterised by excess mucus that is often coloured due to inflammation or chronic infection and recurrent lower respiratory tract symptoms. The most common bronchiectasis subtype is idiopathic followed by localised (often post infectious) damage to the airway. Idiopathic bronchiectasis is often bilateral²⁶. Immune dysregulation leading to exaggerated prolonged mucosal inflammatory responses, leading to airway damage, is probably relevant to disease pathogenesis and exacerbation²⁷. An early study in a Japanese population reported 5 % prevalence of bronchiectasis in patients with idiopathic chronic sinusitis²⁸. However, in individuals that already had idiopathic bronchiectasis then the prevalence of CRS was as high as 45%. This suggests that idiopathic CRS precedes bronchiectasis. A more recent retrospective

review reported almost universal presence of CRS in patients presenting with established idiopathic bronchiectasis to a tertiary centre²⁶. In contrast, in post infectious bronchiectasis, often due to a more localised anatomical airway damage and not a result of pan airway injury from inflammation or infection, the incidence of coexistent CRS was 50%.

CRS prevalence is more or less 100% in patients with bronchiectasis where the host mucosal defect is intrinsic to airway function such as primary ciliary dyskinesia (PCD), cystic fibrosis (CF) and immune compromised states that includes primary immunodeficiency, the most common being common variable immunodeficiency and often forgotten secondary states including HIV²⁹.

Upper airway mucociliary clearance is critical for sinonasal health as stated in the most dramatic manner in PCD and CF, where sinus disease is almost ubiquitous from an early stage and often occurs before progressive and sometimes devastating bronchiectasis is established. With PCD, nasal congestion is present from birth leading to difficulty in feeding as nasal ventilation is severely affected³⁰. Dependent or pooled nasal mucus should alert clinicians of impaired ciliary function and undertake more focused investigation. As any inflammatory or infective process can lead to secondary ciliary impairment as in CF, treating any underlying infection and inflammation is needed before doing screening tests for intrinsic ciliary dysfunction. The saccharin clearance test is helpful, but demonstration of repeated absent or very low levels of upper airway nitric oxide levels should alert the clinician to the possibility of PCD and precipitate formal ciliary evaluation.

It is possible to hypothesise how the upper and lower airways interact in CRS and bronchiectasis. Given the filtering function of the nose, the upper airway is the often exposed to higher amounts of irritants, debris and infectious agents. Thus rhinosinusitis flare can often be the first site of disease exacerbation. Whilst healthy individuals will clear the sinonasal insult and rapidly reach inflammatory resolution, if an underlying mucosal vulnerability is present such as with PCD or CF or primary immune deficient states that promotes inflammation and infection, then persistence and progression of disease can occur. In the upper airway, sinonasal obstruction from oedema, accumulation of inflammatory and infective debris with viscous mucus will promote further infection, activate further potent innate and adaptive immune responses and exacerbate disease activity locally. As upper airway protective mechanisms fail, then lower airway vulnerability rapidly increases. Immune priming and bacterial overspill from upper airway exacerbation has the

potential then to promote lower airway disease priming and later exacerbation. Immune dysregulation leads to an excessive and prolonged response that can lead to a cycle of infection-inflammation-tissue damage that perpetuates itself and aptly termed the ‘vicious cycle’. This cycle can sustain local disease but through the mechanism discussed earlier promote lower airway disease. Such thinking is supported in CF. Studies show strong correlation between CRS severity with lung disease³¹. The demonstration of identical ‘molecular’ bacterial strain in upper and lower airway secretions in the same patient with CRS and bronchiectasis confirms the sinonasal passages can act as a reservoir for lower airway colonisation³². A time course study showing that upper airway colonisation appears first in CF and with time involvement of the lower airway occurs much later also supports the concept of bacterial upper airway involvement and migration to the lower airway³³. Why such a temporal delay between the upper and lower airway colonisation is present is unknown but allows the ENT community an opportunity to intervene at the sinonasal level at an early stage. Emerging consensus is that an early aggressive approach to maintaining sinonasal ventilation, removal of infection and inflammatory material overall may lead to improved upper airway homeostasis and function which in turn will lead to better lower airway outcomes. Unfortunately robust clinical studies are lacking in CRS²³ let alone studies evaluating the response of the upper and lower airway together in associated diseases. This is disappointing and highlights an urgent research priority area.

Vasculitis

Granulomatosis with polyangiitis (GPA), formerly known as Wegener’s granulomatosis, eosinophilic granulomatosis with polyangiitis (EGPA) or allergic granulomatosis (previously referred to as Churg-Strauss Syndrome) and microscopic polyangiitis (MPA) are all anti neutrophilic cytoplasmic antibody (ANCA) associated small-vessel vasculitides with overlapping clinicopathological features. More than 75% of patients with GPA and 100% of EGPA present with upper airway involvement, and precede systemic involvement^{34,35}. Both often overlap with lower airway involvement (45% at presentation and 87% during the course of the disease with GPA and 100% with EGPA)³⁶. It is very rare to see MPA involving the sinonasal system.

GPA can be aggressive with marked nasal obstruction from crusted blood and infected mucus with tissue necrosis and remodelling leading to severe nasal and facial pain. However, a more indolent presentation with classic CRS symptoms and visible mucopus mimicking infection may delay diagnosis. For patients presenting with difficult or frequent acute rhinosinusitis or CRS a vasculitis screen

should be mandatory along with CT scanning. It is more with time that classic bone erosion and remodelling (i.e. saddle nose deformity, turbinate erosion, spontaneous antrotomy, epiphora from tear duct involvement etc.) and conductive hearing loss (up to 30 % of patients) is seen. EGPA needs a high index of suspicion as all patients have CRSwNP with asthma for a substantial duration before they progress to full blown vasculitis³⁵. The blood eosinophil count is important to monitor along with ANCA status, especially during exacerbation periods.

Symptoms of lower airway involvement in vasculitis can be non-specific. Generic respiratory symptoms such as breathlessness at rest or exertion, cough, haemoptysis, wheeze or stridor either alone or in various combinations should alert ENT surgeons that respiratory review is needed, along with at least a chest x-ray. Systemic involvement can be life threatening.

In GPA the working hypothesis is that cANCA directed against proteinase3 (PR3) leads to neutrophil toxicity in vessels by leading to induction of the cell respiratory burst, releasing toxic oxygen radicals and rapid cell degranulation. Both events lead to vessel and local tissue injury. Infection will prime the neutrophils to an active state with increased expression of PR3 on the neutrophil surface. This leads to an amplified ANCA-induced inflammatory response and disease flare. The released inflammatory mediators will further activate neutrophils thus effectively creating an ANCA driven auto-amplifying inflammatory loop. Thus strategies to prevent immune activation are important, and the upper airway in particular is predisposed to air borne triggers and microbes. Treating any coexistent infection is advised to try and attenuate neutrophil activation and there is some emerging evidence that bacterial protein molecular mimicry to cANCA PR3 may promote further ANCA production³⁷. This may explain why cotrimoxazole (trimethoprim-sulfamethoxazole) can prevent disease relapse in GPA with prolonged disease-free survival in association with a marked decrease in respiratory tract infection³⁸. The subgroup of patients with nasal carriage of *Staphylococcus aureus* are reported to demonstrate an increased incidence of GPA relapse³⁹, and thus it is assumed the benefits of cotrimoxazole maybe in relation to clearing such nasal colonisation. In GPA disease limited to the upper airway, corticosteroids and methotrexate are commonly used to induce remission⁴⁰.

Conclusion

ENT surgeons and respiratory physicians must appreciate the spectrum of disease that can co-present in the upper and lower airways. There is an emerging case for treating the airway together and future treatment guidelines must

emphasise such an approach. A joint medical-surgical approach both in the clinic and research setting is recommended.

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Facial paralysis and re-animation

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Abstract

Facial paralysis has dramatic functional and psychological implications for patients. The vast majority of these patients present to an Otolaryngologist for diagnosis and initial management.

This paper offers a brief overview of the various treatment strategies available and their indications.

In facial paralysis eye care is the most important initial intervention to prevent exposure keratitis. Incomplete eye closure and loss of corneal sensation dramatically increase the risk.

The initial differentiation factors include the presence of an intact or divided nerve, duration of palsy (acute or chronic) and whether the paralysis is flaccid or incomplete.

In acute facial palsy where the nerve is intact, a "watch and wait" policy is observed for at least one year to assess if useful facial function returns before irreversible interventions are undertaken. In contrast, in situations where the nerve has been disrupted, the primary aim is to re-establish continuity as soon as possible.

For patients with chronic facial palsy treatment is dependent on whether the paralysis is flaccid or incomplete. In chronic flaccid paralysis no viable muscle exists and therefore dynamic reanimation surgery requires muscle transpositions or free muscle transfers. In the presence of an incomplete palsy of any duration viable facial muscle is presumed to exist. Dynamic procedures therefore also include nerve transfers in addition to muscle transpositions or free muscle transfers.

The cosmetic correction of the multiple deficits associated with the paralysed face is complex, and the

results are highly operator dependent. A multidisciplinary team approach is preferable, ideally in a tertiary care setting to allow a sufficient caseload to maintain skills.

Keywords

Facial paralysis, re-animation, nerve repair, dynamic and static procedures

J ENT Masterclass 2014; 7 (1): 70 - 78.

Introduction

"The face is a picture of the mind with the eyes as its interpreter." – Cicero

Disorders causing facial nerve weakness have dramatic physical and psychological consequences for the patient. Facial paralysis severely hinders mastication, speech production, and eye protection. This has led to the development of numerous reanimation techniques to attempt to restore normality. The ability to restore facial symmetry and a patient's smile is one of the most rewarding skills of a reconstructive surgeon.

Anatomical Considerations

Facial nerve anatomy

The facial nerve carries 7,000 myelinated motor neurons and 3,000 secretory and somato-sensory neurons. It originates from the facial nucleus located at the caudal pontine area. Cortico-bulbar fibers from the pre-central gyrus (frontal lobe) project to the facial nucleus, with most decussating to the contralateral side. The course of the facial nerve and its various segments are outlined in Table 1.

Nerve fiber component

The peripheral nerve can be divided into 3 main components, endoneurium, epineurium, and the perineurium.

Table 1: Summary of Facial Nerve Anatomy	
Intracranial segment	Originates in pons 23-24mm segment within CPA to IAC
Intratemporal	Meatal From IAC to fundus Anterior/superior portion of IAC (Facial nerve superior, cochlear nerve inferior "7-UP, Coke down") 8-10mm Labyrinthine From fundus to geniculate ganglion (narrowest portion) 3-5mm segment Makes 1st genu prior to entering tympanic cavity Greater superficial petrosal nerve
Tympanic/horizontal segment	From geniculate ganglion to 2nd genu 8-11mm Superior to oval window/stapes
Mastoid/vertical segment	2nd genu to stylomastoid foramen Anterior/caudal to lateral SCC Lateral to sinus tympani and stapedius muscle 10-14mm Nerve to stapedius Chorda tympani
Extratemporal Segments	Postauricular Nerve Nerve to stylohyoid Nerve to posterior digastric
Pes Anserinus	Temporal Frontalis Corrugator Procerus Upper orbicularis oculi Zygomatic Lower orbicularis oculi Anastomose with buccal branch Buccal Zygomaticus mm Levator anguli oris Buccinator Upper orbicularis oris Mandibular Lower orbicularis oris Depressor anguli oris Depressor labii inferioris Mentalis Cervical Platysma
Key: CPA= cerebello-pontine angle, IAC = internal auditory canal, SCC = semicircular canal	

Endoneurium - the inner-most portion that is adherent to the Schwann cells and provides the endoneural tube crucial for regeneration. Transection results in a poor prognosis for recovery.

Perineurium – provides tensile strength to the nerve and a protective barrier against infection.

Epineurium – contains the vasa nervorum and is responsible for nourishing the nerve.

Nerve injury can be classified into five main categories according to the Seddon and Sunderland classification system^{1,2}. These categories are based on histological studies displaying damage to various portions of the nerve:

First degree (Neurapraxia)

- Nerve compression / ischaemia.
- Nerve continuity preserved / no Wallerian degeneration.
- Short period of dysfunction; rapid and complete recovery.
 - o Partial loss of function (i.e. paresis instead of paralysis).
 - o No muscle wasting.
 - o No signs of muscular fibrillation or degeneration.

Second degree (Axonotmesis)

- Axon severed but endoneurium of Schwann cell intact.
- Degeneration distal to injury site
 - o Loss of motor, sensory and sympathetic function at injury site.
 - o Muscle denervation distal to injury.
 - o Fibrillation present as well as atrophy.
 - o Recovery time dictated by injury severity (months).
 - o Complete functional restoration.

Third degree (Neurotmesis)

- Intra-fascicular injury with disruption of endoneurium
 - o Wallerian degeneration / axonal decomposition.
- Delayed axonal regeneration
 - o Recovery often incomplete.
 - o Aberrant regeneration with increased risk of synkinesis.
- Motor and sensory function lost in field of injured nerve



Figure 2: Lateral tarsal strip secured via permanent suspension on drill holes in the lateral orbital wall (4/0 Gortex suture).

- o Longer recovery period than 1st and 2nd degree injuries.
- o Despite eventual re-innervation, muscle recovery may be incomplete at best.

Fourth degree (Neurotmesis)

- Undisturbed nerve trunk but site of injury contains ruptured fasciculi, damaged Schwann cells and regenerating axons
 - o Wallerian degeneration.
 - o Possible neuroma formation.
- Complete loss of motor, sensory and sympathetic function
 - o Some degree of spontaneous recovery possible but is nonfunctional.
 - o Synkinesis; aberrant regeneration between fascicles.

Fifth degree (Neurotmesis)

- Complete transection of the nerve, loss of continuity; disruption of all structures in the area of injury.
- Few viable neurons; severely disturbed retrograde neuronal function.
- Axons may regenerate but fail to re-innervate the correct fascicule.
- Recovery is not possible without an appropriate surgical treatment.

Anatomy of Facial expression

Functionally speaking, there are 18 paired muscles that participate in facial expression, however in terms of clinical re-animation and management, focus is put upon the frontalis, orbicularis oculi, zygomaticus major, orbicularis oris, and the lip depressors. Clinical zonal assessment pays particularly attention to the eyelid function, the nasolabial fold and the dynamics of the smile.

The nasolabial fold is comprised of dense fibrous tissue, the upper lip levators, and the striated muscles originating in the superficial fascia underneath the dermis. The nasolabial fold can assume varying shapes and depths and is unique to each individual.

The smile occurs in two stages, firstly, the upper lip levators contract along with the nasolabial fold musculature to elevate the nasolabial fold against resistance from the cheek. Subsequently the levator superior, zygomaticus major and caninus muscles raise the lip and nasolabial fold (NLF) upward. The average maximum spontaneous smile excursion is 7-22 mm (average 17 mm). Smile types have been classified into 3 types³.



Figure 3: Facia Lata Suspension
 a. Pre-operative, complete facial palsy with accompanying gross facial ptosis frequently seen in elderly with facial soft tissue laxity.
 b. Intraoperative photo demonstrating, fascia lata placed on SMAS layer for suspension.
 c. Post-operative photo, facial ptosis has been corrected with fascia lata suspension of commissure and midface. Direct brow lift, drill hole lateral tarsal strip.

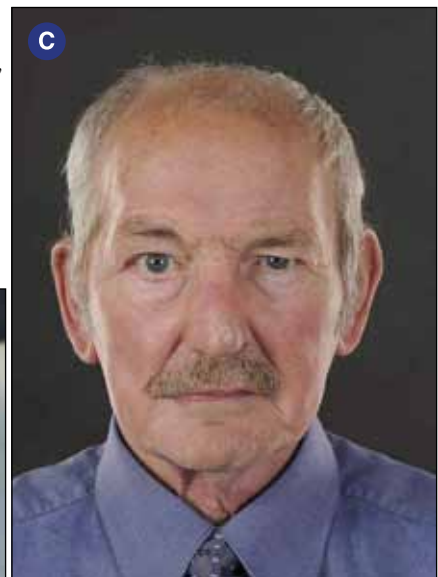


Table 2: Nottingham Facial Nerve Zonal analysis pro-forma		
	Right	Left
Brow		
Ptotic, balanced, hyper-elevated		
Field defect		
Excursion		
Upper lid		
Dermatochalasis		
MRD1 (mm)		
Lagophthalmos (mm)		
Cornea		
Corneal ulceration		
VA		
<i>Bells phenomenon</i>		
<i>Anesthesia</i>		
<i>Dry eye/tear film</i>		
Lower lid		
MRD 2		
Distraction		
Snap test		
Lateral laxity		
Medial laxity		
Finger lift 1/2		
SOUF position		
Nasolabial		
Effaced		
Increased		
Nasal Breathing		
Valve problem		
Position of the nasal base		
Commissure		
Up/down/correct		
Commissure excursion		
(mm)		
Labial depressors		
Platysma		
Key: MRD1 = margin reflex distance-1 which is the distance between the centre of the pupil in primary position and the central margin of the upper eyelid; MRD2 = margin reflex distance-2 which is the distance between the center of the pupil in primary position and the central margin of the lower eyelid; VA = visual acuity; SOUF = suborbicularis oculi fat		

- 1) Zygomaticus major smile - most commonest type which is dominated by zygomaticus major and buccinator muscle, the corners of the mouth elevate first
- 2) Caninus smile - second commonest controlled by levator labii superioris contracting prior to zygomaticus major and buccinators, dominant upward elevation of lip followed by elevation of corners of the mouth

3) Full-denture smile - Least common due to contraction of elevator and depressors of the lips and angles of the mouth, maxillary and mandibular teeth are displayed

Evaluation of Facial Paralysis

The assessment of facial paralysis concentrates on the likely aetiology, duration, degree of paralysis (Table 2), prognosis, presence of synkinesis, age, life expectancy and patient expectations. However in general, factors that are useful in determining management are: acute vs. chronic (> 2 years) duration, partial vs. complete paralysis, and the availability of a proximal facial nerve stump for co-adaptation⁴.

Partial vs. complete paralysis

In partial facial paralysis the facial muscles have been partially re-innervated resulting in reduced excursion. If the excursion is felt to be adequate to allow satisfactory facial expression, the contra-lateral healthy side excursion is reduced with neuromuscular retraining and botulinum toxin to improve symmetry⁴. If excursion is inadequate on the affected side, it is supplemented with muscle / nerve transfers or a free muscle transfer. Complete (flaccid) paralysis is characterised by failure of re-innervation, which will require surgical intervention. Acutely (< 2 years) re-innervation techniques can be employed. If however the delay is > 2 years, re-innervation techniques are contraindicated as the affected facial muscles undergo irreversible atrophy and fibrosis. The lost functional muscle must be replaced with either a dynamic muscle transfer or free muscle transfer to regain useful excursion.

Facial Assessment

Using a systematic zonal approach to examination addresses in turn the brow, cornea (upper/lower tarsus), midzone (nasolabial fold), smile (oral commissure) and lower lip depressors⁵. This allows a prescribed management plan to address each of the deformities. A structured assessment form is useful for this purpose (Table 2). There are various facial nerve specific questionnaires that can also be used to aid treatment planning and comparison between interventions

The Nottingham Otolaryngology Facial Nerve Service has employed several questionnaires:

1. House-Brackmann Grading Scale (HBGS) (Table 3)⁶.
2. Sunnybrook Facial Grading System (SFGS) (Table 4)⁷ – Video recording of face during repose and during five specific facial movements (for SFGS).
3. Zonal Summary (as below).
4. The Facial Clinimetric Evaluation (FaCE) Scale - a patient graded quality of life (QOL) instrument⁸.

5. Synkinesis Assessment Questionnaire – a patient graded instrument designed to assess facial synkinesis⁹.

Ancillary Investigations

Electromyography (EMG) – electrodes inserted directly into muscle, presence of voluntary action potentials indicates at least partial innervations.

Electroneuronography (ENoG)- transcutaneous stimulation of facial nerve at styloid foramen, recording muscle response. This is only useful after 72 hours have elapsed (time taken for Wallerian degeneration), but can be helpful in determining prognosis for idiopathic paralysis.

Management

A multidisciplinary team approach is helpful in the management of facial paralysis, and includes – otolaryngology - facial plastic reconstructive surgery and neurotology; ophthalmology; neurosurgery; neurophysiology and physiotherapy. This should also ideally be in a tertiary centre with a sufficient throughput of patients to maintain skill levels required for favourable outcomes.

The management aims are: corneal protection, symmetry of the face at rest, and restoration of a symmetrical smile. Candidates for intervention are those with nerve transection

Table 3 House-Brackmann Grading Scale

Grade	Description	Characteristics
I	Normal	Normal facial function
II	Mild dysfunction	Slight weakness on close inspection; normal tone and symmetry at rest
III	Moderate dysfunction	Obvious weakness +/- asymmetry, but not disfiguring; synkinesis, contracture or hemifacial spasm; complete eye closure with effort
IV	Moderately severe dysfunction	Obvious weakness or disfiguring asymmetry; normal symmetry and tone at rest; incomplete eye closure
V	Severe dysfunction	Barely perceptible motion; asymmetry at rest
VI	Total paralysis	No movement

injury, facial paralysis of 1 or more years without physical or electrical signs of recovery, congenital facial dysfunction, patients with incomplete recovery from facial paralysis (often with synkinesis and hypertonia and/or no useful excursion).

Table 4: Sunnybrook Facial Grading System

Resting Symmetry Compared with normal side	Symmetry of Voluntary Movement Degree of muscle excursion compared to normal side						Synkinesis Rate the degree of involuntary muscle contraction associated with each expression			
	Standard expressions	Unable to initiate movement	Initiates slight movement	Initiates movement with mild excursion	Movement almost complete	Movement complete	None ¹	Mild ²	Moderate ³	Severe ⁴
Eye (choose only one) Normal 0 Narrow 1 Wide 1 Eyelid surgery 1	Brow Lift	1	2	3	4	5	0	1	2	3
Cheek (naso-labial fold) Normal 0 Absent 2 Less pronounced 1 More pronounced 1	Gentle Eye closure	1	2	3	4	5	0	1	2	3
Mouth Normal 0 Corner dropped 1 Corner pulled up/out 1	Open mouth smile	1	2	3	4	5	0	1	2	3
	Snarl	1	2	3	4	5	0	1	2	3
	Lip pucker	1	2	3	4	5	0	1	2	3
		Gross asymmetry	Severe asymmetry	Moderate asymmetry	Mild asymmetry	Normal asymmetry				
Total Resting symmetry score Total x 5	Total Voluntary movement score Total x 4						Synkinesis score Total			
Voluntary movement score – (minus) Resting symmetry score – (minus) Synkinesis score = Composite Score										
Key: 1. No synkinesis or mass movement; 2. Slight synkinesis of one or more muscles; 3. Obvious; 4. Disfiguring synkinesis/gross movement of several muscles										

Acute Facial Paralysis

The management of the eye in facial palsy is the most important intervention for facial paralysis to avoid catastrophic exposure keratopathy and blindness. In the presence of incomplete eye closure and normal corneal sensation (intact corneal reflex), these patients can be managed with a regular eye lubricant regime and eye taping. Urgent Ophthalmology review is required when; there are symptoms indicating corneal involvement e.g. a red painful eye; in the presence of incomplete eye closure and reduced corneal reflex sensation - even in the absence of symptoms. A comprehensive eye examination including visual acuity, visual fields, fundoscopy, and slit lamp examination for assessment of the tear film and corneal integrity is essential.

Were the nerve is intact, such as Bell's palsy, some advocate utilising investigations such as ENoG or EMG as a prognostic indicators, but conventionally the management

for the first year is physiotherapy. In acute situations where the nerve has been disrupted, attempts at re-establishing continuity is made either primarily or in the presence of a nerve gap, using interposition grafts. In the absence of a proximal stump then a nerve transfer maybe required.

In acute cases where there is no chance of recovery, e.g. nerve transaction, neural re-innervation techniques should be undertaken as soon as practically possible. Neural techniques can be roughly divided into primary repair nerve interposition grafts and nerve substitution. The best result from any techniques is House-Brackman Grade III. (Summary figure 1).

Primary repair

The preferred option when a tension free repair can be performed and may require releasing proximal or distal ends or rerouting the mastoid segment. It is best undertaken



Figure 1: Minimally Invasive Temporalis Tendon Transposition
 a. Pre-operative incomplete facial palsy, with some residual facial tone three years following Acoustic Neuroma surgery (facial nerve intact).
 b. Poor facial excursion despite some facial tone. A complex case as any poorly performed surgical intervention can worsen residual facial function.
 c. Intra operative, the use of an intraoperative transcutaneous electrical stimulation of the temporalis muscle aids setting the muscle at it optimal working length to achieve maximal excursion (Boahene KD, 2014)18
 d. 1st post-operative visit at 2 weeks for clip removal. Status of dynamic rehabilitation with first attempts at smiling in clinic (produce through biting). Good excursion of approximately 7mm is already present, with good facial symmetry. Also note upper lid blepharoplasty, lower lid transorbital canthoplasty and brow suspension through temporal incision have been performed. All procedures performed by author (C.F). Patient highly satisfied with result.



within 72 hours with a microsurgical repair of the epineurium or perineurium¹⁰.

Nerve interposition grafts

Nerve interposition grafts are used in the presence of a nerve gap when a tension-free primary end-to-end anastomosis is unachievable. Nerve interposition grafting requires both proximal and distal nerve stumps to be available for neurorrhaphy. Common donor interposition grafts include the Greater auricular (6cm length), Sural (30cm length), medial cubital (15cm length) nerves^{10,11}.

Nerve substitutions

Where the proximal nerve stump is not available, one can use a local expendable motor donor nerve as a substitute, such as cranial nerves XII, V (masseteric) and VII (contralateral side- usually buccal branch)¹².

Chronic Flaccid Facial Paralysis

The zonal approach is ideal for planning intervention with the upper and lower face reanimated separately in order to avoid

mass movement. Both static and dynamic procedures can be employed to yield a satisfactory result. (Summary figure 4).

Static Procedures

Brow suspension

Ptotic brow tissue can frequently cause visual field defects in the elderly, which paradoxically leads to hyper elevation of the contralateral side and results in greater asymmetry. The aesthetic position of the brow should be at the orbital rim in men, and slightly above the orbital rim in woman, with the apex at the lateral limbus. There are various techniques described such as the transblepharoplasty browpexy, direct brow lift, midforehead lift, static sling brow suspension, endoscopic and coronal brow lift⁵.

Upper lid Procedures

Lid loading is commonly performed for lagophthalmos, and lid retraction and is achieved using gold weight usually from 1-1.4 grams. It is a simple office technique that is reversible but it has been shown to have significant rates

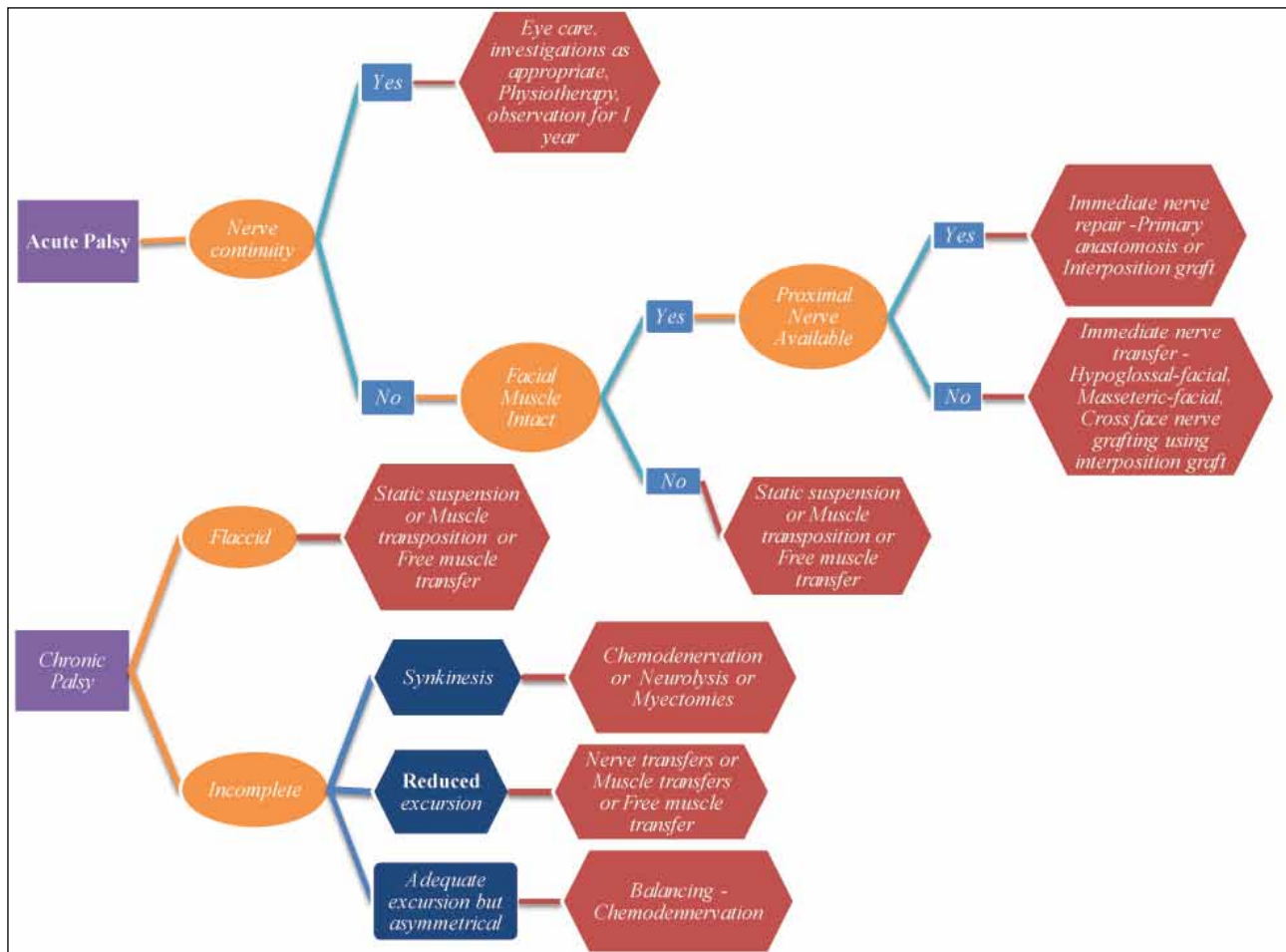


Figure 4: Treatment Flow Chart.

of complications including 13% for bulging of the upper lid, and 6 % for migration and erosion through the skin¹³ that can be reduced by the placement of temporalis fascia or fascia lata as an overlay free graft.

Lower lid procedures

Lower lid malposition and paralytic ectropion are the common manifestations resulting from paralysis of the orbicularis oculi. In mild and moderate lateral lid malposition, a lateral tarsal strip procedure secured through permanent suspension on drill holes in the lateral orbital wall is effective, but requires a lateral canthotomy and cantholysis with excision of skin and conjunctiva - risking overlapping of the eyelids (Fig 2).

Nasolabial fold and oral commissure

The recreation of a nasolabial fold and elevation of the oral commissure is important for function (speech, oral continence) and facial symmetry. In the modern era of facial reanimation surgery dynamic reanimation is preferred in almost all cases. If however there is a patient preference is for static suspension, this can be achieved with fascia lata suspension (Fig 3), but there are a variety of other materials available (acellular dermis, e-PTFE and suture techniques), depending upon an individual surgeon's preference.

Dynamic Procedures Nasolabial fold and oral commissure

Treatment options for patients with a chronic flaccid palsy include static suspensions or dynamic procedures such a muscle transpositions (such as Temporalis) or free muscle transfers (such as Gracilis) as there is no functioning muscle. In instances of chronic incomplete paralysis (with inadequate) excursion these dynamic procedures are indicated, but nerve transfers are also possible as the facial muscles are presumed to be functioning. The rationale for nerve transfer in this situation (chronic incomplete) is that smile production is complex involving different contributions from lip elevators and depressors. Therefore a reanimation of the smile is may be better achieved by re-innervation of the native muscles, by nerve transfers compared with a one vector replacement achieved with either a free muscle transplant or muscle transposition.

Muscle transfers

The main options for muscle transfer are masseteric and temporalis muscle transfers in the presence of intact trigeminal motor function. The masseter is now less commonly used due to its unfavourable vector of pull and the contour defects it creates at the angle of the mandible. The classic technique popularized by Gilles in the 1930s transposes the temporalis muscle over the zygomatic arch and attaches fascial extensions to the muscle to reach the

commissure and upper lip 14. Smile excursion is produced by activation of the temporalis through biting. The main limitations being that it produces an unsightly contour defect from the reflected muscle over the zygomatic arch, and temporal hollowing which are noticeable at rest and even more prominent during contraction. This has been overcome by alternative techniques where the temporalis tendon is transferred to the nasolabial fold, as described by McLaughlin, Labbe and Byrne¹⁵⁻¹⁷.

One of the author's (C.F) preference is for the "Minimally Invasive Temporalis Tendon Transposition"¹⁷, where the insertion of the temporalis tendon to the coronoid is divided through a nasolabial fold incision and transferred to the nasolabial crease. The key to adequate excursion from any muscle transfer is setting the muscle at the right tension (its normal resting tension)¹⁸ (Fig 1), as an overstretched muscle or flaccid muscle will contract poorly. In the case of Minimally Invasive Temporalis Tendon Transposition a fascia lata extension graft to the oral commissure of 1-3 cm is almost always required. The smile is not spontaneous and requires rehabilitation, but patients can very quickly learn to trigger a smile without the chewing motion due to neural plasticity between trigeminal and facial cranial nerves. The great benefit of temporalis muscle transfers is the speed with which patient can have a useful smile (in 2 weeks) in contrast to free muscle transfers which when combined with cross face nerve grafts can take up to 1.5 - 2 years for movement to occur.

Free muscle transfer

Classically patients considered for free muscle transfer have no viable facial muscles, either through chronic facial palsy, tumour resection or congenital facial palsy.

The neuronal donor for the free muscle transplant are the same as those for nerve re-innervation (contralateral facial nerve, masseteric, hypoglossal and spinal accessory). Of all the possible neural targets only the ipsilateral/contralateral facial nerve can reliably achieve spontaneous smile and this is often the deciding factor.

The Gracilis muscle free transfer remains one of the most popular with its ease of harvest and low donor site morbidity although it has a relatively short neurovascular pedicle and requires a two staged approach for contralateral facial nerve grafting¹⁹. The role of free muscle transfer in our practice however is limited to instances where the temporalis muscle is insufficiently strong for useful excursion or where trigeminal nerve is also damaged precluding the use of temporalis muscle.

Lower Zone Static and Dynamic Rehabilitation

Iatrogenic damage to the marginal mandibular branch of the facial nerve is the commonest cause of paralysis of the lower lip depressors.

Several techniques have been described to address the lower lip depressors such as cranial nerve VII–VII transfer, contralateral myectomy, contralateral chemo denervation, ipsilateral digastric or platysma muscle transfer 5, 20, 21.

Hypertonia and synkinesis

Synkinesis has been defined as the unintentional movement of one area of the face that occurs as a result of intentional movement of another. Synkinesis often takes 3–6 months following injury to become apparent. First line therapies are physiotherapy and biofeedback therapy, second line approaches involve chemodenervation using botulinum toxin. In cases of resistant synkinesis surgical treatments such as selective neurectomies and myectomies and cross-face nerve grafting are options^{5,22}.

Conclusion

Facial paralysis is devastating for any patient at any age. It is important for otolaryngologists, who manage in excess of 80% of peripheral facial paralysis, to have an understanding of the options available to patients with facial paralysis to arrange a timely referral for appropriate facial nerve rehabilitation. The successful management of these patients can be complex and ideally this should be undertaken in centres where there is a dedicated multidisciplinary team. We would recommend the following referral criteria to such tertiary centres:

1. Complete paralysis no hope of recovery (nerve transection).
2. Facial paralysis in the presence of an intact nerve, of 1 year or more without physical or electrical signs of recovery.
3. Presumed Bells palsy > 3 month duration with no/limited recovery.
4. Any Chronic paralysis (> 2yrs) where recovery is incomplete, and patient is unhappy with current facial function.
5. Presence of facial synkinesis.
6. Frozen face (hypertonia + synkinesis) after incomplete recovery.
7. Diagnostic dilemma of aetiology of facial palsy.

By improving the understanding of the treatment options available and centralising care to specialist centres, the hope for more reliable and improved outcomes for all patients with facial paralysis may be realised.

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The principles and applications of botulinum toxin in the face and neck

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Abstract

The applications of Botulinum toxin (BoTN) in the face and neck has rapidly expanded, with ongoing research continuing to develop novel indications and improve our understanding concerning mechanisms of action. This article reviews the principles and indications of BoTN in the head and neck, as well as the face, discussing both cosmetic and non-cosmetic applications. Botulinum toxin serves as an effective, minimally invasive treatment option in a range of cosmetic and non-cosmetic indications. Side effects are few and transient with an excellent safety profile.

Keywords

Botulinum toxin; Cosmetic; Non-Cosmetic; Face; Neck

Acknowledgements

None

Conflicts of Interest

None.

Source of Funding

None.

J ENT Masterclass 2014; 7 (1): 79 - 86.

Introduction

The applications of Botulinum toxin (BoTN) in the face, head and neck, has rapidly expanded over the last two decades. This can be ascribed to its extended use in aesthetic industry, for rejuvenating the aging face, with excellent results, that became popular in the late eighties. This article provides an overview of the principles and indications of BoTN in the face, head and neck, discussing both cosmetic and non-cosmetic applications. Additionally it offers guidelines to the use of BoTN, for various indications.

Pharmacology and mechanism of action

Seven distinct serotypes of BoTN exist, and are known as A, B, C1, D, E, F, and G. Only A and B serotypes are available for clinical use at present. BoTN-A is the most commonly used serotype and is secreted in three forms, 300 kDa (kilo Daltons), 500 kDa and 900 kDa.

Botulinum neurotoxin blocks the presynaptic neuromuscular junction, preventing acetylcholine release thus inducing flaccid paralysis. The three principal steps in the toxin-mediated paralysis are: binding; internalisation; and inhibition of neurotransmitter release, thus resulting in reversible chemical denervation. The denervation and recovery exhibits three distinct phases. In the initial phase, non-collateral axonal sprouting occurs [Figure 1A]. These incipient nerve terminals eventually establish a new functional neuromuscular junction that replaces the original motor endplate [Figure 1B]. After approximately 3 months, the new terminals regress and the parent terminal re-establishes its functional core.

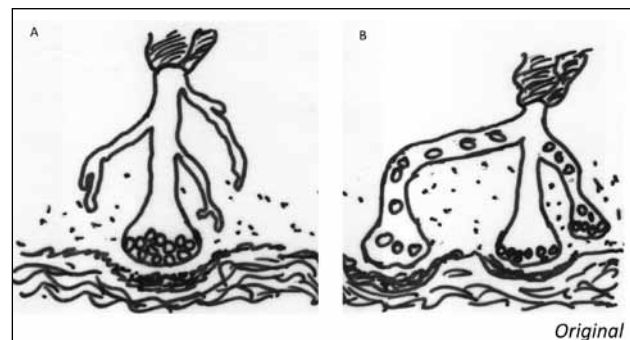


Figure 1: Botulinum toxin inducing denervation and recovery in three distinct phases: (A) Non-collateral axonal sprouting occurs. (B) New functional neuromuscular junction replacing the original motor endplate.

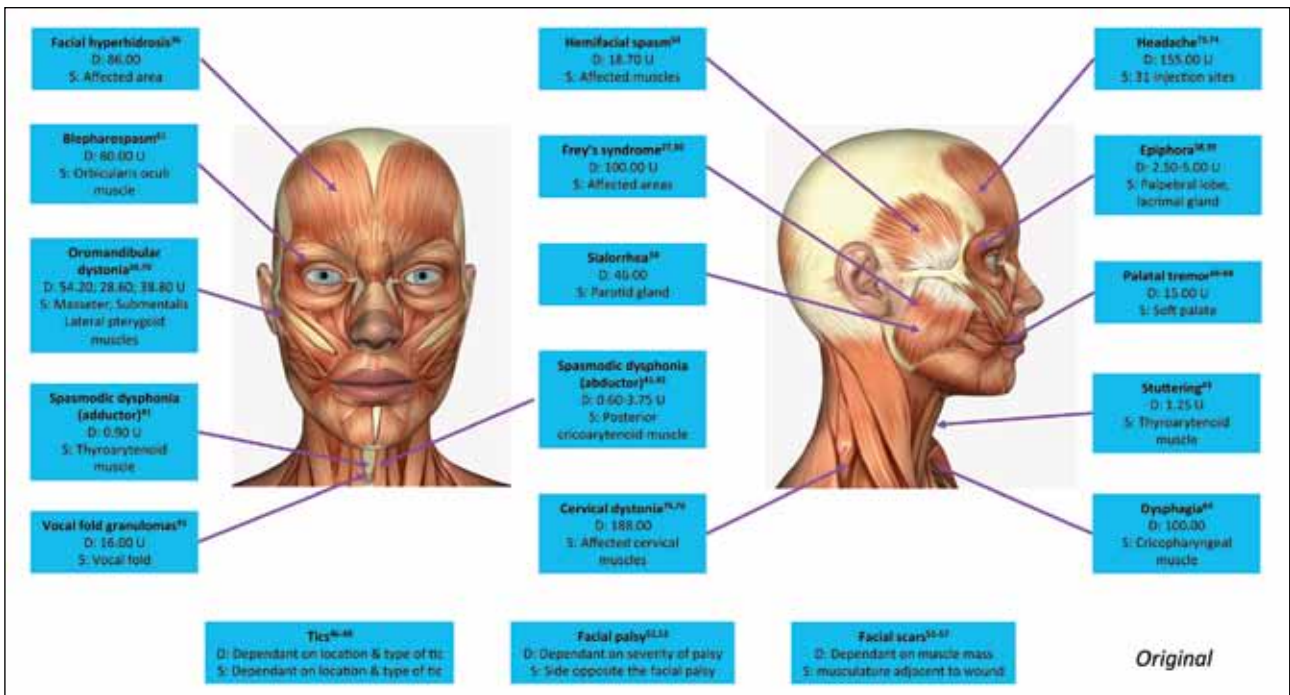


Figure 2: Injection sites of BoTN for cosmetic conditions included in this study. D = Dose; U = Units; S = Site of injection. Doses are total doses for BoTN-A. Image provided by Can Stock Photo Inc[©].

General principles of use:

The BoTN is reconstituted with 0.9% saline, depending on manufacturer’s guidelines. The drug is administered at single, or more commonly, multiple injection sites, as appropriate. The total volume injected varies depending

on the dilution used, titrating up to the optimal doses [Figures 2 and 3]. The senior author (AD), recommends 1 ml luer lock syringe with a 30 or 32 Gauge needle for injections. Studies indicate that treating aesthetic facial zones rather than isolated areas produce better outcomes with

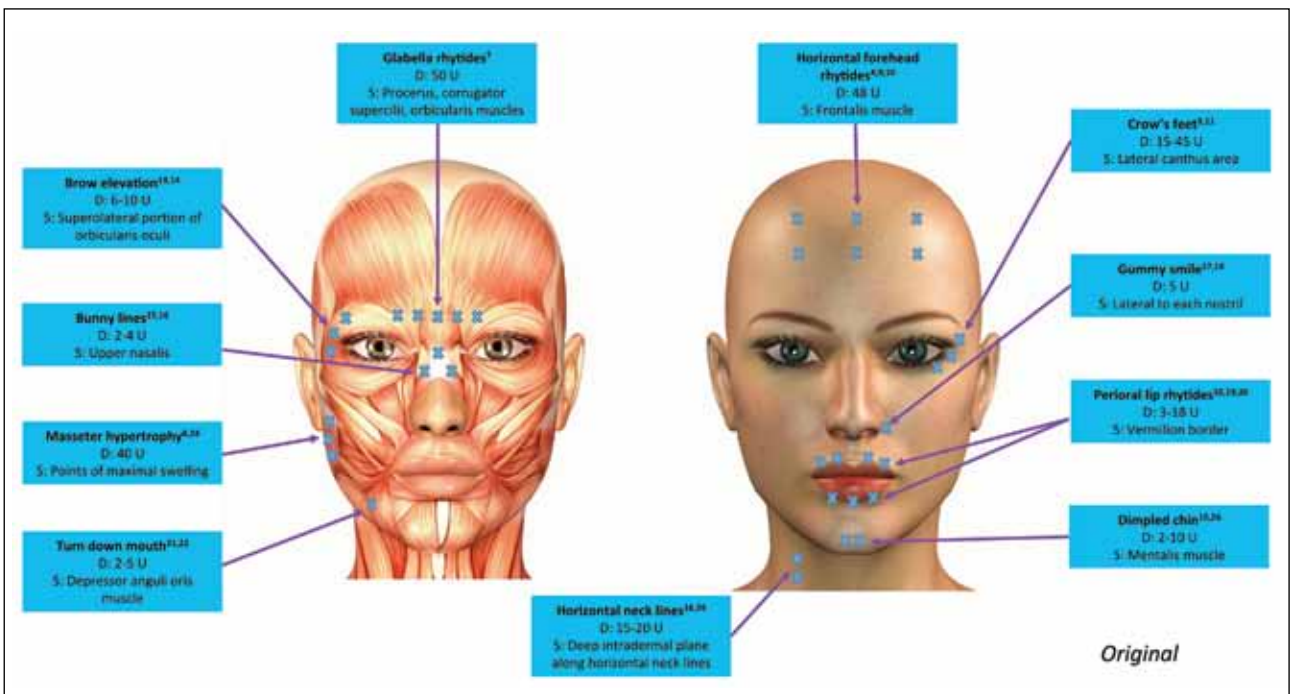


Figure 3: Injection sites of BoTN for non-conditions included in this study. D = Dose; U = Units; S = Site of injection. Doses are total doses for BoTN-A. Image provided by Can Stock Photo Inc[©].

a more natural, and aesthetic look¹. BoTN is best applied into areas of wrinkling due to dynamic motion, as static wrinkles and deep folds respond poorly. Males generally require higher doses of BoTN to achieve the similar results compared to females owing to increased muscle mass^{2,3}.

The doses should be titrated depending on patient factors such as muscle bulk, desired effect and outcome. A detailed knowledge of muscular anatomy and the interaction of these muscles both in animation and at rest are paramount in achieving consistent good results. The use of electromyographic monitoring (EMG) is often recommended in non-cosmetic treatment to ascertain exact injection site e.g. vocal cord injection.

Contraindications and side effects

BoTN carries several contraindications and side effects [Tables 1 and 2] respectively. Side effects are temporary in nature lasting for 3-4 months and generally injection site specific. Complications are easily avoidable in expert hands.

COSMETIC APPLICATIONS

The cosmetic use of BoTN was first discovered in 1990 serendipitously and has become increasingly popular⁴. Consumers have become more comfortable with injectables owing to minimal risks and no downtime when compared with other aesthetic interventions. Moreover recent economic challenges appear to have resulted in growing numbers of patients turning from surgical interventions to injectables as a lower cost option⁵. [Figure 2].

Rationale for use of BoTN in medical aesthetics:

With aging, reduced elasticity of the tissues and downward pull of gravity results in hyperdynamic contraction of underlying muscles particularly in the forehead, glabellar and periocular areas. This results in the appearance of skin creases perpendicular to the direction of muscle contraction. Similar changes also lead to formation of

Table 1: Contraindications of BoTN
Contraindications
Known hypersensitivity or allergy to any component in BoTN formulation
Pregnancy
Breastfeeding
Neurodegenerative diseases or disorders of the neuromuscular junction
Concurrent use with aminoglycoside antibiotics
Signs of systemic infection
Infection at location of injection.
Unrealistic expectations.

Table 2: Side effects and complications	
Site	Side effects and Complications
Non-specific	Bruising, headache, nausea, fatigue, malaise, pain, flu-like symptoms, erythema, secondary non-responsiveness, undesired muscle weakness, focal twitching, angioedema, anaphylaxis
Glabellar complex	Ptosis of upper eyelid,
Frontalis	Brow ptosis
Brows	Cockeyed/Spock appearance
Periocular	Diplopia, ectropion, keratitis, brow asymmetry, blepharoptosis, lagophthalmos.
Lacrimal Gland	Ptosis, diplopia, decrease tearing and xerophthalmia
Perioral	Asymmetric smile, oral incompetence,
Soft palate	Dysphagia, plummy voice, velopharyngeal insufficiency
Cervical muscles/ Neck	Dysphagia, vocal cord paralysis, airway incompetence.
Aerodigestive tract (cricopharyngeus and Vocal cords)	Aspiration, dysphagia, stridor

wrinkles and fine lines around mid and lower face as well as the neck^{4,6}. The use of BoTN-A temporarily chemically denervates the injected muscles, thus reducing contractions resulting in ameliorating lines and creases. The following section discusses the site-specific aesthetic applications of BoTN-A. The doses mentioned are from peer-reviewed publications, and it should be noted that the doses may vary considerably depending on the desired clinical outcome.

Upper face

Glabellar rhytids

These include vertical, oblique and horizontal creases secondary to the action of procerus and corrugator supercilii muscles. Studies demonstrate excellent results following injection of BoTN-A in the procerus, corrugator supercilii and orbicularis muscles^{1,2,7,8}. A randomised double blind study by Monheit et al⁷ found a total dose of 50 U (units) across 5 sites to be optimal in terms of safety and efficacy.

Horizontal forehead rhytides

Activity of the frontalis muscle is responsible for these rhytides. Studies typically report the use of 4-8 injection sites in a triangular distribution halfway between the hairline and the eyebrow^{4,9,10}, though the injection sites

should be tailored to treat the specific areas of creases, relating to contraction of frontalis muscle. Higher total doses of up to 48 U have resulted in greater efficacy and longer duration compared to lower (16 U) total doses⁹.

Crow's feet

These are periocular rhytids, secondary to contraction of the lateral aspect of the orbicularis oculi muscle when smiling. Several studies describe the effectiveness of BoTN-A for the treatment of crow's feet^{3,11,12}. Three injections into the lateral canthal area of each eye, 1cm away from the orbital rim at total doses of 15-45 U have been found to produce significant improvements lasting up to 12 weeks^{3,11}.

Altering brow aesthetics (brow elevation)

BoTN can work to temporarily paralyse the superolateral portion of the orbicularis oculi muscle (depressor of lateral brow) causing brow elevation. Total doses of 6-10 U injected into the superolateral portion of the orbicularis oculi muscle below the lateral half of the brow on each side, has been shown to provide quantitative brow elevation^{13,14}. Similar results are seen in the medial brow when glabellar complex is treated because of the paralysis of the medial brow depressors.

Mid face

Bunny lines

These are perinasal, resulting from contracting the transverse portion of the nasalis. Injections of 2-4 U of BoTN either side of the upper nasalis has been found to weaken the mimetic musculature responsible for bunny lines^{15,16}.

Gummy smile.

This describes excessive gingival display during smiling. When caused by a hyper-functioning levator labii superioris alaeque nasi muscle, BoTN-A injections can serve as an effective treatment modality. Total doses of 5 U are injected at one or two sites per side lateral to each nostril into the muscle. Injection sites are determined by smiling and palpation to ensure accurate muscle location before injection^{17,18}. It is important to rule out orthognathic conditions for optimal outcome.

Perioral rhytides

These rhytides are related to hyperdynamic orbicularis oris muscle during activities such as cigarette smoking or sustained pursing of the lips. Injections of BoTN-A at total doses ranging from 3-18 U at the vermilion border has been found to weaken the lip sphincter, improving appearance of rhytids^{10,19,20}. This procedure carries a high

risk of complications relating to incompetence of the oral sphincter.

Turned down mouth

Hyperactivity of the depressor anguli oris muscle can result in the appearance of 'turned down mouth'. Bilateral injections of 2-5 U of BoTN A into these muscles, has been found to successfully reverse this effect on corners of the mouth^{21,22}.

Masseter hypertrophy

Masseter hypertrophy may present as either unilateral or bilateral painless swelling(s) in the region of the angle of the mandible. Its aetiology is not well understood. Several studies describe reduction in the thickness of the masseter following intramuscular BoTN-A injection²³⁻²⁵. Three injections of BoTN are administered into points of maximal swelling, seen and palpated on clenching. Total doses have been reported at 40 U^{4,24}.

Lower face and neck

Dimpled chin

The appearance of a dimpled chin is partly caused by contraction of the mentalis muscle. A two point injection of BoTN-A into the mentalis muscle at total starting doses of 2-10 U has been found to help restore the smooth appearance of the chin^{10,26}.

Horizontal and vertical neck lines (platysmal bands)

These lines are caused by the superficial musculoaponeurotic system (Platysma muscle) attachments in the neck. Total doses of 15-20 U of BoTN-A injected into the deep intradermal plane in divided doses of 1-2 U at 1 cm intervals along horizontal or vertical neck lines can work to soften and erase these lines^{16,26}.

NON-COSMETIC APPLICATIONS

BoTN has an array of non-cosmetic uses. For simplicity we have grouped indications into the following subsections: A – Glandular; B – Laryngeal; C – Facial; D – Oesophageal; E – Oral; F – Pain. see Figure 3.

A. Glandular

For glandular disorders, BoTN works by inhibiting the exocytosis of acetylcholine vesicles, blocking neurotransmission across the neuromuscular junction, thereby reducing glandular secretion²⁷.

Frey's syndrome (gustatory sweating)

This typically occurs after parotidectomy and less commonly other forms of facial surgery and trauma, owing to aberrant regeneration of cut parasympathetic

fibres. Several studies have reported beneficial and long lasting effects following treatment with BoTN²⁷⁻³⁰. Injection is intradermal into affected areas with total mean doses reported at 100 U, representing 7.5 U per 4cm².^{27,30} Multiple injections (20-30) in a grid fashion are advised for optimal results centred on the affected areas. The area may be delineated with starch iodine test or based on careful history in most clinical situations.

Sialorrhoea

BoTN is a well-recognised treatment for excessive drooling^{31,32}. A recent meta-analysis of RCTs confirmed BoTN to effectively reduce sialorrhoea in both adult and paediatric patients³³. Injection is into the body of the parotid gland at a mean total dose of 46 U³⁴. Injection into the body of each submandibular gland has been found to improve results further³⁵.

Facial hyperhidrosis

Intradermal injections of BoTN-A into multiple affected sites at mean total doses of 86U have been found to significantly reduce sweat production in patients with facial hyperhidrosis³⁶. Duration of effect has been reported as 27 months³⁷. The senior author also has noticed reduced redness of the facial skin in patients with conditions such as rosacea.

Epiphora

BoTN injection into the palpebral lobe of the lacrimal gland at total doses of 2.5-5.0 U has been found to be of considerable benefit in epiphora^{38,39}. Wonjo³⁸ in the largest series to date found that symptoms “mostly or completely improved” in 74% of injected patients.

B. Laryngeal

Spasmodic dysphonia

BoTN can work to block the involuntary action-induced laryngeal hyperkinesias associated with spasmodic dysphonia⁴⁰. Blitzer⁴¹ in a treatment series of 1300 patients found significant improvements in adductor spasmodic dysphonia following bilateral injection of BoTN-A into the thyroarytenoid muscles at mean total doses of 0.9U. There is a relative sparsity of data concerning the use of BoTN for abductor spasmodic dysphonia. However studies report improvements following injection of 0.6-3.75 U of BoTN-A into the posterior cricoarytenoid^{41,42}. Injection under EMG is recommended to help establish accurate injection site.

Stuttering

There is only one case series showing that injection of 1.25 U of BoTN-A into each thyroarytenoid muscle is a

safe and effective treatment modality for persistent stuttering⁴³. Further research is required to confirm these findings as well as elucidate mechanism of action.

Vocal fold granulomas

Injection of BoTN into the affected vocal fold has been found to be an effective and safe treatment option for vocal fold granulomas; and appears to work by inducing temporary paresis of vocal folds, preventing on-going friction with the opposing arytenoid⁴⁴. Mean total dose has been reported as 16U of BoTN-A⁴⁵.

Tics

BoTN-A injections for both motor and phonic tics have been demonstrated to be effective and well tolerated, reducing tic frequency and severity⁴⁶⁻⁴⁸. Mechanism of action is poorly understood with dose dependant on location and type of tic.

C. Facial

Facial palsy

Several studies report the effective use of BoTN for facial palsy^{49,50}. Injection is into the non-paralysed side of the face at doses dependant on severity of the palsy^{51,52}. The BoTN appears to work by decreasing the relative hyperkinesis on the normal side. BoTN has also successfully been used to reduce the post paralytic synkinesis that may occur following recovery from a facial palsy, with injection into the affected side^{53,54}.

Facial scars

The effective use of BoTN for facial scars has been reported in a range of studies including RCTs⁵⁵⁻⁵⁷. Peri-operative injection into the musculature adjacent to the wound induces temporary paresis of underlying musculature, decreasing tension vectors on wound edges. The dose of BoTN required is dependent on the muscle mass responsible for the tension vectors.

Blepharospasm

BoTN for blepharospasm is the treatment of choice with three RCTs demonstrating its efficacy⁵⁸⁻⁶¹. Injections into the orbicularis oculi muscle at mean total doses of 80U per eye inhibit the involuntary eyelid muscle contractions that characterise this condition⁶¹.

Hemifacial Spasm

This is characterised by recurrent, involuntary contractions of the muscles innervated by the facial nerve⁶². Mean total doses of 18.7 U of BoTN into affected muscles have been shown to help inhibit these contractions, with significant long-term improvements in symptom severity⁶³.

D. Oesophageal

Dysphagia

Rigid oesopharyngoscopy guided injection of BoTN at doses of up to 100 U into the cricopharyngeus muscle has been found to be an effective treatment option for cricopharyngeal dysphagia⁶⁴. It is thought that the toxin works to inhibit the cricopharyngeal contractions that occur during deglutition^{64,65}.

E. Oral

Palatal tremor

This is characterised by rhythmic involuntary movement of the soft palate, and is thought to cause objective tinnitus due to audible clicks generated by the action of the soft palate on the membranous Eustachian tube^{66,67}. BoTN injection with a starting total dose of 15 U into the soft palate at the insertion of both tensor veli palatini and levator veli palatini can prevent these palatal contractions and significantly improve symptoms⁶⁶⁻⁶⁸.

Oromandibular Dystonia

This results from involuntary, action-induced spasms of masticatory, lingual and pharyngeal musculature⁶⁹. Injections into the masseter, submental and lateral pterygoid muscles at mean total doses of 54.2 U70, 28.6 U70 and 38.8 U69 respectively have been successful in blocking these involuntary muscle spasms producing favourable results.

F. Pain

Headaches

The use of BoTN as a prophylactic therapy for migraine is supported by numerous RCTs⁷¹⁻⁷³. Total doses of 155 U divided amongst 31 injection sites have resulted in significant reductions in migraine days, frequency and severity^{73,74}. It has been postulated that BoTN inhibits the release of peripheral nociceptive neurotransmitters, thereby blocking the central pain processing systems that generate the headache⁷³.

Cervical Dystonia (Spasmodic torticollis)

BoTN is the first line therapy for cervical dystonia^{75,76} and works to block the involuntary stimulation of neck muscle contractions that characterise this painful condition. Mean total dose has been reported at 188U, injected into affected cervical muscles⁷⁵.

Conclusions

Since its approval by the Food and Drug Association over 20 years ago, the use of BoTN in the face and neck has

flourished. The literature supports its effective and safe use in an array of cosmetic and non-cosmetic indications, often resulting in considerable improvement in quality of life. On-going research is required to develop novel indications, improve current applications and better understand its mechanisms of action.

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The expanded endonasal approach to skull base tumours

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Abstract

The expanded endonasal approach (EEA) to skull base tumours has evolved over the past 15 years from a highly controversial procedure performed by a few pioneers on a small subset of skull base lesions to a well-accepted series of operations, used widely across the world, for an ever-expanding array of lesions. This paper will discuss the current indications for the expanded endonasal approach in skull base surgery and the anatomic subsites that can be addressed with this approach. In addition, this paper will discuss the reconstructive options for EEA, and will review the results of this operation for a variety of tumours.

Keywords:

Anterior skull base, Endonasal approach, Expanded endonasal approach

J ENT Masterclass 2014; 7 (1): 87 - 91.

Introduction to Expanded Endonasal Approach

The key to the EEA is minimally invasive surgical access to the skull base using the nares as natural openings. Typically, the surgery is performed, at least in part, as a two-surgeon, four-handed operation carried out by a Neurosurgeon and an Otolaryngologist – Head and Neck Surgeon. In the classical description of the approach, the right inferior turbinate is lateralized, and the right middle turbinate resected to gain space for the endoscope, which is brought in through the right nostril. Nasoseptal flaps may be raised (see below), and a posterior septectomy is performed. The operating surgeon operates binarily (through both nares) while his or her partner performs the endoscopy, with high resolution views afforded to both surgeons from the endoscope displayed on monitors.

A key to safe performance of EEA is a fundamental understanding of the relevant anatomy. The development of image guidance techniques has been a great boon to this field, but cannot replace anatomic comfort in the area. Identification of the location of the carotid artery, either unilaterally or bilaterally, through its' six distinct segments (parapharyngeal, petrous, paraclival, parasellar, paraclinoid, and intradural) is of course of paramount importance, as are the spatial locations of the optic nerve and chiasm, as well as other cranial nerves that are critical to EEA in various locations¹.

Reconstruction is an important consideration in EEA surgery, and generally needs to be considered before the approach is completed. Early in the surgical experience with EEA, non-vascularized reconstruction techniques were popular, including grafts (such as fat, muscle, or fascia, with fascia lata being quite popular) and/or tissue sealants (such as Tisseel²). These reconstructive techniques were broadly effective, but were not reliable to prevent CSF leaks, especially in high risk cases (high CSF pressure, wide openings through the dura, obese patients, etc). CSF leak rates were often unacceptably high early in the experience with EEA. It was the introduction of the posteriorly based nasoseptal flap (NSP), first introduced by Haddad and Bassagasteguy³, and popularized by Carrau and colleagues⁴, that allowed for a marked reduction in CSF leak rates and other intracranial complications. This flap, based on the posterior septal artery, is raised before the posterior septectomy, and left pedicled posteriorly during the tumour resection (Figure 1). It allows reliable coverage of dural defects, and encourages rapid re-mucosalisation of the ventral skull base. The introduction of the NSF reduced CSF leak rates

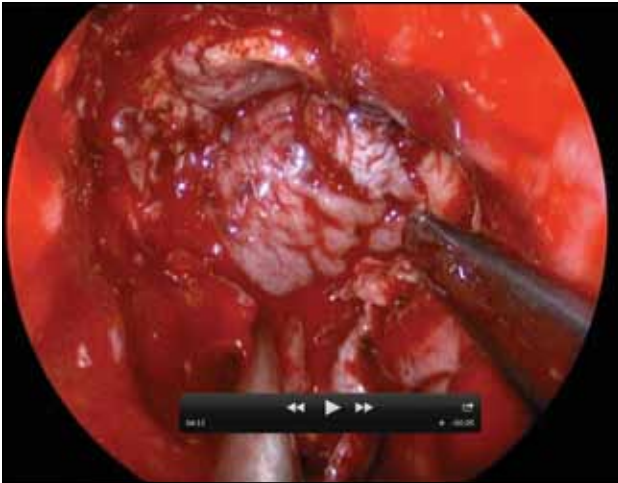


Figure 1: A nasoseptal flap being inset into the ventral skullbase for reconstruction.

dramatically, and was in many ways the innovation that transformed EEA surgery from a novel but risky procedure to a reproducible, safe, and widely adoptable surgical strategy. A later modification allowed for reconstruction of the denuded anterior septum left behind by the elevation of the NSF with an anteriorly based reverse flap, raised from the contralateral side⁵ (Figure 2).

Not all EEA cases require a NSF, and many practitioners continue to use non-vascularized reconstructions in simple cases at low risk for CSF leak. The NSF can be recycled for revision cases; it can be raised off the ventral skull base prior to tumour re-resection, and returned to its position covering the skull base after completion of the surgery⁶. For cases in which the NSF is already used, or is unavailable for another reason (e.g. tumour invading the pedicle of the flap posteriorly), a multitude of other flap options exist⁷, including a flap harvested from the lateral

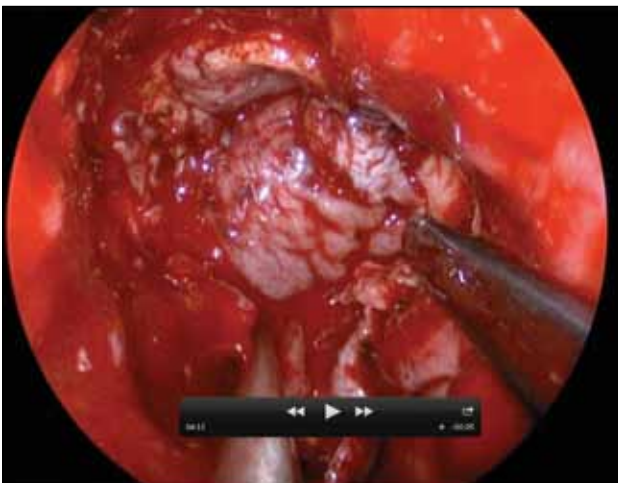


Figure 2: The “reverse flap” being rotated into position covering the denuded anterior septum.

nasal wall⁸, a pedicled pericranial flap⁹, a pedicled temporo-parietal flap transferred into the skull base¹⁰, turbinate flaps¹¹, a pedicled buccinator flap¹², or even free flaps transferred into the skull base. In addition, some surgeons use a “rescue flap”, in which they design mucosal incisions at the posterior septum to allow for the development of a nasoseptal flap if and only if the case requires it, while using more simple reconstructive techniques in cases at low risk for CSF leak^{13,14}. This technique can allow for less resection of the posterior nasal septum; it has been suggested that this would result in a reduction in nasal morbidity, including anosmia, epistaxis, and crusting. Other modifications to the basic technique of EEA have been described. These include preservation of the middle turbinate¹⁵, and mucosal sparing techniques within the sphenoid and ventral skull base.

Indications and Uses

EEA surgery was first applied routinely to lesions in the sella turcica. For these lesions, a wide sphenoidotomy is performed, and the bone overlying the sella is drilled away (Figure 3, 4). Anatomic descriptions were key to developing the surgical approaches for pituitary lesions, and included the landmarks for the carotids laterally, the optic chiasm and nerves superiorly, and the clivus inferiorly. Piecemeal dissection and removal of pituitary tumours was the norm; recently, en bloc resection of the pituitary through EEA has been described and is becoming more common (Figure 5). Endoscopic management of pituitary tumours has in many centers around the world supplanted traditional microsurgical techniques, largely because of the superior visualization afforded by modern endoscopes and high-resolution video processing. Many centers have published large surgical volumes for these tumours with low rates of morbidity and mortality. Goudakos et al in 2011 published a meta-analysis and systematic review of endoscopic vs.

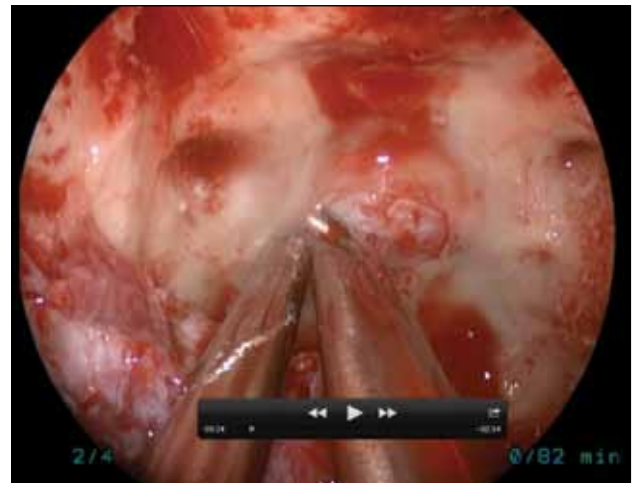


Figure 3: Bone removal over the sella turcica after wide sphenoidectomy.

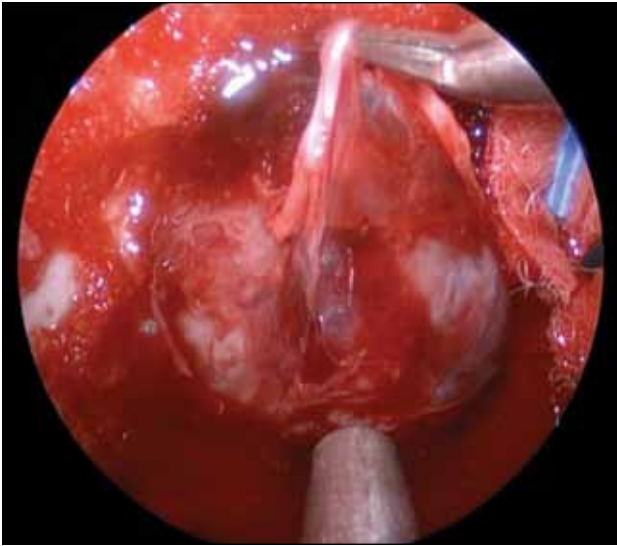


Figure 4: Exposure of the pituitary tumour.

microscopic trans-sphenoidal removal of pituitary tumours¹⁶. They described similar rates of remission of hypersecretion, gross total removal of tumour, and CSF leaks, while showing that EEA had reduced hospital stays. In addition, the incidence of surgical morbidity was much lower in the EEA group (1.2% vs. 13% in the microsurgery group), as was the incidence of post-operative diabetes insipidus (15% vs. 28%).

Tumours in the suprasellar region, including meningiomas and craniopharyngiomas, have been addressed through EEA as well. Craniopharyngiomas are benign tumours arising from embryological squamous cell rests of the craniopharyngeal duct. Surgery is the mainstay of treatment of these tumours; this represents a significant surgical challenge, because of their location adjacent to many vital intracranial structures. The transcranial route to remove these

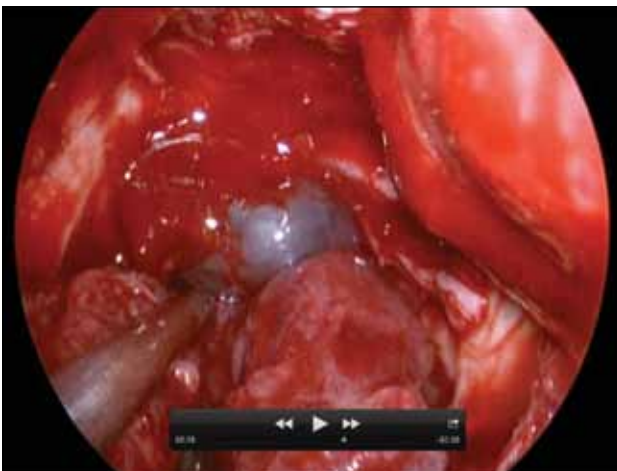


Figure 5: En bloc resection of pituitary tumour, with intact diaphragma sellae.

tumours was limited by the need to transgress cranial nerves and vascular structures as the tumour is accessed from a subfrontal or lateral approach¹⁷. EEA offers direct access and visualization of these tumours, and has become the preferred route of access for many centers. In 2012 Komatar et al¹⁸ published a systematic review of the results of EEA for these lesions, showing significantly greater rates of gross total resection (67% vs. 43%) and visual preservation (56% vs. 33%) compared to intracranial resection. CSF leak rates were higher with EEA (18% vs. 3%), but seizures were only seen in the intracranial cohort (0% vs. 9%). The classification of craniopharyngiomas based on their relationship with the stalk – infundibulum axis has enhanced the surgical planning for these lesions. The resection of craniopharyngiomas was also made significantly less morbid by the introduction of the pituitary transposition technique, where the pituitary gland can be elevated, pedicled on its blood supply, and moved out of the way of the suprasellar surgical resection, only to be returned to its normal position with intact function after the resection is complete¹⁹. In addition to craniopharyngiomas, suprasellar meningiomas have been successfully addressed with EEA as well²⁰.

EEA has also been applied to lesions in the clivus, and has been used to perform clival resection to access lesions posterior to the clivus, such as in the foramen magnum or even the brainstem. Chordomas and chondrosarcomas represent the most common lesions within the clivus itself, while meningiomas and haemangiomas are most commonly approached using EEA after clival resection. In 2009 Stippler et al²¹ published a series of 20 clival chordomas, and noted that a further 26 cases had been reported in the literature to that date. Since then, multiple authors have published series of clival chordomas successfully treated with EEA with low complication rates²²⁻²⁴. EEA has become an extremely common method of treating sinonasal malignancies, including those lesions that transgress the cranial base. In many cases EEA represents a minimally invasive alternative to traditional anterior craniofacial resection. EEA affords excellent visualization of the ethmoids and frontal sinuses, and through a systematic approach can be extended to visualize the cribriform plate and anterior cranial base. This usually requires a Draf 2 or Draf 3 frontal sinusotomy, wide anterior and posterior ethmoidectomies, and control of the anterior and posterior ethmoid arteries. The lamina papyracea can be resected if needed, and a subcranial resection of the cribriform and anterior skull base can be performed using endoscopic visualization. Resection of the anterior fossa dura and even limited brain resection can be accomplished through this technique.

Carrau et al described the contraindications to resection of sinonasal and anterior skull base malignancies; these include extension lateral to the mid-orbital line, skin

invasion, maxillary invasion requiring a total maxillectomy, and orbital invasion requiring orbital exenteration²⁵. Reconstruction after endoscopic anterior craniofacial resection is critical, and can include the nasoseptal flap, lateral vault flap, or pericranial flaps. Comparison of outcomes for sinonasal and anterior skull base malignancies between EEA and traditional open skull base surgery is difficult, because of the wide variability in histology and the inevitability of selection bias. However, Devaiah et al²⁶ in a systematic review of published articles on esthesioneuroblastoma (olfactory neuroblastoma) found a higher survival rate in the EEA cohort compared with traditional open skull base surgery. At present there are no large trials showing inferiority of EEA for these tumours.

In addition to anterior skull base malignancies, EEA techniques have been applied to the surgical management of nasopharyngeal cancer (NPC) as well. Of course, radiation therapy (or, more commonly, chemoradiation therapy) remains the primary treatment for NPC. Recurrent NPC has traditionally been treated with facial disassembly techniques, including the maxillary swing. EEA offers access to the nasopharynx, and the ability to resect any lateral extension of the NPC that remains medial to the carotid artery. Results of endoscopic nasopharyngectomy and, if necessary, re-irradiation with intensity modulated radiotherapy have been promising in comparison to re-irradiation alone²⁷. Many lesions of the orbit can be treated with EEA. EEA, after a wide sphenoidotomy, affords excellent access to the optic nerve canals as they approach the orbital apex. In some cases of Graves' disease optic nerve decompression is necessary for resolution of symptoms, even after orbital decompression (done either endoscopically or through open approaches)²⁸. EEA allows for removal of the bone over the optic nerve in a minimally invasive fashion.

This may also be of benefit in cases of intracranial hypertension, with fenestration of the optic nerve sheath if necessary²⁹. In addition, tumours in the medial orbit can be addressed through EEA, by surgical removal of the lamina papyracea, and if necessary the medial orbital floor. Access to these lesions can often be facilitated by the detachment of the extra-ocular muscles; sometimes tension on specific muscles can exert pressure on these orbital tumours and present them more readily to the dissecting surgeon³⁰.

A variety of benign and malignant tumours can arise in the pterygo-palatine and/or infratemporal fossa, and are quite amenable to resection or debulking via EEA as well. Pathologies in the pterygo-palatine or infratemporal fossa include schwannomas, juvenile nasopharyngeal

angiofibromas, meningiomas, salivary gland malignancies, rhabdomyosarcomas, and lymphomas. The endoscopic anatomy of the pterygo-palatine and infratemporal fossae has been well described³¹, and trans-ptyergoid approaches (which involve endoscopic resection of the medial maxillary wall and drilling of the pterygoid wedge) allow wide visualization of the vascular and neural structures in the medial infratemporal fossa and pterygo-palatine fossa, even including access to the foramen ovale, foramen rotundum, or Meckel's cave³².

Resection of the odontoid process may be indicated in cases of spinal cord compression by the odontoid. Rheumatoid arthritis (with arthritic pannus) and basilar invagination (a craniocervical malformation) are the most common indications for odontoid resection. Traditionally, the odontoid was removed transorally, usually with a palatal split. EEA offers a direct approach to the odontoid without the need for palatal splitting or retraction, and has been performed with acceptable morbidity³³. Lastly, EEA has been used to provide drainage of petrous apex granulomas; the access that EEA affords has been useful to drain these lesions, and to insert splints to maintain patency for the site of drainage³⁴.

Results and Complications

The morbidity of EEA in large series has been quite acceptable. Kassam et al in a review of the first 800 cases at University of Pittsburgh Medical Center identified a CSF leak rate of 15.9%³⁵. They noted a rate of transient neurological deficits of 2.5%, with permanent neurological deficits in 1.8%. Intracranial infection, a principal concern of early opponents of this procedure, was only identified in 1.6%, while post-operative mortality occurred in 0.9% of patients. It is important to note that the above-mentioned CSF leak rate included the period before the adoption of vascularized skull base reconstruction; a subsequent series published using the NSF on 150 consecutive patients, collected prospectively, showed a reduction in CSF leak rates to 4.0%.

Recent studies have looked at quality of life indicators after EEA; these appear to be superior to those of patients undergoing transcranial approaches to the skull base. Gil et al examined patients undergoing the subcranial approach to the anterior skull base, and found (on a 1-5 scale) a significant drop in QOL overall scores, with a best mean score of 2.81 found 6-24 months after surgery³⁶. Pant et al did a similar analysis with EEA patients, and found a mean QOL score of 3.4 at 1-3 months and 4.3 at 3-6 months after surgery³⁷. Other authors have found similar results^{38,39}. Kirkman in a recent systematic review found that, for anterior skull base tumours, quality of life indicators

dropped less and returned to normal more quickly for endoscopic skull base resections compared to open⁴⁰.

Conclusions

EEA is now a reproducible, minimally invasive surgical strategy for a wide variety of benign and malignant tumours of the skull base. Surgical teams around the world have expanded the anatomic areas amenable to EEA, and have demonstrated its efficacy and safety. It is now fully integrated into the surgical armamentarium for skull base tumours.

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Improving outcomes in endoscopic sinus surgery

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Abstract

Endoscopic sinus surgery is often performed for patients with chronic rhinosinusitis with persistent symptoms despite a trial of maximum medical therapy. Data collected in the UK Audit of Surgery for Chronic Rhinosinusitis¹ shows that this achieves large improvements in mean SNOT22 scores across patient groups. However, at an individual level 30% of patients rated the results of surgery as only fair or poor at 12 months, and nearly 1 in 5 patients had undergone revision surgery by 5 years. This review will focus on how to optimise results from endoscopic sinus surgery.

Key words

Endoscopic sinus surgery, improving outcomes.

J ENT Masterclass 2014; 7 (1): 92 - 97.

Patient Selection

The correct diagnosis and patient selection is paramount to the success of surgery. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) provides a clear diagnostic definition, based in symptoms but supported by positive findings on either endoscopy or CT (figure 1)².

The importance of having supporting findings is demonstrated by a study where patients meeting the symptomatic definition for CRS (chronic rhinosinusitis) underwent same day CT and endoscopic examination³. This study found that 50% of patients had both normal endoscopy and CT imaging, and found the sensitivity of a symptom-based definition alone to be 89%, but with a specificity of 12%. Therefore using symptoms alone, we are likely to be over-diagnosing CRS in as many as half of our patients – these patients with rhinitis and facial pain should not normally considered for sinus surgery.

Nonetheless, the wide variation in surgical intervention rates (Fig 2a), and data from the UK audit suggests that

patient selection could be improved. Nearly 100 patients having surgery in the Audit had symptoms considered within the normal range (Fig 2b, <9.2 on SNOT-22), and perhaps more importantly 1 in 4 patients with CRS without polyps having sinus surgery for CRS had scans with Lund-Mackay scores considered to be in the normal range (Fig 2c, <4.3 on LM⁴). More careful pre-operative selection will avoid unnecessary surgery, exposing patients to risks of intracranial and intraorbital complications, and should improve results.

It can be difficult to manage patients who strongly believe their post nasal drip or facial pain to be sinogenic despite normal CT and endoscopy. However, it is better to spend time discussing the findings and reviewing the CT with the patient than taking the easier option of simply listing for surgery. Unfortunately, simply demonstrating normal test results is often inadequate, and an explanation to the underlying cause, and alternative treatment options are usually required⁵.

Figure 1: Definition of Chronic Rhinosinusitis (EPOS guidelines)

<ul style="list-style-type: none"> • Inflammation of the nose and paranasal sinuses
<ul style="list-style-type: none"> • Characterised by two or more symptoms: <ul style="list-style-type: none"> • One must be either nasal blockage/ obstruction/ congestion or nasal discharge (anterior or posterior nasal drip) • ± facial pain/ pressure • ± reduction or loss of smell
<ul style="list-style-type: none"> • And either endoscopic signs: <ul style="list-style-type: none"> • Polyps and/ or • Mucopurulent discharge primarily from middle meatus and/ or • Oedema/ mucosal obstruction primarily in middle meatus
<ul style="list-style-type: none"> • And/ or CT changes: <ul style="list-style-type: none"> • Mucosal changes within the osteomeatal complex and/ or sinuses

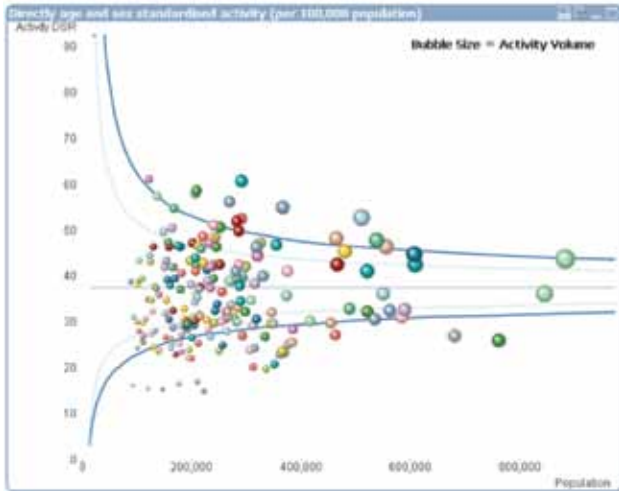


Figure 2a: Standardised activity per 100,000 population for endoscopic sinus surgery by PCT in 2012.

Consider secondary CRS and exclude malignancy

Any patient with unilateral polyps on endoscopy should be investigated urgently – if CT confirms unilateral disease urgent histological examination to exclude malignancy should be performed. For unilateral CRSsNP (chronic rhinosinusitis without nasal polyps), particularly with cacosmia, odontogenic CRS should be considered. The incidence appears to be rising, with up to 40% of cases of CRS proposed to be of dental origin in some series^{6,7}. CT scans will often reveal periapical lucency or retained roots, and concurrent dental care is usually required (fig 3) routinely.

CRS can be secondary to inflammatory diseases that affect the mucosa, such as Wegener’s granulomatosis, sarcoidosis, and Churg-Strauss syndrome. Particular attention to characteristic autoimmune symptoms (renal and joint problems, diffuse symptoms, fatigue in association with nasal crusting and recalcitrant sinusitis) by thorough history and examination is important.

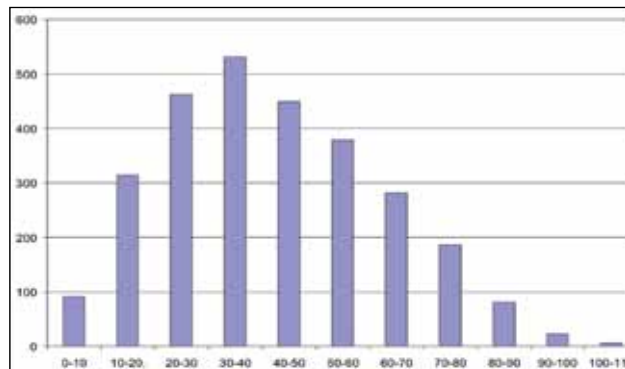


Figure 2b: Preoperative SNOT-22 scores for 3,128 patients undergoing surgery for CRS in the National Audit of Surgery for Chronic Rhinosinusitis and Nasal Polyps.

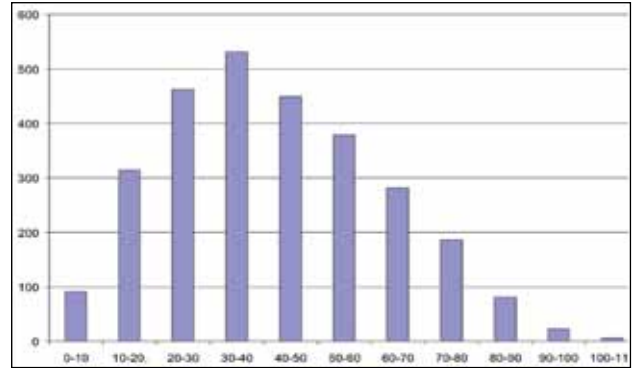


Figure 2c: Lund-Mackay scores of patients with CRSsNP undergoing sinus surgery in the National Audit of Surgery for Chronic Rhinosinusitis and Nasal Polyps.

However, as the nose is often the first site of presentation of these conditions, they should be considered in the absence of a classic presentation. In selective cases, screening with a full blood count, total IgE, CRS, ESR, common auto-antibodies including ANCA and serum angiotensin converting enzymes is beneficial.

Immunodeficiency should be considered when there is a history of repeated upper and lower respiratory infections since childhood, skin sepsis, recurrent herpes, thrush or warts, or chronic diarrhea. Often the diagnosis is made only when CRS is refractory to normal treatment. IgG subclass levels are significantly lower in the CRS population than in matched control groups, and some case reports have suggested benefit from treatment with IVIG (intravenous immunoglobulin therapy)^{8,9}. However, larger cohort studies have shown no clinical difference in symptom severity, both before and after medical and surgical treatment, indicating questionable relevance^{10,11}. IgG deficiency is most common, and results in recurrent



Figure 3: Odontogenic CRS – periapical lucency visible in setting of unilateral CRSsNP.

upper respiratory tract infections, while IgG3 and IgG4 deficiencies are less likely to be clinically important. In cases of recurrent upper and lower airway infection it is prudent to assess for immunodeficiency, measuring IgA, IgG and IgM levels. In some cases, the ability to mount a functional response to vaccination with protein antigens is also useful – Specific antibody deficiency is defined by a dysfunctional response despite normal serum concentrations of IgG, A and M.

Set realistic patient expectations

Particularly in CRSwNP (chronic rhinosinusitis with nasal polyps), surgery is unlikely to be a ‘quick fix’ but is an adjunct to ongoing medical care by allowing better access to topical therapy. Most patients will notice a clinically significant improvement in their symptoms, but will not achieve complete resolution of symptoms (Fig 4). 1 in 5 are likely to undergo further surgery within 5 years. It is therefore essential to counsel patients accordingly, as those expecting a ‘cure’ of their CRS are likely to be disappointed. Patients who have already had previous surgery, those with aspirin sensitivity and nasal polyps (Samter’s triad) and those with extensive osteoneogenesis are at higher risk of a poor outcome and requiring further surgery.

Pre-operative medication

Meta-analysis suggests a statistically significant benefit of preoperative steroids on intraoperative blood loss when compared with placebo. However, the difference in blood loss was 28ml, and therefore this may not be considered sufficiently clinically significant to justify routine use in all patients. Although the studies do not allow sub-group comparison, it is likely to be most beneficial in patients with extensive nasal polyps.

Patients should be encouraged to stop smoking at least three weeks before surgery.

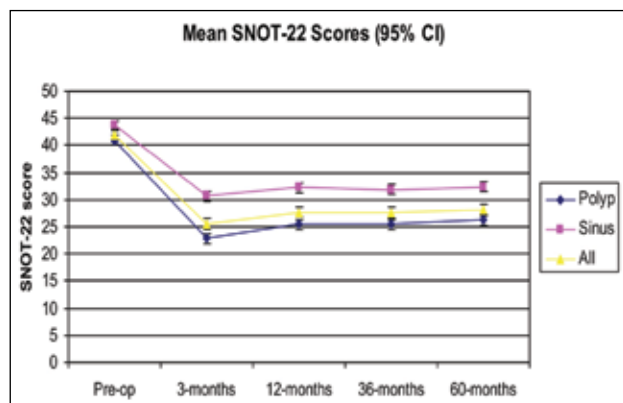


Figure 4: Changes over time in mean SNOT-22 scores 3,128 patients undergoing surgery for CRS in the National Audit of Surgery for Chronic Rhinosinusitis and Nasal polyps.

Aspirin irreversibly inhibits the enzyme cyclooxygenase which is essential for platelet function. The effects persist for the duration of the platelet lifespan, which is for 7 – 10 days. Patients must therefore stop aspirin, and avoid other NSAIDs for 10 days before surgery. Clopidogrel has an irreversible effect on platelet aggregation, and should also be stopped 10 days before surgery. It is a more potent antiplatelet drug, with often more specific indications, such as after cardiac stenting, and cessation should only be advised after consultation with a cardiologist.

A number of herbal remedies and dietary supplements have an anticoagulant action, including garlic, ginko, and ginseng. Patients often omit these when asked about medication usage, and supplement consumption should be specifically questioned.

Anaesthesia

Some surgeons strongly advocate use of Total Intravenous anaesthesia (TIVA) in order to achieve a better surgical field¹², and a recent meta-analysis has supported this with a mean reduction of 75ml of intraoperative blood loss compared with inhalational techniques¹³. The most important issue is to achieve mild hypotensive anaesthesia in the absence of rebound tachycardia or use of vasodilators. We aim for a mean arterial pressure of 75mmHg, and a heart rate of 60 bpm in a patient with no predisposing cardiovascular comorbidity. Reinforced flexible laryngeal mask airways have been shown to be safe for use in ESS, and have a favourable effect on the operative field compared with endotracheal tubes. The use of a throat pack does not reduce the incidence of postoperative nausea and vomiting, but causes throat pain¹⁴. If there is a concern about contamination of the throat pack may be avoided by placing a truncated merocel in the post-nasal space¹⁵. Inadvertent intraoperative hypothermia is common¹⁶. It should be avoided by the use of warming blankets in order to avoid increased intraoperative blood loss, postoperative infection and cardiovascular events.

Topical preparations to minimise intraoperative blood loss vary significantly between units. Where cocaine is used on it’s own, or as part of a modified Moffet’s solution, the risks of cardiac toxicity should be considered and attention paid to the maximum dosage which can be applied to the nasal mucosa of 1.5mg/kg. Adrenaline may be applied topically at 1 in 1000 concentrations on neuropathies or ribbon gauze without significant systemic effect.

The patient should be placed in a reverse Trendelenberg position, with the eyes exposed but corneas protected using simple eye ointment. Pupils should be inspected at the start of the procedure, to allow reassessment of the pupillary reflex in the event of an orbital complication.

Pre-operative planning

It is essential to have a CT scan available during ESS. This should ideally be tri-planar, allowing a 3D reconstruction to be visualised.

Anatomical variations, which may increase the risk of complications during surgery, may be identified using CLOSE inspection (Fig 5). For example, asymmetry in the depth of the cribriform niche, dehiscence in the lamina papyrcea, an anterior ethmoid artery exposed in a suprabullar recess or the presence of a posterior sphenoidal (formerly Onodi) cell may all be identified on the CT.

Perhaps more importantly the scan is used for pre-operative planning of surgery. There is no such thing as a 'standard FESS' and surgery should be tailored according to the extent of disease on the CT scan. 3D reconstruction of the scans using the building block technique described by Wormald¹⁷ facilitates an understanding of the drainage of the frontal sinus and the ethmoid air cells.

Surgical Technique

There is a wide range of surgical instruments available, and the surgeon should use what works best in their hands. Randomised trials have failed to identify any benefit in terms of symptomatic outcomes of using powered instrumentation¹⁸ but operative time was reduced. The combination of suction to maintain the operative field while allowing precise resection of polyps and soft tissue is ideally suited to the principles of ESS. However, complications when using microdebriders can be catastrophic due to the ability of the debrider to draw soft tissue into the blades – in the orbit this can result in irrevocable damage to the medial rectus or optic nerve. Similarly, balloon technology has been shown to be non-inferior to conventional instruments in terms of outcome¹⁹, but has some advantages in terms of recovery and need for post-operative debridement which must be considered against the disposable costs.

A meta-analysis of the impact of image-guided sinus surgery found no benefit in terms of ability to complete the operation or revision surgery, but did find the risk of major complications was reduced²⁰. This is a valuable tool

in selected cases, particularly in revision cases when landmarks are absent.

Surgery should normally commence with a straight endoscope, but angled scopes (30 or 45 degree) are invaluable when operating in the maxillary and frontal sinuses. It should proceed in a stepwise manner on one side of the nose, while topical vasoconstriction is applied to the other nasal cavity on neuropathies.

Surgery usually begins with removal of nasal polyps, where present. These should be sent for histological examination. In the case of unilateral polyps, known inverting papilloma, or friable polyps, the entire specimen should be sent. The next step is uncinectomy, exposure and sometimes enlargement of the maxillary ostium. The CT scan should be examined with regard to a lateralised uncinete which may increase the risk of orbital penetration – in such cases a retrograde approach is safer. Retained uncinete and accessory ostia are amongst the most common features identified in revision ESS^{21, 22}, and ensuring these first steps are performed correctly is vital. Examination with a 30 degree scope and palpation with a ball probe will allow complete removal of the uncinete and visualisation of the natural ostium. If the ostium is patent, it need not be enlarged in every case. However, if the aim of surgery is to permit post-operative access to medical therapy, cadaveric studies suggest that a healed ostium of at least 4mm is required to allow irrigation fluid to penetrate into the maxillary sinus²³.

Ethmoidectomy is performed according to the extent of mucosal disease on pre-operative CT, and according to the aims of surgery; more complete removal of bony partitions will allow better post-operative access to topical therapies. The lateral lamella of the cribriform niche is a common site for iatrogenic CSF leakage, while the lamina papyrcea must be avoided laterally – however, identifying the position of the lamina and skull base allows a safe outside-in approach. The use of through cutting or powered instruments facilitates removal of bony partitions. The orbital floor, or roof of the maxillary sinus, is a reliable landmark as dissection progresses posteriorly, as it is always lower than the roof of the sphenoid sinus and lowest point of the cribriform niche. The skull base usually slopes downwards, and therefore back to front dissection along the skull base once this has been identified in the sphenoid reduces the risk of intracranial penetration. Approaching the sphenoid through the sphenoidal recess, through its natural ostium, is the safest approach to the sphenoid and minimises the risk of optic nerve injury if a sphenoidal cell is missed on the pre-operative CT scan.

Figure 5: CLOSE Inspection CT checklist

• C Cribriform niche depth & symmetry, Carotid dehiscence
• L Lamina papyrcea, Lateralisation of uncinete onto orbit
• O Sphenoidal (Onodi) cell, optic nerve dehiscence
• S Sphenoid sinus, Skull base dehiscence
• E Ethmoid arteries, Extent of disease

Frontal sinus surgery, if required, may be performed at the start of surgery, with the intact face of the ethmoid bulla defining the posterior limit of the frontal recess and protecting the anterior ethmoid artery. Alternatively, it is often the last stage in surgery. Angled scopes and specialised instruments are essential. The key to frontal sinus surgery is the identification of the agger nasi cell, and removal of the roof – ‘uncapping the egg’. This is incomplete in 73% of revision frontal sinus surgeries²².

A full discussion of the operative techniques performed during ESS is beyond the scope of this article. Cadaveric training on dedicated courses is extremely useful in refining surgical technique. Meticulous technique, with mucosal preservation, is key to successful surgery. Excessive stripping of mucosa is likely to lead to neo-osteogenesis, which is a poor prognostic sign.

Nasal Packing

Removable nasal packing increases mucosal trauma and post-operative discomfort, and can lead to foreign body reactions. It is not necessary in the majority of ESS cases and should only be used if adequate haemostasis has not been achieved intraoperatively^{24,25}. Absorbable nasal dressings have been suggested to hinder adhesion formation and aid haemostasis but review of the available randomised controlled trials shows no advantage over not packing²⁶.

Role of histological examination

Standard histological reporting on nasal polyps and mucosal biopsy following ESS does little more than exclude malignancy. However, the identification of eosinophilic CRS (defined by more than 10 eosinophils per high powered field)²⁷ is important to predict those at increased risk of post-operative recurrence, and where long-term post-operative medical care can be targeted.

Post-operative care

Post-operative debridement is frequently performed in the US following FESS, but may be impractical within the constraints of the NHS. Debridement involves removing the nasal crusting and secretions, and is usually well tolerated. A recent systematic review identified RCTs, 4 comparing debridement versus no debridement and 2 comparing debridement with increased frequency of debridement. Of the first four studies, 2 showed no benefit and two only showed some benefit in nasal congestion²⁸.

Budesonide nasal irrigations have been shown to give significantly improved SNOT 20 and endoscopy scores post-operatively when compared with no steroid use.



Figure 6: Poor post-operative result; radical turbinectomy with inferior meatal antrostomy and septal perforation, heavy purulence and recurrent polyps.

As budesonide is delivered through a high pressure and high volume system, it is able deliver irrigation to the sinuses effectively²⁹.

A recent meta-analysis reviewed the use of intranasal corticosteroid use post-operatively in patients with CRSwNP. It showed a significant improvement in post-operative symptoms and polyp score, and a decrease in polyp recurrence³⁰ (Figure 6).

When you still get a poor result

Check patient compliance with medical therapy carefully, and reconsider the possibility of secondary CRS. Examine the nose carefully for evidence of recirculation of mucus, synechiae or incomplete surgery.

Biofilms have been implicated in CRS, with a recent study showing a prevalence of 71%³¹. They consist of bacteria within an extracellular matrix and do not respond as well to conventional treatment and are therefore associated with more severe disease. Post-operative outcomes are adversely affected, with a persistence of CRS symptoms and a higher rate of antibiotic courses when compared with biofilm negative patients. Current research is being directed at exploring antibiofilm treatments and their efficacy³². Johnson’s Baby Shampoo may be added to saline irrigation in an attempt to disrupt biofilms, and the addition of mupirocin to the lavage may directly target ongoing infection.

Conclusions

Careful diagnosis and patient selection, meticulous surgical technique and ongoing medical management are key to a successful outcome from endoscopic sinus surgery. Despite this some patients will still have a disappointing result due to unfavorable host responses.

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Lumbar spinal drainage in otolaryngology

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Key words

key words

J ENT Masterclass 2014; 7 (1): 98 - 102.

Introduction

First described by Vouch in the 1960s, continuous cerebrospinal fluid (CSF) drainage is carried out using a fine bore catheter inserted transcutaneously into the lumbar subarachnoid space¹. Approximately half a litre of CSF is produced by the choroid plexus of the ventricles and by capillary filtration daily and reabsorbed at a rate of 10 to 15ml per hour via the arachnoid villi. This leaves approximately 150 ml in the ventricles and subarachnoid space which results in a normal CSF pressure of 5-10 mm Hg. In order to reduce the CSF pressure to 0 mm Hg, the ideal volume of CSF to be drained is 10 to 15ml per hour.

CSF leak may be secondary to traumatic or iatrogenic dural tear. Spontaneous CSF leaks also occur and are more likely in patients with a background raised intracranial pressure (ICP). The first steps in the management algorithm of a CSF leak are bed rest, positioning of patient with head of bed elevation and use of stool softeners to reduce ICP. If these measures fail, more invasive techniques can be used and include controlled external CSF drainage and surgical repair. Early insertion of lumbar spinal drains has been described by multiple authors in order to facilitate wound closure^{2,3}, particularly in procedures that involve the dura of the skull base.

The role of lumbar spinal drains has not been defined in the literature, with similar results achieved with or without

LSD⁴⁻⁷. Because of a lack of familiarity of the technique, it is less likely to be used in ENT routinely but we have found it a useful technique in our centre. We describe our practice which involves input from Neuroanaesthetists and Neurosurgical colleagues.

Insertion of lumbar spinal drain

This is carried out by a neurosurgeon or a neuroanaesthetist prior to or more often immediately post-operatively under sterile technique. The equipment required is shown Figure 1.

- The patient is positioned in the right or left lateral position (similar to a lumbar puncture), with knees tucked up towards the chest.
- A spinal needle is inserted through L4/5 intervertebral space into the sub arachnoid space.



Figure 1: The lumbar drain kit: needle with plastic core, syringe, 16G catheter, connectors, drain bag.

- A lumbar drainage catheter 16G is introduced through the needle to approximately L1/T12 where it is left to float in CSF.
- The needle is removed and the catheter attached to a closed sterile CSF collection system or drainage bag via a 3-way tap open to the patient.
- The catheter is secured by a clear occlusive dressing e.g. a large tegaderm dressing, ensuring there is no kink. The dressing edge is double secured with adhesive tape.

The 'zero' reference point is the surgical wound site, thus the drainage bag should be positioned at the ear/skull base height with the patient lying flat and adjusted to wound height when he/she stands up (Figure 2). Calibration is important if CSF pressure is being monitored, which is not usually carried out on Otolaryngology patients.

Figure 2(b). Position of 'zero' reference point whilst patient is standing up.

Management

CSF flows into the drainage bag by gravity. The amount of CSF drained depends on the height of the drain and the position of the patient/degree of head elevation. Initially the collection drain is sited at wound level or to the level at which it will drain CSF. The vertical height of the drain can be adjusted to achieve the desired output per hour as dictated in the operative notes. The lower the drain height, the greater is the expected CSF output.

Drain-specific instructions

- Patient position e.g. bed rest, lying flat or with slight head elevation
- Amount of CSF to be drained per hour (usually 10-15ml/hour)



Figure 2(a): Position of 'zero' reference point whilst patient is lying semi-recumbent. **2(b).** Position of 'zero' reference point whilst patient is standing up.

- Avoid strong opiate analgesia and sedatives which may mask changes in neurological status

General Care

- Use universal precautions and maintain aseptic technique at all times.
- Instruct patient to ask nurse for help with position change in order to prevent disconnection, over or under-drainage. When changing patient position, clamp the drain and place at appropriate height.
- General observations including temperature, every 4 hours.
- Monitor detailed neurological status (using the Glasgow Coma Scale).
- Record the drain height and volume of CSF every hour.
- Monitor CSF colour (colourless, blood-stained) and clarity (clear, cloudy) as in Figure 3.
- Monitor the condition of lumbar spinal catheter dressing.
- The drainage bag should be changed daily by clamping the drain and closing the 3-way bag to the patient.
- Daily CSF sampling by qualified nurse or medical practitioner.
- Monitor white cell count and C-reactive protein levels every 2 days.
- Call Neurosurgical team if any change.



Figure 3(a): clear (normal) CSF, **(b)** Blood stained CSF.

Complications

Patients with lumbar spinal drain in situ should be closely monitored for potential complications. It is common to have some discomfort at the drain insertion site. Minor complications reported in the literature include subjective low pressure headache especially on sitting up, nausea and vomiting, reported in 59% of Roland's cohort⁸. Inherent major risks of lumbar spinal drains include pneumocephalus, meningitis, and cerebral herniation^{8,9} which may prolong the hospital stay by 3 to 7 days¹⁰.

Overdrainage (typically > 20/30ml/hr)

Overdrainage may occur if the drainage bag is placed too low or its height is not adjusted when the patient sits up or stands up. Normal CSF pressure runs between 5 to 15cm of H₂O. Valsalva manoeuvres such as coughing, sneezing or straining may increase intracranial pressure hence CSF drainage and thus should be avoided. Overdrainage may precipitate serious complications such as pneumocephalus¹¹ (Figure 4), subdural haematoma or brainstem herniation producing impaired neurological status and can be potentially fatal. With a fistulous connection, air can enter the intracranial space in response to a negative pressure gradient (from overdrainage) causing pneumocephalus, or rarely tension pneumocephalus, where the brain is compressed by trapped air¹². This is more common in large anterior skull-base repairs with high pressure from the respiratory tract forcing air intracranially especially with a



Figure 4: Axial CT Brain showing marked pneumocephalus secondary to LSD overdrainage.

bout of coughing. To avoid this problem, a tracheostomy is placed in all of our patients undergoing large anterior skull-base resections. An incidence of 11% of pneumocephalus is reported in Glasscock's series of 80 patients having acoustic neuroma surgery¹³. If suspected, the patient is laid flat or in the Trendelenburg position, the drain is turned off (3-way tap closed to patient), high concentration Oxygen is provided via facemask (to absorb nitrogen from air in the intracranial space), an urgent brain computed tomography (CT) scan and a neurosurgical consult are obtained. Treatment consists of burr hole and tap if significant pneumocephalus.

Under drainage or blockage

A blocked LSD or under drainage may result in CSF leak from any site. Find out whether the patient has a salty taste in the back of their throat and check the nasal cavity (CSF rhinorrhoea), ears (CSF otorrhoea), surgical wound site and drain insertion site. Ensure the drain is not kinked and adjust the height as required (start by lowering the drainage bag). Only a qualified practitioner may attempt to manipulate the catheter to unkink it, to aspirate the catheter or flush the drain tubing. In addition, bedside glucose oxidase stick tests have also been used to distinguish between CSF rhinorrhoea and ordinary respiratory secretions or tears. This has however has been demonstrated to have poor sensitivity¹⁴.

Disconnection

Disconnection can occur if the catheter is not advanced sufficiently at the time of placement. Excessive patient movement may also dislodge it. CSF leakage at the surgical wound site and fluid collection at the lumbar spinal catheter site can provide clues that the catheter is not in the spinal subarachnoid space. The patient is laid flat, the distal end of the catheter is clamped and the exposed ends are covered with a sterile occlusive dressing before organising a replacement catheter, if still required.

Infection

A blocked drain, CSF leakage at the surgical wound site and prolonged duration of CSF drainage are risk factors for bacterial meningitis in this group of patients. A rate of 1.9 to 4.2% of meningitis is reported in the literature^{8,15,16}. The patient may show signs of meningeal irritation (neck stiffness, headache) and pyrexia. A CSF sample, taken by a qualified practitioner, should be sent for urgent gram stain, microscopy, culture and sensitivity. The patient is treated with antibiotics as per local microbiology guidelines +/- removal of the lumbar spinal catheter. Cephalosporins offering broad coverage with excellent spinal fluid penetration, are typically used in our practice following microbiology advice.

Pain

Nerve root irritation by the catheter may result in temporary radicular lower limb pain and paraesthesia. Pain not relieved by analgesia or change of patient position may respond to slight withdrawal of the catheter.

Other rare major complications reported in the literature include unilateral occlusion of posterior cerebral artery and unilateral vocal cord paralysis. These complications were reversed following cessation of lumbar drainage⁸.

Lumbar spinal drain removal

The lumbar drain is usually left in situ for 4-5 day¹⁷. It is usually removed by the nursing staff using aseptic technique with the patient in the right or left lateral position. The adhesive tape to the lower back is removed, the fine bore catheter is eased out and a clear occlusive pressure dressing is applied.

Care post catheter removal

- Keep patient flat for 1-2 hours
- Check for CSF leak from surgical wound site, CSF otorrhoea or rhinorrhoea and at LSD insertion site
- Gradually increase activity level
- Monitor for headaches and neurological status
- If there is persistent leakage of CSF from the lumbar catheter site, a suture is inserted with an overlying pressure dressing

Discussion

The management of a lumbar drain is generally regarded by Otolaryngology nurses and medical staff with unease, mainly due to unfamiliarity with these drains. In the West of Scotland, all patients who require a lumbar drain are transferred to the regional Neurosurgical unit for drain management. Although in most institutions, Otolaryngologists do not look after lumbar drains, we need to be familiar with their use in order to consent patients appropriately and also to trouble shoot in case a neurosurgical colleague is not available immediately to review patients with such drains. A general guide to the management of lumbar drains is provided in this paper.

The main Otolaryngology indication for using lumbar spinal drains is to divert CSF from a dural fistula or an area of dural repair in order to reduce CSF pressure, thus allowing time for the fistula or surgical repair to heal. The aim is to drain 10 to 15 ml of CSF per hour to maintain a CSF gradient of 0 mm Hg over 5 days (range 3-7 days)

depending on indication for insertion¹⁸. Several techniques of reducing CSF pressure by controlled drainage are reported in the English literature. In our unit, the standard technique of gravity CSF continuous drainage system is used¹⁹. The 3 way tap can also be opened every hour to release a pre-determined volume of CSF¹⁵. The third technique reported is CSF drainage at a set rate through a flow-regulated drainage pump²⁰⁻²² which allegedly reduces the rate of infection as there is less manual manipulation of the spinal catheter, better control of flow rate which is less dependent on patient position and less CSF pressure changes occur, although there is no concrete evidence in the literature that it is a superior technique.

Successful use of lumbar drains has been reported in trans-sphenoidal pituitary surgery²³, craniofacial resection requiring large skull base resection²⁴, retrosigmoid or translabyrinthine acoustic neuroma excision, in perilymphatic gusher at stapedotomy or cochleostomy¹⁷ and complications of endoscopic sinus surgery⁷. Early insertion of LSD facilitates wound closure, particularly in procedures that involve the skull base. There is a reported 87% reduction in CSF leak post operatively in patients having excision of acoustic neuromas^{2,3}. A meta-analysis of 25 studies showed an incidence of CSF leak after vestibular schwannoma surgery of 9.5 to 10.6%²⁵. Lumbar spinal drains have been shown to stop CSF leak (rhinorrhoea, incisional and otic) in 78% of post-operative retrosigmoid vestibular schwannoma excision and 57% of translabyrinthine vestibular schwannoma excision²⁶. This systematic review of 25 studies excluded lumbar drains inserted at primary surgery.

In addition, lumbar spinal drains are favoured in patients with high failure rate of CSF repair such as those with high BMI, those with spontaneous CSF leak (likely to have benign raised intracranial pressure), large skull base defects and patients having revision repair of CSF leak to maximise the chance of successful repair²⁷. Ventricular shunts can also be used.

Conclusion

Lumbar spinal drains can be associated with some serious complications, thus should be used judiciously, selectively and tailored to individual patient's requirement. We advocate its use in patients who require large skull base resection e.g. anterior skull base resection in olfactory neuroblastoma; for access in translabyrinthine vestibular schwannoma excision or in well established post-traumatic anterior and lateral skull base CSF leaks.

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Paragangliomas of the head and neck

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Abstract:

Paragangliomas (PGLs) are rare tumours derived from the paraganglia of the autonomic nervous system. An increase in the understanding of their genetic aetiology along with advances in surgical and radiotherapy techniques have increased debate around the optimal management of patients with these tumours, necessitating a multidisciplinary approach. This article aims to provide an overview of the natural history, pathology and the potential management of these lesions, highlighting recent developments and potential future avenues of treatment.

Keywords

Paraganglioma, management, genetics, skull base

J ENT Masterclass 2014; 7 (1): 103 - 108.

Introduction:

Paragangliomas (PGLs) are rare tumours derived from the paraganglia of the autonomic nervous system. An increase in the understanding of their genetic aetiology along with advances in surgical and radiotherapy techniques have increased debate around the optimal management of patients with these tumours, necessitating a multidisciplinary approach. This article aims to provide an overview of the natural history, pathology and the potential management of these lesions, highlighting recent developments and potential future avenues of treatment.

Anatomy, Histology and Function:

Paraganglia (the structures that give rise to paragangliomas) are aggregations of hormone-secreting cells often associated with neural and vascular structures. They appear to have both endo- and paracrine functions in maintaining homeostasis although their exact role remains poorly understood. Paraganglia in the head and neck are associated with the parasympathetic nervous system whereas those in the thoraco-abdominal region are associated with the sympathetic¹ (the largest paraganglial structure is the adrenal medulla).

Paragangliomas are benign neoplasms that form from paraganglial tissue. The commonest sites for paragangliomas in the head and neck region, in order of frequency, are the carotid body, the tympanic cavity (associated with Jacobsen's nerve), the jugular bulb and the vagus nerve. Occasionally, paragangliomas have been identified within the larynx, sinuses, orbits, thyroid and associated with other cranial nerves; specifically the facial and the hypoglossal nerve². Overall these neoplasms are rare, comprising approximately 0.03% of all human tumours³. Their true clinical incidence is difficult to determine but reports range from 1:30,000 to 1:500,000⁴.

Nomenclature:

Currently, the World Health Organisation supported nomenclature of these lesions is based around the associated or presumed structure of origin and the term "paraganglioma"⁵. Examples of this in the head and neck region are the tympanic, jugular, jugulo-tympanic, carotid body or vagal paragangliomas. Historical descriptions of these lesions, referenced within the literature, were based on: histological appearance (glomus), staining characteristics (chromaffin/non-chromaffin) or physiological function (receptoma / chemodectoma)⁶.

Symptoms and Signs:

These depend on the site of the primary lesion. Patients with tympanic or jugulo-tympanic tumours will commonly describe pulsatile tinnitus and/or hearing loss, which on testing may be of a conductive, sensorineural or mixed type. Other symptoms such as vertigo, headache or aural fullness may be reported.

A blue, violaceous mass behind the tympanic membrane can sometimes be viewed although differentials of this include a high jugular bulb or an aberrant carotid artery. Rarely, a tympanic or jugulo-tympanic paraganglioma will erode through the tympanic membrane and will sometimes cause otorrhagia (aural haemorrhage). Other signs include blanching of the mass on pneumatic otoscopy (Browns

sign) and observation of decreased pulsations with carotid compression (Aquino sign)⁷. Auscultation over the mastoid region may reveal a bruit.

In more locally advanced cases, neurological deficits may be seen. Progression into the temporal bone may cause a facial nerve palsy. Compression of cranial nerves IX, X and XI at the jugular foramen may result in Vernet syndrome (dysarthria, dysphagia and shoulder weakness). The addition of Horner syndrome (miosis, ptosis and anhidrosis), suggests compression of the cervical sympathetic chain which constitutes Villaret syndrome⁸.

Carotid paragangliomas often present with a slowly enlarging lateral neck mass. These are pulsatile and non-tender and may be freely moveable in a horizontal plane but not in a vertical plane (Fontaine’s sign)⁹. A carotid bruit may be auscultated. As these enlarge they may project into the lateral oropharynx and in later stages, deficits in cranial nerves VII, IX, X, XI and XII can be seen¹⁰.

Vagal paragangliomas may occur anywhere along the course of the cervical Vagus nerve although they commonly arise from the inferior nodose ganglion. These present in a similar fashion to carotid paragangliomas, with a slowly enlarging neck mass, however they may be located slightly more cranially⁴. Again, progression to involve the jugular foramen may cause lower cranial nerve deficits which must be looked for during clinical examination.

Overall, the incidence of functioning head and neck paragangliomas is low, although approximately 1- 4.5%^{11- 13}

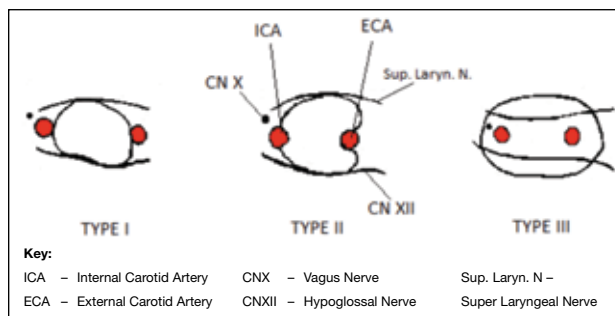


Diagram 1: Shamblin Classification of Carotid Paragangliomas.

may present with catecholamine excess. Symptoms including flushing, diaphoresis, headaches, diarrhoea, palpitations and labile hypertension may occur and should prompt appropriate investigation.

Tumour Classification Systems:

Shamblin Classification:

This system classifies carotid paragangliomas into Type I, II and III (see Diagram 1). Type I tumours are small and can be easily dissected from the carotid vessels in a peri-adventitial plane. Type II tumors are larger and more adherent and may partially surround the vessel. Type III tumors are large and encase the carotid vessels/bifurcation¹⁴.

The Fisch and Mattox staging system is used to classify Jugulo-tympanic paragangliomas and can be seen in Table 1¹⁵.

Table 1: Fisch& Mattox classification of jugulo-tympanic (temporal bone) paraganglioma ^{15,16}	
Class	Characteristics
A	Tumour arising along the tympanic plexus on the promontory of the middle ear. Produces minimal erosion of promontory.
B	Tumour originating in the canalistympanicus of the hypotympanum and invades the middle ear and mastoid. The carotid foramen and canal are intact. These tumours can invade bone, but the cortical bone over the jugular bone is intact.
C	Tumours arise in the dome of the jugular bulb and destroy overlying cortical bone. Spread inferiorly along the jugular vein and lower cranial nerves, posteriorly into the sigmoid sinus, superiorly toward the otic capsule and IAM, laterally to the hypotympanum and middle ear, medially to the jugular foramen and CPA. Sub classification is made on the degree of erosion of the carotid canal: C1 - Erodes carotid foramen but does not invade carotid artery C2 - Destroys the vertical carotid canal between the carotid foramen and carotid bend C3 - Grows along the horizontal portion of the carotid artery but does not reach the foramen lacerum C4 - Grows to the foramen lacerum and along the carotid artery to the cavernous sinus.
D	Tumours that have intracranial extension. These are sub classified below: De Intracranial but extradural De 1 - Displaces posterior fossa dura <2cm De 2 - Displaces posterior fossa dura >2cm Di Intracranial extension with intradural extension Di 1 - Intradural extension <2cm Di 2 - Intradural extension >2cm Di 3 - Intradural extension that makes the tumour unresectable

Genetics

Parangliomas may arise spontaneously, as part of an inherited syndrome or in association with other tumour syndromes that have a predisposition to the development of pheochromocytoma. These include multiple endocrine neoplasia type 2 (MEN 2), von Hippel-lindau disease (vHL) and neurofibromatosis type 1 (NF1)¹⁶.

Overall, approximately 20-40% of paragangliomas are inherited. Recognition that paragangliomas tend to occur clustered within families led researchers in the Netherlands during the 1990's to map a locus of homozygosity to chromosome 11¹⁷. Researchers were then able to sequence the abnormal individual gene, 'SDHD' (succinate-ubiquinone oxidoreductase subunit D). Subsequent, further research has identified other paraganglioma syndromes associated with 'SDHB', 'SDHC' and 'SDHAF'.

Inheritance

All of the SDHx genes are associated with multiple head and neck paragangliomas and are inherited in an autosomal dominant manner.

Of particular note is the fact that SDHD families demonstrate 'genomic imprinting'. This means that while the genotype is transmitted in an autosomal dominant manner from either parent, the phenotype is only manifest if the individual inherits the gene from their father. This can lead to an apparently bland family history where disease is obscured in the family tree because 'silent' genotypes are passed through generations. An example of this can be seen in Diagram 2.

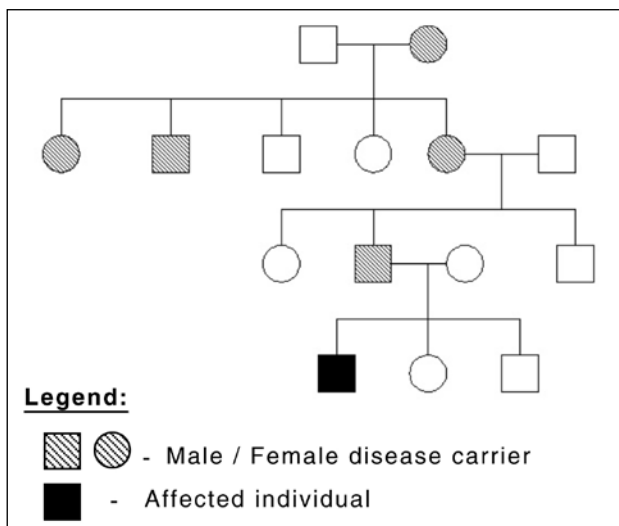


Diagram 2: A sample family tree illustrating how disease can be hidden within families due to maternal imprinting. This diagram was originally published in "Clinical Otolaryngology" and is produced with the permission of the Editor³².

Mechanism of Pathogenesis:

Although the SDHx genes responsible for paraganglioma syndromes are found on different chromosomes (11 and 1), they each form a subunit of a tetrameric protein: 'mitochondrial Complex II' (MCII): a protein that forms part of the electron transport chain in mitochondria. It is postulated that SDHx mutations lead to the generation of a 'pseudohypoxic' state in which a build up of succinate (due to reduced MCII activity) leads to the stabilisation of hypoxia-induced factor (HIF-1 α)¹⁸. This then binds to HIF-1 β which stabilises its structure and these then pass to the nucleus. Here the HIF complex binds to HIF-responsive elements (HRE) which results in transcription of different pathways relevant to tumourigenesis¹⁹. These include up-regulation of vascular endothelial growth factors (VEGF) and Endoglin (ENG) which are critical in angiogenesis. BNIP3 and Cyclin D1 (CCND1), that have roles in cell survival and proliferation respectively, are also up-regulated.

Each of these are potential targets for medical therapy which will be discussed later.

Genetic Counselling and Screening

If a paraganglioma syndrome is suspected, patients should be offered genetic testing in the context of a multidisciplinary team with both clinical genetic and otolaryngology expertise.

The authors would recommend offering screening to the following groups:

- Patients with multiple head and neck paragangliomas or findings of a paraganglioma and pheochromocytoma
- Patients with a positive family history
- Patients with functioning or metastatic tumours
- Patients presenting at a relatively young age (currently recommended as <50 years)

Based on comprehensive cost-effectiveness data, initial testing for the SDHD, SDHB and SDHC genes is recommended followed by SDHAF and TMEM127 if the initial screening is negative^{19,20}. There are currently further genes that have been identified occurring in familial paraganglioma syndromes [Table 2]. As a result of this, the list of genes screened for may increase in the future.

Investigation of paragangliomas

Biochemical:

All patients with a paraganglioma should be investigated with 24-hour measurement of urinary catecholamines. A

Table 2: Familial Paraganglioma Syndromes ¹⁹				
Syndrome	Gene	Inheritance	Percent With H+N PGLs	Risk of Malignancy
Familial paraganglioma Type 1 (PGL1)	SDHD	AD with paternal imprinting	79-97%	Low
Familial paraganglioma Type 2 (PGL2)*	SDHAF2 (SDH5)	AD with paternal imprinting	0-42%	Low
Familial paraganglioma Type 3 (PGL3)	SDHC	AD	88%	Low
Familial paraganglioma Type 4 (PGL4)	SDHB	AD	29-43%	High
NA	SDHA	Insufficient Data	<3%	Insufficient Data
NA	TMEM127	Insufficient Data	2-4%	Insufficient Data
NA	MAX	Insufficient Data	<1%	Insufficient Data

AD = Autosomal Dominant; NA = Not Applicable
 * = Data from the only two studies in the literature analysing this gene

positive results should trigger prompt radiological investigation to rule out a synchronous pheochromocytoma.

Radiological:

Detailed imaging is essential to plan interventions and further management. Commonly, a combination of magnetic resonance imaging (MRI) with gadolinium enhancement and high resolution computer tomography (CT) to demonstrate the bony anatomy are used. Classically, a ‘salt and pepper’ appearance can be seen on MRI with the ‘pepper’ representing flow voids and the ‘salt’ component representing hyper-intense foci (due to slow flow) on T2-weighted images¹⁶. An example Figure 1.

Radio-nucleotide imaging is often used secondarily to MRI and CT in terms of diagnostic imaging, however these techniques offer excellent opportunities to screen the whole body; especially where MRI or CT may be equivocal or in post- surgical cases to identify recurrent or residual disease. Whole body positron emission tomography (PET) using 18Fluorine L-3,4-dihydroxyphenylalanine (18F-DOPA) or 18fluoro-deoxy-D(18FD)-glucose is highly sensitive to paraganglial tissue and has been shown to be more sensitive than MR imaging in some studies²¹.

Management

Surgery and radiotherapy techniques have both been employed to treat paragangliomas. Overall, decisions regarding treatment are increasingly being made within multi-disciplinary teams and must take into account tumour, patient and institution factors.

A full discussion of all the surgical techniques employed is beyond the scope of this article; however, this review

will focus upon some areas of controversy and new developments.

Surgery or Radiotherapy?

Two recent systematic studies comparing outcomes of surgery versus radiotherapy in carotid, jugular and vagal paragangliomas have been published.

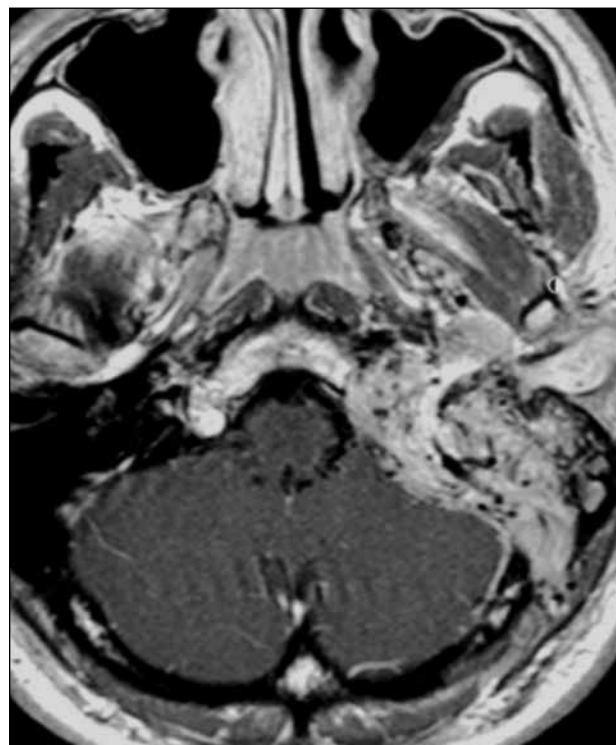


Figure 1: Axial T2 weighted MRI of a left sided Jugulo-tympanic paraganglioma demonstrating ‘salt and pepper’ appearance.

With carotid body tumours, surgery has traditionally been the mainstay of treatment. In a recent review of the literature, a total of 2175 patients reported in 67 articles underwent surgical excision whereas 127 were treated with external beam radiotherapy (EBRT). The long term control of disease was obtained in 93.8% with surgery versus 94.5% with EBRT. New onset cranial nerve deficits occurred in 22.2% (483/2175) of the surgery group with no new onset nerve deficits in the EBRT group. The incidence of carotid artery resection was 12.5% as a result of tumour encasement or injury with reconstruction in 9.7%. Permanent stroke occurred in 3%²².

With regards to jugular and vagal paragangliomas, a large review of the literature included 41 studies containing 1084 patients with jugular paragangliomas (JPG) and 226 patient with vagal paragangliomas who had surgical interventions. Long-term control of the disease was achieved in 78.2% and 93.3% of patients, respectively. A total of 715 patients with JPG had been treated with radiotherapy (461 EBRT and 254 stereotactic radiosurgery). Control of the disease was obtained in 89.1% and 93.7% of the patients, respectively²³. Outcomes of jugular paragangliomas treated with surgery or radiotherapy were compared and showed that tumor control failure, major complication rates and the number of cranial nerve palsies after treatment were significantly higher in the surgical series²³.

While these data would suggest that radiotherapy would seem to be the treatment of choice for most patients, it should be remembered that the studies cited are historical cases series rather than controlled trials and will often be not comparing equivalent tumours. A further factor to consider is the treatment of pulsatile tinnitus: this is often controlled by surgery but not by radiotherapy and may lead the multi-disciplinary team to offer surgery when other factors (tumour control and cranial nerve deficits) are perceived as equal.

Tumour Embolisation

This is standard practice when carrying out surgery on tumours involving the skull base. All significant feeding vessels must be identified and are usually branches of the ascending pharyngeal artery. Patients should be aware of the risk of cerebrovascular accident, reported at approximately 1%.

Carotid artery stenting

In cases where carotid artery sacrifice would not be possible due to an inadequate contra-lateral circulation, it is possible to insert a stent 2-3 months prior to surgery. This allows the carotid artery with adherent tumour to be

stripped away leaving the stent - upon which a 'neointima' has formed – in situ²⁴.

Total Vs Subtotal resection with preservation of cranial nerve function

While total removal of tumour is the aim in some tumours, in larger lesions involving cranial nerves, a sub-total clearance to preserving nerve function is appropriate. With tumour doubling times in the order of 10 years, it is the authors' experience that removal of the bulk of tumour is often sufficient to arrest growth: any remnant tissue may be monitored and treated with radiotherapy if there is evidence of further significant enlargement. This approach may be even more appropriate in familial cases where lesions may be bilateral.

Potential Future Treatments

Angiogenesis inhibitors are being increasingly used as neoadjuvant therapies in the management of colorectal, breast and brain cancers. They may also become a treatment option for paragangliomas in the future. There are currently only case reports of using the tyrosine kinase inhibitor, Sunitinib, in malignant paragangliomas and these have shown a reduction in tumour sizes and an increase in progression free survival^{19,25-27}. There is currently a multicentre, single arm phase II clinical trial, (Study of Sunitinib in Patients with Recurrent Paraganglioma/Phaeochromocytoma – SNIPP Trial) recruiting which may lead to further information and uses of these agents in the management of paragangliomas.

Cyclin dependant kinases (CDK's) are responsible for controlling the cell cycle. A protein product of CCND1, Cyclin D1, which is responsible for cell proliferation has shown immunoreactivity in head and neck paragangliomas²⁸. An overexpression of this protein has also been identified in breast, colon and parathyroid cancers²⁹⁻³¹. Recent trials, including a phase II study of ER+/HER2- breast cancer, have shown some promising results using second generation drugs such as the CDK 4/6 inhibitor PD0332991 coupled with letrozole³³. These medications may show some potential in the chemotherapeutic management of paragangliomas in the future.

As discussed earlier, another product of pseudo-hypoxia is the up-regulation of BNIP3. This protein has a role in influencing tumour cells away from an apoptotic pathway towards an autophagic pathway, thereby increasing cell survival. This occurs in an mTOR – dependent pathway. Inhibiting mTOR enhances tumour cell death¹⁹. In addition to this, autophagy inhibitors, such as Chloroquine, result in a reduction of BNIP3 expression and subsequently reduce tumour growth³⁴. These agents have shown promise

in hypoxia-induced glioblastoma models in vivo and may lead to a new treatment for paragangliomas^{19,34}.

Conclusion

Paragangliomas are rare lesions of the head and neck with unusual anatomical, functional and genetic diversity. Their management should almost always be multi-disciplinary (the exceptions would be small neck or otological lesions) and should take into account the natural history of the disease, which is often indolent. The priority in management should be a preservation of neurological function over tumour clearance and this often leads to a more conservative approach to treatment: either in the form of limited surgery or in the use of radiotherapy. Increasingly, innovative medical treatments are offering new treatment modalities that may well prove invaluable particularly in treating patients with multiple and bilateral lesions.

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Thyroglossal duct abnormalities – tips for success

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Abstract

Thyroglossal duct cysts are the most common congenital abnormalities in the cervical region. They may contain all functioning thyroid tissue, so ensuring a normal thyroid is present prior to removal is essential. Presentation is common in childhood but also occurs in adults. Knowledge of the embryology of the thyroid is key to successful surgical management. Following introduction of the Sistrunk's procedure over eighty years ago recurrence following surgery has reduced. However, more extensive procedures such as central compartment neck dissection may be required for persistent disease. This paper will highlight the steps in diagnosis, management and treatment that will minimise complications and lead to a successful outcome.

Keywords

Thyroglossal duct cyst, congenital, embryology, paediatric, surgical procedures

J ENT Masterclass 2014; 7 (1): 109 - 112.

Introduction

Thyroglossal duct cysts are the most frequently occurring congenital cysts of the neck. Their estimated incidence is up to 7%¹, and they are found equally in males and females. They may arise at any point along the embryonic connection (duct) between the thyroid gland and the foramen caecum of the tongue. Presentation is generally with an anterior neck lump that elevates with swallowing and tongue protrusion. The diagnosis is clinical, although ultrasound is required pre operatively to establish the presence of normal thyroid tissue. The management is surgical with an "en bloc" resection of the cyst and tissues superior to it including the central portion of the hyoid bone and a cuff of tongue base tissue avoiding a mucosal breach into the oral cavity. A wide excision is performed to prevent recurrence. A step-by-step approach to surgery is presented later in this article. Often

discussed, but rarely seen, is thyroglossal duct carcinoma, with an estimated incidence of 1% of all thyroglossal duct cysts². The most common pathology observed is papillary thyroid carcinoma.

Embryology of the thyroid gland and thyroglossal duct cysts

A thyroglossal duct cyst may occur at any point in the migratory path the thyroid takes from the foramen caecum of the tongue to its natural position in the anterior neck. By the third week of gestation, the thyroid arises in the inferior pharyngeal gut, a point that is later recognised as the foramen caecum. The thyroid then descends as a bilobed diverticulum anterior to the pharynx and developing laryngeal structures, lying anterior to the trachea by the seventh week of gestation³. The hyoid bone, which subsequently develops in a lateral to medial fashion has a close relationship to the ductal tract⁴. Involution of the tract normally takes place by week ten of gestation, and the thyroid tissue becomes functional around week twelve. The descent of the thyroid is shown in figure one.

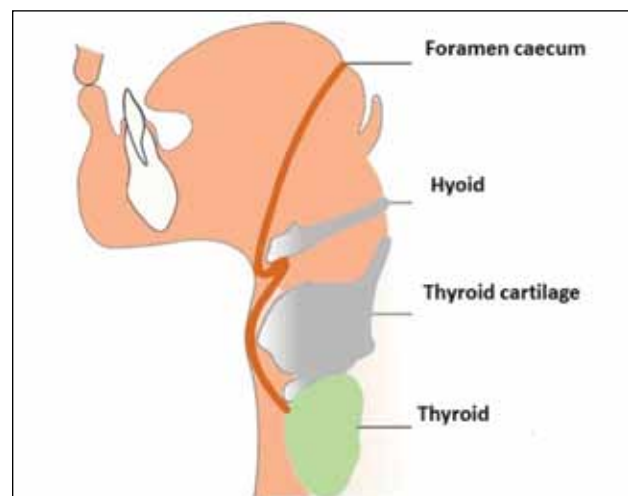


Figure 1: The descent of the thyroid gland.

Histology

Thyroglossal duct cysts are lined with squamous or respiratory epithelium. There is often an inflammatory infiltrate (macrophages, lymphocytes and neutrophils). Thyroid epithelium or follicles are not seen in all cases⁵. Cholesterol granulomas are also occasionally seen⁶. It is recognised that throughout the duct but particularly in the suprahyoid region, the tract may display a branching pattern, like a tree. This may only be apparent histologically and not at the time of surgery. This means that in the suprahyoid region, no attempts should be made to dissect out the tract and a normal cuff of tissue around the tract should be removed. Variable relationships of the tract to the hyoid have been described including anterior to the hyoid, posterior to the hyoid and in rare cases, the tract running through the hyoid⁷.

Presentation

Thyroglossal duct anomalies may present at any age. The usual presentation is a round smooth painless midline neck lump that elevates with swallowing and tongue protrusion. A typical presentation is seen in figure 2. One third of patients will have experienced infection of a thyroglossal cyst and up to one quarter of patients develop a cutaneous fistula in association with the cyst⁸. Rare presentations include airway compression, which can be fatal particularly if the cyst is centred around the tongue base region⁹. When the anomaly is a carcinoma, the presentation is similar to benign disease, however, the lesion may be harder, fixed and associated with cervical adenopathy¹⁰. In adults, particularly males, a cyst may sit deep to the thyroid notch on the thyrohyoid membrane and be barely palpable despite being of significant size. There is some evidence highlighting differences in clinical presentation in children and adults and these are covered below.

Children

- The mean age of presentation is five years¹¹



Figure 2: Typical appearance of a thyroglossal duct cyst in a child.

Adults

- More likely to present with symptoms other than mass¹² (pain, dysphagia)
- Infection rates higher than in children¹³
- More likely to require pre operative biopsy to rule out malignancy¹⁴

Differential Diagnosis

The differential diagnosis of midline neck masses is limited and can be aided by thinking of the structure of origin. The main two alternative diagnoses to consider are lymphadenopathy and dermoid cysts, these are outlined in table one below.

Table one: Differential diagnosis of thyroglossal duct cyst	
Differential Diagnosis	Tips for diagnosis
Dermoid cyst – a cyst with cutaneous elements (formed by congenital entrapping of ectodermal and mesodermal structures during embryologic fusion)	Clinical: Will not move with tongue protrusion, superficial on palpation Intraoperative: If the specimen is incised; a dermoid will contain yellow cheesy material and a thyroglossal filled with clear or amber coloured fluid
Lymphadenopathy	Clinical: Will not move with tongue protrusion Radiological: Lymph nodes have demonstrate a fatty hilum and are discrete entities on ultrasound
Intra- thyroidal pathology	Clinical: May not move with tongue protrusion (although will with deglutition) Radiological: Pathology within the thyroid will be readily identifiable on ultrasound
Plunging ranula	Clinical: An intra oral component will be evident, will not move with tongue protrusion, will have a slightly lateral presentation
External or combined laryngocoele	Clinical: Rare, will not move with tongue protrusion, will expand with valsalva manoeuvre Radiological: Best seen on CT imaging

Investigation

Although the clinical diagnosis is normally straightforward, there is one investigation that is indicated in all cases of thyroglossal duct cyst and that is ultrasound. This confirms the presence of a normal thyroid gland, so that excision of the thyroglossal duct cyst does not inadvertently remove all functioning thyroid tissue,

which may be contained within the duct/cyst. Other investigations such as fine needle aspiration are indicated in adults if the clinical diagnosis is not obvious, or malignancy is suspected.

Treatment

The treatment of thyroglossal duct cysts is surgical. Successful surgical management involves removal of the thyroglossal duct tract in its entirety. Walter Ellis Sistrunk popularised the removal of the central portion of the hyoid and proposed removal of a small core of tissue from the tongue base including mucosa. His modification of the technique in 1928 no longer involved taking the oral cavity mucosa with the tongue base. Sistrunk's procedure, as opposed to removal of the cyst alone, dramatically decreases rates of recurrence. Recurrence rates nowadays are in the order of 3 – 5%¹⁵.

Sistrunk's Procedure

- With the neck in extension, a horizontal neck crease incision is placed over the cyst between the hyoid and thyroid (if there is a fistula, incorporate this in a skin ellipse with the incision)
- The strap muscles are retracted but if inflamed a small cuff of the strap muscles is excised in continuity with the cyst
- The cyst is mobilised and the thyrohyoid notch identified which is in continuity with the thyrohyoid membrane superiorly. Sweep superiorly on the thyrohyoid membrane to lead directly to the hyoid
- Skeletonise the body of the hyoid where division is planned by removing the soft tissue attachments
- The hyoid mid portion is held with Allis forceps then divided with either Mayo scissors or bone cutters. When properly transected, the cut edges of the hyoid spring apart
- The deep extent of dissection at this point is the thyrohyoid membrane
- A finger can be placed intra-orally on the tongue base/ vallecula to push down and facilitate the removal of a wedge of tongue base and ensure no entry into the oral cavity. A superior wedge of tongue muscle is dissected out. Cutting diathermy will reduce bleeding in this area
- Examine the specimen. It should include the cyst, a cuff of tissue, a portion of the hyoid bone and tongue base musculature
- The wound is closed and a drain is placed

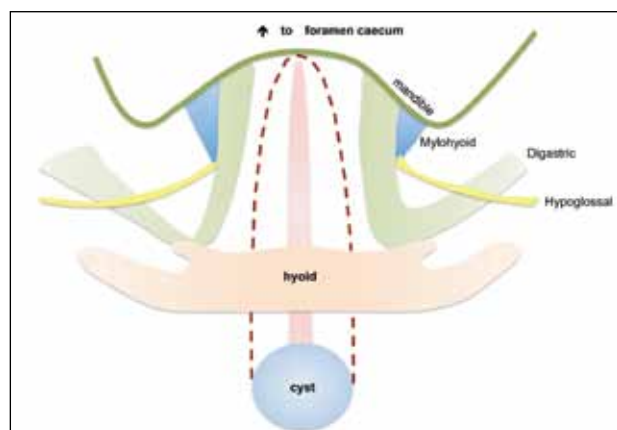


Figure 3: Diagram of Sistrunk's procedure (dotted red line represents area of excision).

Complications

The majority of complications are wound related and involve infection, dehiscence, seroma or haematoma. The rate of wound related problems is around 30%¹⁶. A neck drain is advised in these patients, as haematoma is relatively common and in an enclosed space may evolve into airway compromise. Bleeding may occur from vessels, cut muscle edges, the tongue base and the cut edges of the hyoid bone (particularly when the hyoid is fully calcified in adults). Meticulous haemostasis with bipolar diathermy is recommended. Bleeding from bone edges can be difficult to control with bipolar and a small amount of bone wax or haemostatic mesh in this situation may help.

Another recognised, but fortunately rare complication is hypoglossal nerve injury. This is easily avoided by judicious dissection around the body of the hyoid staying medial to the lesser cornu. Iatrogenic perforation of the airway is rare. Small perforations can be managed by local repair. Failure to recognise the anterior laryngeal framework and dissection of the thyroid cartilage in place of the hyoid is associated with significant morbidity. This is more likely to occur in children where the hyoid partially overhangs the thyroid cartilage¹⁷.

As mentioned previously, hypothyroidism is prevented by ensuring a normal thyroid is present on ultrasound imaging prior to resection of the thyroglossal duct tract. Finally, recurrence is a problem in less than 5% of cases but in children this can be as high as 10%, and even higher in cases of repeated infection¹⁸.

What to do with a recurrence

Factors associated with recurrence are pre operative infection, misdiagnosis of a thyroglossal duct cyst, any excision procedure which is less extensive than a Sistrunk's procedure and the operator's surgical experience and

background¹⁹. When faced with a recurrence, repeat imaging should be performed, this may localise the site and extent of recurrence. If a Sistrunk's procedure has not been performed, then this would be the next logical step. If however, this has been performed then considering the histological arborisation of the entire tract that may occur then a wider en bloc excision including tongue base, should be considered.

Top Tips

- USS to establish presence of normal thyroid tissue
- Treatment is surgical at presentation- future infection may reduced the chances of successful clearance and there is a small cancer risk
- Wide excision is important
- Staying on the thyrohyoid membrane safely approaches the deep aspect of the hyoid
- Adequate excision of the hyoid bone is aided by good surgical exposure and removal of soft tissues where division planned
- Use bone cutters to divide the hyoid in adults
- Remember bone wax if the hyoid is bleeding following transection
- Cutting diathermy is useful for the tongue base resection
- Examine the specimen at the end of the procedure and ensure middle portion hyoid bone is present
- Put a drain in overnight

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Lymphomas of the head and neck: presentation, diagnosis and current management

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ABSTRACT

Many cases of lymphoma are diagnosed in the Ear, Nose and Throat Departments with lymphoma accounting for 5% of all head and neck malignancies. Both nodal and extra-nodal sites may be involved - the most common being at Waldeyer's ring. Most head and neck lymphomas are B cell non-Hodgkin's lymphomas.

Head and neck lymphoma involvement can compromise critical structures such as the airway and optic nerves, so an early diagnosis and initiation of treatment should be prompt, and ideally within a specialist oncology centre.

Once the pathological diagnosis has been conformed, treatment involves a combination of chemotherapy, immunotherapy and radiotherapy. The overall prognosis for patients presenting with a head and neck lymphomas is good, particularly for those with limited stage disease.

Modern imaging techniques such as PET-CT have an important role in the diagnosis and staging of lymphomas and may be used to guide management. Advances in the molecular characterisation of the disease and the development of novel targeted agents may also improve outcomes, especially in chemo-resistant disease.

Key words

Lymphoma, head and neck, Non Hodgkin's, Hodgkin's, extra-nodal

J ENT Masterclass 2014; 7 (1): 113 - 119.

Introduction

Lymphomas frequently present via the ENT clinic, accounting for approximately 5% of all head and neck malignancies¹. The head and neck (H&N) is the second most common site of extra-nodal lymphoma after the gastrointestinal tract². About 1/3 of extra-nodal lymphomas arise in the H&N³.

In addition to extra-nodal sites, lymphomas commonly involve H&N lymph nodes, representing 10% of all referrals with cervical lymphadenopathy⁴.

Sites of involvement

Over 50% of H&N extra-nodal lymphomas (HNENL) arise in Waldeyer's ring, a ring of lymphoid tissue within the tonsils, nasopharynx, base of tongue and soft palate. Of these the most common site is the tonsil, accounting for approximately 2/3 of cases, followed by the nasopharynx^{3,5}.

The salivary glands are affected in 10-15% cases of HNENL³ and constitute 2-5% of salivary neoplasms overall⁶. The majority arise within the parotid gland.

Primary thyroid lymphomas represent up to 5% of all thyroid tumours and 10% of all HNENL³. Orbital malignancies are rare, but in adults over half are due to lymphoma⁷. These account for approximately 10% of all HNENL.

Less common sites include the oral cavity, nasal cavity, larynx and paranasal sinuses.

Histological subtype

Lymphomas are a heterogeneous group of malignancies and their classification has evolved over the years. The

current widely accepted classification is the WHO classification which is complex and comprises >40 categories based on cell of origin, differentiation and clinical behaviour. However lymphomas can be broadly divided into Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL) which are further divided into B cell and T cell NHL⁸

NHL can also be considered as either high- or low-grade. High-grade lymphomas tend to grow rapidly and behave aggressively. Low-grade lymphomas usually follow a more indolent clinical course, with slow progression over months to years. A proportion of low-grade lymphomas will undergo high grade transformation with time however. For follicular lymphoma the rate of transformation is approximately 3% per year⁹.

The majority of HNENL are B-cell-NHL¹⁰. This includes high-grade lymphomas such as diffuse large B cell lymphoma (DLBCL), Burkitt's lymphoma and low-grade lymphomas such as follicular lymphoma (FL), and mucosal associated lymphoid tissue (MALT) lymphomas.

Certain anatomical sites are characteristically affected by particular types of B-NHL. Most lymphomas of the tonsil and other parts of Waldeyer's ring are high-grade, mainly DLBCL¹¹.

Salivary gland lymphomas are typically low-grade, with MALT or follicular lymphoma being the most frequent^{6,12}. There is an established association between salivary MALT lymphomas and Sjogren's syndrome¹³.

Orbital lymphomas are also predominantly of low-grade histology. In a series of nearly 200 patients 43% were MALT lymphomas, followed by lymphoplasmacytic lymphoma then follicular lymphoma. 10% were high-grade DLBCL¹⁴.

The most common histological subtype of thyroid lymphoma is DLBCL (60-80%) followed by MALT lymphoma and follicular lymphoma¹⁵. In around 50% of cases there will be a history of Hashimoto's thyroiditis¹⁶.

H&N T-cell NHL is rare in the western population. In the H&N, the most recognised variant is (Natural Killer/T-cell) NK/T cell lymphoma of the nasal type which is associated with the Epstein Barr virus. These tumours typically involve the nasal cavity and para-nasal sinuses.

Hodgkin's lymphomas frequently present with cervical lymphadenopathy and so are often seen in the ENT clinic, but unlike NHL rarely involve extra-nodal sites⁴.

Presentation

The most common presentation of H&N lymphomas is painless cervical lymphadenopathy, which is classically described as rubbery and fixation to underlying structures is uncommon.

Patients may also present with local symptoms relating to the site of extra-nodal disease. Lymphomas of the tonsil and tongue base often present with sore throat and dysphagia. Nasopharyngeal lymphomas may cause nasal obstruction and auditory dysfunction.

Parotid lymphoma typically manifests as a painless swelling. Facial nerve involvement is rare. Lymphoma involving the orbit may lead to proptosis or diplopia. Conjunctival lymphoma usually presents as a fleshy salmon-pink patch on the conjunctiva.

Most patients with thyroid lymphoma present with a mass and rarely acutely with stridor and airway compromise.

The most common symptoms of NK/T cell lymphoma are nasal obstruction and epistaxis. These tumours tend to be locally invasive and often extend into the para-nasal sinuses, sometimes causing facial swelling. There may be invasion into the orbit causing proptosis, or inferiorly through the palate creating a defect – the classic lethal midline granuloma¹⁷.

Constitutional symptoms such as weight loss, night sweats, fever and lethargy are present in approximately a third of patients at diagnosis. These are more commonly seen in patients with HL⁴.

Diagnosis

A full history should be taken and a thorough examination performed. The history should include the presence or absence of B symptoms (weight loss >10%, night sweats and fever > 38°C), whether there is any history of autoimmune disease and risk factors for HIV and hepatitis.

Examination

This should be guided by symptoms but should include assessment of the oral cavity, nasal cavity, nasopharynx, oropharynx, and larynx. Examination under anaesthetic may be required.

The neck and all other lymph node regions should be examined. The abdomen should be examined for hepatosplenomegaly. Testicular examination should be performed in males.

Histology

For diagnosis and classification of lymphoma a whole lymph node excision biopsy remains the investigation of choice^{18, 19}. This is because analysis of the lymph node architecture may be needed to accurately subtype the lymphoma. It should also provide sufficient tissue for the multiple diagnostic tests that may be required including immunohistochemistry, cytogenetics and fluorescent in-situ hybridisation.

In cases where a lymph node excision biopsy is not feasible, for example extra-nodal disease only or difficult to access sites, core biopsy is recommended. Fine needle aspiration cytology alone is unlikely to be adequate for diagnosis and characterisation of lymphoma²⁰.

Imaging

Imaging investigations in H&N lymphomas are used to establish the extent of local disease and for staging. For the assessment of local disease the preferred imaging technique depends on the site. In many cases this will be with magnetic resonance imaging.

18F deoxyglucose positron emission tomography (PET)-CT is now considered the optimal imaging technique for staging of all FDG avid lymphomas²¹ If PET-CT imaging is not available a CT neck, thorax, abdomen and pelvis with contrast should be completed.

Other investigations

- FBC, LFT, LDH, ESR and beta 2 microglobulin
- HIV, Hepatitis B and C serology is recommended in all new lymphoma diagnoses²².
- Bone marrow aspirate and trephine biopsy should be performed in all cases of NHL. It is no longer recommended as a routine staging investigation in HL as PET-CT imaging is highly sensitive in diagnosing marrow infiltration²¹.
- Lumbar puncture and CSF analysis in patients at high risk of central nervous system (CNS) involvement.

Key point

Corticosteroids such as dexamethasone or prednisolone should not be started in cases of suspected lymphoma until a histological diagnosis has been confirmed and imaging completed. This is because steroids have a cytotoxic effect in lymphoma, and may cause rapid regression of the tumour, making subsequent biopsies and imaging difficult to interpret.

Staging in lymphoma

Conventional staging of lymphomas uses the modified Ann Arbor criteria²³. This is based on the anatomical

distribution of disease along with A or B to indicate the absence or presence B symptoms, and E to denote an extra-nodal site. Table 1

Table 1: Modified Ann Arbor criteria for lymphoma staging

Stage I	Involvement of a single lymphatic site (i.e., nodal region, Waldeyer's ring, thymus, or spleen) (I); or localized involvement of a single extra-lymphatic organ or site in the absence of any lymph node involvement (IE).
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II); or localized involvement of a single extra-lymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE).
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extra-lymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE, S). Splenic involvement is designated by the letter S.
Stage IV	Diffuse or disseminated involvement of one or more extra-lymphatic organs with or without associated lymph node involvement, or isolated extra-lymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver or bone marrow, lungs or cerebrospinal fluid.

Several validated prognostic indices exist for lymphomas such as the International Prognostic Index (IPI) for DLBCL, Follicular lymphoma International Prognostic Index (FLIPI) and Hasenclever score for HL. These incorporate factors such as age and blood results in addition to the Ann Arbor stage, and can be used to risk-stratify the patient²⁴⁻²⁶.

Management

The management of head and neck lymphomas (HNL) follows the same principles as lymphomas in general. Treatment is determined by the histological subtype, stage of the lymphoma and the prognostic risk group of the patient, and should take account of the patient's co-morbid illnesses and functional status. Patients should ideally be managed in a specialist centre.

Hodgkin's Lymphoma

The majority of patients with HL present with early stage disease (Ann Arbor stage I-IIA). The current standard of

care for this group is combined modality therapy with 2-4 cycles of chemotherapy followed by radiotherapy^{27,28}.

For advanced disease a longer course of chemotherapy is given with the option of consolidation radiotherapy for sites of bulk disease or incomplete response²⁹⁻³¹.

Doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) is the standard first line chemotherapy regimen for HL.

The prognosis for HL is excellent with 5 year survival rates in excess of 95% for those with early stage disease^{28,32}.

Non Hodgkin's lymphoma

High grade NHL

For localised early stage DLBCL combined modality therapy is also recommended with 3-4 cycles of R-CHOP chemo-immunotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) followed by RT^{33,34}.

In advanced disease (Stage III or IV) or when there are other adverse prognostic features a longer course of chemo-immunotherapy should be delivered, and RT reserved for those with bulk disease at presentation or where there is concern about response to treatment.

Consideration should be given to central nervous system (CNS) prophylaxis in those with high risk of CNS relapse, for example disease involving the paranasal sinuses. Involvement of the tonsil alone is not an indication for intrathecal chemotherapy³⁵.

Despite the aggressive nature of DLBCL the majority of patients will be cured. For patients with low risk DLBCL disease 4 year overall survival is excellent at 94%, for those with high risk disease 55% OS at 4 years²⁵.

For Burkitt's lymphoma and other high risk high grade lymphomas, more intensive chemotherapy regimens are used with CNS prophylaxis as standard.

Low grade NHL

For those with localised low grade B cell NHL radiotherapy alone can be curative. In MALT lymphomas, radiotherapy produces local control rates of >95% at 10 years. With distant failure rates of 10-20% over the same period, effectively over ¾ of patients are cured by radiotherapy. 36

Unfortunately the majority of patients with low grade lymphomas have advanced disease at diagnosis and are

generally considered as incurable, although treatment may produce durable remissions and median survival is 7-10 years. Options include watching and waiting if asymptomatic, systemic treatment with chemotherapy +/- immunotherapy, or radiotherapy for isolated symptomatic sites. Early initiation of chemotherapy has not been shown to improve survival^{18,37}.

Radiotherapy for head and neck lymphoma

There has been a move towards reducing both radiotherapy field sizes and radiation doses in the treatment of lymphomas. This is with the aim of reducing late toxicity from the treatment.

Extended field radiotherapy has been superseded by involved field radiotherapy (IFRT). This is treatment of the clinically involved lymph node/s and the lymph node region in which they are located. It is based on pre-chemotherapy disease

For cervical lymphadenopathy IFRT would be the entire ipsilateral neck from the skull base to the supraclavicular fossa, levels II-V For tonsillar lymphoma the conventional radiotherapy volume would include the entire Waldeyer's ring and the ipsilateral neck.

Involved site radiotherapy (ISRT) is treatment of the site of the involved lymph nodes (e.g. cervical nodal levels), and involved node radiotherapy (INRT) is treatment of only the clinically affected nodes with a concentric margin. Whilst ISRT and to a lesser extent INRT are becoming increasingly popular especially in the context of CMT, many would consider IFRT to remain standard practice particularly when radiotherapy is given alone.

The recommended radiotherapy dose for high grade lymphomas in the post chemotherapy setting is 30-36Gy³⁸. This is significantly less than the radiation doses used in the treatment of squamous carcinomas of the head and neck, which are typically in the region of 60-70Gy, and reflects the radio-sensitivity of lymphomas.

For the radical treatment of low grade lymphomas 24Gy in 12 fractions is an accepted schedule³⁸. It has even been shown that effective palliation can be achieved from a very low dose treatment, such as 4Gy in 2 fractions, which causes minimal toxicity³⁹.

New radiotherapy technologies, such as intensity modulated radiotherapy (IMRT) can reduce treatment related toxicity by limiting dose to critical structures such as the salivary glands, optic nerves and chiasm^{40,41}.

Key point

Lymphomas are highly chemo and radiosensitive and generally respond quickly to treatment. A dramatic clinical response may be seen within 12-24 hours of starting therapy. Tracheostomy formation should therefore be avoided if possible. Focus should be on obtaining a prompt tissue diagnosis and imaging so that definitive treatment can be started without delay.

NK/T cell lymphoma nasal type

NK/T cell lymphoma nasal type is a locally aggressive HNL, most common in Asia and Central and South America⁴². It is usually localised at diagnosis, with 70-80% presenting with limited disease⁴³.

Radiotherapy is considered the main line of treatment for those with limited stage disease and recent evidence suggests that early use of radiotherapy within CMT improves the outcome. Complete response rates of between 66 and 95.4% have been reported following radiotherapy⁴⁴⁻⁴⁶. The radiotherapy doses in these series ranged between 40 and 65Gy, and the accumulating evidence suggests that doses of ≥ 50 Gy are required, which is much higher than in other types of lymphomas and normally requires IMRT⁴⁷.

Outcomes with anthracycline based chemotherapy regimens such as CHOP have been consistently poor⁴⁸. More recently a number of phase II trials have evaluated the use of L- asparaginase containing regimens such as SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide), with promising results. One proposed strategy is that radiotherapy should be sandwiched between two courses of SMILE⁴⁹.

Future developments**Risk-adapted therapy**

This is the selection of patients for treatment according prognostic risk. For example in early stage HL a subgroup of patients with a favourable prognosis has been identified, who can be given an abbreviated course of ABVD chemotherapy (2 cycles) followed by lower dose of radiotherapy 20Gy in 10 fractions⁵⁰.

Response-adapted therapy

In both HL and DBLCL, response on PET-CT scans performed early in chemotherapy has been shown to predict long-term outcome⁵¹⁻⁵³. There are several current trials examining response-adapted strategies, with escalation of treatment for poor response on early PET-CT and de-escalation for favourable responses.

Novel agents

A proportion of all lymphomas are chemo-resistant and not cured by conventional chemotherapy or radiotherapy. Alternative treatment strategies are required which target and inhibit discrete biological pathways. The monoclonal antibody Brentuximab vedotin is a novel antibody drug conjugate which targets CD30 a cell surface antigen which is expressed on Hodgkin Reed Sternberg cells. Recent phase I and II studies in relapsed and refractory HL has revealed excellent overall response rates with minimal toxicity⁵⁴. Other novel agent compounds such as ibrutinib, which targets the B cell receptor are producing encouraging results in chemo-resistant forms of B cell NHL⁵⁵.

Conclusion

H&N presentation of lymphoma is relatively common but diverse in terms of the site of disease, symptoms and histological type. Initial diagnosis and assessment frequently require specialist expertise. Treatment is tailored to the disease type and individual patient's prognosis. Localised disease has excellent prognosis and is generally treated with combined modality approach with short course chemotherapy and local radiotherapy. Modern imaging, advanced radiotherapy techniques and the development of novel targeted agents all have the potential to further improve outcomes.

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Hyperthyroidism, thyrotoxicosis & thyroiditis: Causes, investigation & management

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Abstract

Thyrotoxicosis is the clinical condition that results from excess circulating thyroid hormones. Hyperthyroidism is over production and secretion of thyroid hormone. This review describes the conditions that result in thyrotoxicosis outlining the diagnostic methods used to distinguish between the causes. Medical, radioiodine and surgical treatments of hyperthyroidism are discussed.

Key words

Thyrotoxicosis, thyroiditis, management.

J ENT Masterclass 2014; 7 (1): 120 -125.

Introduction

Thyrotoxicosis refers to the clinical syndrome that results from tissue exposure to elevated levels of circulating thyroid hormones. *Hyperthyroidism* is used to describe thyrotoxicosis resulting from overproduction of thyroid hormones by thyrocytes (eg. Graves’ disease). Thyrotoxicosis can occur in the absence of hyperthyroidism, for example a short-term thyrotoxicosis can occur when stored hormones are released in a destructive thyroiditis. The causes of thyrotoxicosis are listed in Table 1. Graves’ disease, toxic multinodular goitre and solitary toxic nodule account for 95% of cases. Causes such as Hashimoto’s thyroiditis or drug related thyrotoxicosis are less common and rarely require surgical intervention.

Clinical Presentation & Systemic Manifestation of Thyrotoxicosis

Thyroid hormone excess affects almost all organ systems and the symptoms and signs of thyrotoxicosis are similar regardless of cause of the hormone excess. Clinical consequences depend on the severity & duration of the disease, age, extrathyroidal manifestations and the specific cause of the thyrotoxicosis. Widespread effects occur due

Group	Disease	Relative Frequency
Thyrotoxicosis of thyroidal origin	Graves’ Disease	70%
	Toxic Adenoma	5%
	Multinodular Toxic Goitre	20%
	Iodine-induced thyrotoxicosis	<1%
	TSH-secreting adenomas	<1%
	Neonatal thyrotoxicosis	<1%
Associated with thyroid destruction	Subacute thyroiditis	3%
	Silent thyroiditis	3%
	Amiodarone-induced thyrotoxicosis (type 2)	<1%
Thyrotoxicosis of non-thyroidal origin	Factitious thyrotoxicosis	Very rare
	Thyroid hormone poisoning	Very rare
	Struma ovarii	Very rare
	Metastatic thyroid cancer	Very rare

to the stimulation of metabolic processes and activation/sensitisation of the sympathetic nervous system (Table 2). Presentation in the elderly may be more subtle than in younger patients. Apathetic thyrotoxicosis¹ occurs in older patients when features of sympathetic reactivity are largely absent, and patients may present with severe depression, weight loss, occult atrial rhythm disturbance

System	Effects
General	Weight reduction, nervousness, irritability, heat intolerance, fatigue, poor sleep
Skin	Warm, moist palms, hyperhidrosis, urticaria, itching, exacerbation of eczema
Eye	Periorbital oedema, lid lag & retraction, chemosis, exophthalmos, ophthalmoplegia, redness, loss of vision
CNS	Irritability, worsening of psychiatric conditions, stupor, coma
CVS	Tachycardia, Cardiomegaly, heart failure, rhythm disturbance
Respiratory	Dyspnoea
Bone	Reduced bone mineral density
Fertility/ reproduction	Gynaecomastia, infertility, light or absent menstrual periods
Metabolic	Hyperglycaemia, hypercalcaemia
Gastrointestinal	Diarrhoea/ Hyperdefecation
Neuromuscular	Tremor, myopathy, paralysis

and a small goitre. Graves' disease has additional features, due to the immunological basis of the disease, in particular thyroid eye disease (Table 2).

Laboratory Diagnosis of Thyrotoxicosis

Thyrotoxicosis is biochemically confirmed when blood tests demonstrate elevated levels of circulating thyroid hormone levels with associated suppression of thyroid-stimulating hormone (TSH). Thyroxine (T4) and tri-iodothyronine (T3) are commonly measured in their respective free states (free T4 and free T3²). TSH is suppressed in thyrotoxicosis due to negative feedback of thyroid hormones on the anterior pituitary, but can be normal or elevated when a TSH secreting pituitary tumour is present or with thyroid hormone resistance³. Subclinical thyrotoxicosis is present when TSH is suppressed without overt elevation of free T4/T3. Once thyrotoxicosis is identified the aetiology should be established. The presence of extra-thyroidal signs and the size and shape of a goitre help identify the cause, although in 30% a goitre may not be palpable.

Graves' Disease

Graves' disease is the commonest cause of thyrotoxicosis accounting for approximately 70% of cases. Initially described in 1786 by Parry, an English physician from Bath, he did not publish his findings during his lifetime. In the English speaking world it has become known as Graves' disease after Robert

Graves, an Irish physician who described it in the early 19th century, while in mainland Europe it is known as Basedow's disease following von Basedow's description in 1840 in Germany.

Graves' affects 2% of women, and there is a female to male ratio of 10:1⁴. It is an autoimmune disease that can occur throughout life although typically presents in young women between 20-40 years of age. Geographical variations are reported and Graves' disease is more common in tobacco users⁵.

Pathogenesis

Genetic factors are important in the development of Graves' disease. Graves' disease is more common in Caucasians and has been linked to MHC-HLA class II gene polymorphisms, most notably DRB3. Other autoimmune conditions are associated with Graves' disease. Debated triggers for Graves' disease include stress⁶, smoking⁵ and antibodies to infections including *Yersinia enterocolitica*⁷ which may cross react with TSH receptors.

Although the pathogenesis of Graves' disease has not been fully elucidated antibodies acting against the TSH receptor (TSH stimulating antibodies are found in the circulation of >90% of untreated cases^{3,8}). Patients with Graves' have been found to have 3 classes of antibodies (neutral, blocking and stimulatory). The clinical picture depends on the balance of these antibodies. In classical Graves' hyperthyroidism the preponderance of stimulatory antibodies results in the overproduction of thyroid hormone in an unregulated fashion. Antibodies to other thyroid antigens are frequently present (anti-thyroperoxidase, and anti-thyroglobulin). Inflammatory cells infiltrate the thyroid with the production of cytokines. There is associated hyperplasia and hypertrophy of thyroid follicles resulting in goitre formation. The combination of both stimulatory and destructive thyroid antibodies may explain the variable course of Graves' following medical treatment, with remissions and hypothyroidism in some patients.

Diagnosis

The diagnosis of Graves' is confirmed clinically when thyrotoxicosis is present in a patient with a diffuse goitre, with extra thyroidal signs such as thyroid eye disease or dermopathy (eg pretibial myxoedema). Anti-thyroglobulin and anti-thyroid peroxidase antibodies are elevated in 80%. Thyroid stimulating antibodies are measured in cases where the diagnosis is uncertain. Nuclear medicine imaging shows diffuse uptake in the thyroid and is used to distinguish between Graves', toxic multinodular goitre, toxic nodule and inflammatory thyroiditis.

Thyroid Eye Disease (Thyroid Ophthalmopathy, Graves' ophthalmopathy)

Eyelid retraction and lag are common non specific eye signs which can occur in all causes of thyrotoxicosis. They are caused by the sympathetic innervation of levator palapabrae superioris carried via the IIIrd cranial nerve. Specific Graves' thyroid eye disease is clinically evident in >30% of patients⁹. Eye signs include; eye discomfort and grittiness, proptosis 30%, extra ocular muscle involvement 10%, while corneal involvement and optic nerve compression are uncommon.

The cause of ophthalmopathy remains under investigation but is thought to be due to an immune response to antigens present in retro orbital tissues that are shared with the thyroid, or antigens which can cross react with the TSH receptor. Ophthalmopathy is more common in people who smoke and the signs can be unilateral (10%). CT and MRI of the orbit are useful in determining degree of extra-ocular muscle enlargement. Treatment for milder forms is directed at symptom control and includes lubricating eye drops, elevation of the head of the bed and occasionally diuretics. Active inflammation may respond to immunosuppressive treatments including corticosteroids and azathioprine. External beam radiotherapy has been used to reduce inflammation and enlargement of extraocular muscles. In cases where the optic nerve is threatened and acuity reduced orbital decompression by an experienced surgeon may be necessary.

Identifying the aetiology of thyrotoxicosis

Commonly the aetiology is clinically evident and the treatment choice straightforward. The presence of thyroid eye disease & a diffuse goitre with a bruit are classical features of Graves' disease. Distinguishing between Graves' disease and toxic nodular disease in the middle-aged individual without extra-thyroidal manifestations may be more difficult. In addition to clinical assessment, measurement of thyroid antibodies, high-resolution ultrasonography and nuclear medicine imaging may be helpful. The absence of conventional antibodies does not exclude auto-immune thyroid disease. The pattern of tracer uptake on the nuclear medicine scan (iodine^{-123, -131} or technetium^{-99m}) can be helpful in identifying toxic nodularity particularly.

Identifying the aetiology of thyrotoxicosis within 12 months post-pregnancy can be particularly difficult. Destructive inflammatory thyroiditis is common during this period, but similarly Graves' disease may present or be exacerbated at this time. Absent or low isotope uptake on a nuclear medicine scan is supportive of destructive thyroiditis in such cases (and can be performed with careful planning in the breast-feeding mother).

Treatment of Thyrotoxicosis

Medical Treatment/ Anti-thyroid Drugs

Anti-thyroid drugs are used to render a patient euthyroid to either Induce a remission or as preparation for 'definitive' treatment (radioiodine or surgery). The main thioamide anti-thyroid medications used are Methimazole (USA/ Europe) or Carbimazole (UK), and Propylthiouracil (PTU). Carbimazole is rapidly metabolised to Methimazole. These agents are concentrated within the thyroid and interfere with the action of thyroid peroxidase with consequent reduction in thyroid hormone synthesis. In addition PTU partially inhibits the conversion of T4 to T3 in peripheral tissues, potentially reducing the levels of the active T3 hormone more quickly than carbimazole¹⁰. PTU is preferred in pregnancy as it is less likely to cross the placenta due to protein binding. Propranolol can be used to block the sympathetic effects of thyroid hormones whilst anti-thyroid medication takes effect (~ 2-4 weeks). Anti-thyroid medication is generally well tolerated and may be used in a titration regimen or as part of a "block and replace" strategy.

Treatment Strategies

In the titration regimen a high starting dose of carbimazole is gradually reduced to maintain a euthyroid state. In block and replace, a high dose (e.g 40 mg carbimazole daily) is continued to fully block endogenous thyroid hormone production and thyroxine is added after 4-6 weeks to maintain a euthyroid state. Monitoring is required as the dose of thyroxine may need adjustment. Treatment is optimally continued for 12-18 months based on analysis of 4 randomised clinical trials¹¹. The dose of methimazole used does not influence subsequent recurrence rates. Remission is variable but about 60% of patients develop subsequent recurrence¹⁰.

Side effects of the thioamide drugs can be major or minor. Major side effects are rare and include agranulocytosis,(0.5%) hepatitis, aplastic anaemia, and vasculitis or liver disease (with PTU) and require the medication to be stopped. On starting thioamide medication patients should be warned to seek urgent medical advice should they develop a sore throat, mouth ulceration, or fever. Minor side effects occur in up to 5% of patients include a skin rash, pruritis, urticaria, arthralgia, myalgia, and transient leukopenia. These effects may respond to a reduction in dose or substitution of one thioamide for another although there can be cross reactivity.

Radioiodine Therapy

Radioiodine can be used as first line treatment, or for recurrence following treatment with anti-thyroid drugs or

subtotal thyroidectomy. Its use was first reported in the early 1940's and it rapidly became the main form of definitive therapy, replacing the role of surgery for small uncomplicated goitres. Today the use of radioiodine varies throughout the world with a predominant role as the primary treatment of Graves' in the USA¹² whilst in Europe antithyroid drugs are usually used as first line therapy.

Radioiodine is most suitable for patients with a small goitre and in the absence of thyroid eye disease. It is contraindicated in pregnancy, for those breast feeding or for those planning to become pregnant within six months of therapy. Radioiodine may be unacceptable to those with contacts with children due to the need to avoid close contacts for several weeks following treatment. Radioiodine is relatively contraindicated in children due to the concerns of inducing thyroid cancer and secondary neoplasias in later life, although radioiodine is used in some pediatric centres and studies to date have not confirmed these concerns. Radioiodine is best avoided in those with severe ophthalmopathy as it is recognised that ophthalmopathy worsens in about 15% of patients following treatment¹³. Glucocorticoid cover at the time of radioiodine may prevent deterioration in thyroid eye disease.

Prior to radioiodine treatment patients should have their hyperthyroidism controlled and are typically treated with a thioamide drug until they are clinically euthyroid, although radioiodine is frequently given without pre-treatment for those with mild hyperthyroidism. Antithyroid drugs may be stopped several days prior to treatment to maximise radioiodine uptake and prevent treatment failures. Non controlled studies suggest PTU has a longer radioprotective effect than carbimazole¹⁴, although no difference was found between the 2 classes of drugs in a recent meta-analysis. Radioiodine is administered orally as I¹³¹, which emits particles that are destructive to thyroid follicular cells. The effects of radioiodine are not immediate and continue for months following treatment. Symptomatic improvement takes approximately 6-8 weeks. Hypothyroidism is the major consequence of radioiodine treatment occurring in approximately 20% of patients at one year], and eventually causes permanent hypothyroidism in the majority³. Thyroid replacement therapy is commenced when TSH levels start to rise above the normal range. For patients with persistent hyperthyroidism following an initial radioiodine therapy a second dose can be administered at 4-6 months¹⁵.

Surgical Treatment

Indications

Surgery is the treatment may be considered the treatment of choice for patients with: large goitres and/or compressive

symptoms, when radioiodine is contraindicated, with an FNA suspicious for malignancy, for patients with severe thyroid eye disease, for children, or for patient preference. Surgery has the advantage of providing tissue for histological assessment.

Preparation for surgery

Prior to surgery hyperthyroidism should be controlled, to reduce the risk of thyroid storm in the peri-operative period. Lugol's iodine (3 drops three times a day) can be administered in the 7-10 days prior to surgery to reduce the vascularity of the thyroid as an adjunct to antithyroid medications to aid the surgeon, although this is not necessary for all patients. For patients with difficult to control thyrotoxicosis and those intolerant of thioamide drugs, a team approach with endocrinologists and anaesthetists is particularly important. High dependency care may be necessary for this select group of patients. Large doses of iodine can be given prior to surgery to stun the thyroid (Wolf Chaikoff effect). This can be achieved using large doses of Lugol's iodine or iodine containing radiological contrast agents¹⁶. Beta-adrenergic blockers should be used to control the adrenergic effects provided there are no relative contraindications such as asthma when a cardio selective B blocker may be considered.

Total and subtotal thyroidectomy

Historically subtotal thyroidectomy (ST) has been the procedure of choice. A meta-analysis of 35 studies from 1965-1998 demonstrated that 93% of 7241 patients surgically treated underwent a subtotal thyroidectomy compared to 538 undergoing total thyroidectomy¹⁷. However the procedure of ST has not been well defined. The primary aim of surgical treatment is to resolve hyperthyroidism and avoid recurrence. This objective is not achieved in all patients undergoing ST. A further aim of ST is to leave the patient euthyroid without the need for thyroxine., yet with this approach around 25% develop hypothyroidism. On the basis that ST does not achieve its aims in 30-40%; patients have uncertainty about their outcome; require long-term follow up; incidental malignancy is found in approx 4.5% but has been reported in up to 9% in some series¹⁸, near total thyroidectomy (TT) has been increasingly proposed as the surgical procedure of choice in Graves disease^{19,20}. The published data suggests that there is no significant difference in complication rates between ST and TT in experienced hands¹⁷.

Surgery has a beneficial effect on reducing TSH receptor antibody levels for many patients, which appears to be similar for both surgical procedures at twelve months, but may be better maintained beyond 12 months in total thyroidectomy patients²¹. While surgery is preferred to radioiodine in

patients with ophthalmopathy, the course of eye disease for an individual patient following surgery remains unpredictable.

Toxic multinodular goitre and Toxic adenoma

Medical control of thyrotoxicosis does not induce long-term remission of toxic nodules as it can do in Graves’ thyrotoxicosis. Definitive treatment can be radioiodine for a non- compressive and cosmetically acceptable goitre, a small toxic nodule, and for those wishing to avoid surgery. Total thyroidectomy is the surgical procedure of choice for a large toxic multinodular goitre. This avoids possible regrowth of the goitre and recurrent thyrotoxicosis.

Thyroid lobectomy is the surgical procedure of choice for a solitary toxic nodule as it provides tissue for histology, while the normal contralateral lobe means the patient is likely to be euthyroid postoperatively, and the risk of radioiodine induced hypothyroidism is removed (The risk is reported to be small due to the toxic nodule suppressing and inhibiting radioiodine uptake on the remaining thyroid, but can occur).

Amiodarone & thyrotoxicosis

Amiodarone is a widely used anti-arrythmic drug that contains iodine. It causes thyrotoxicosis, through 2 potential mechanisms. 1. Iodine induced thyrotoxicity, 2. Amiodarone induced Thyroiditis. The standard maintenance dose of amiodarone for the cardiac patient (200 mg/d) can increase serum iodide levels by 40-fold. This excess may exacerbate thyrotoxicosis in prone individuals with underlying thyroid disease and is referred to as a amiodarone-induced thyrotoxicosis (AIT- type I). As a result of cytotoxic effects amiodarone and metabolites may have destructive effects on thyrocytes resulting in AIT-type II. Distinguishing between these types of AIT can be difficult. In AIT-type II thyroid uptake of isotope is absent or markedly reduced. The very long half-life of amiodarone results in long-term effects on the thyroid, even many months after cessation of amiodarone. High-dose thioamide drugs and potassium perchlorate can be used to treat AIT-type I, but commonly thyroidectomy is required, especially if continuation of amiodarone treatment is indicated. Glucocorticoids are used to reduce destructive thyroiditis and are effective in controlling thyrotoxicosis in many patients with AIT-type II but often the duration of treatment is 6 months or more and thyroidectomy should be considered in individual cases²².

Thyroiditis

This term describes a group of disorders that result in inflammation of the thyroid gland. The aetiologies and pathogenesis of conditions causing thyroiditis vary considerably and the causes are listed in Table 3.

Table 3: Classification of thyroiditis
Infectious Thyroiditis Bacterial, Fungal, Parasitic
Subacute (De Quervain) thyroiditis
Autoimmune thyroiditis Hashimoto thyroiditis Lymphocytic thyroiditis Post-partum thyroiditis
Thyroiditis associated with other thyroid disorders Graves’ disease Focal thyroiditis in papillary carcinoma
Radiation thyroiditis
Miscellaneous Sarcoidosis, Drug-associated, amyloidosis

Infective thyroiditis (excluding viruses) is rare and usually due to suppurative bacterial infections. Gram positive organisms, streptococcal and staphylococcal species are the most common agents and spread to the thyroid is usually blood borne. Pain, tenderness and increased temperature are the characteristic findings. Ultrasound examination can be useful and guide FNA for diagnosis. Appropriate antibiotic therapy is curative in the majority but lobectomy may be required, especially in recurrent disease.

Sub-acute thyroiditis is a well-defined, self-limiting entity that results in painful thyroid inflammation with release of thyroid hormones. There is a female preponderance and viral infection is considered the pathological mechanism. The histological appearance is of granulomatous infiltration of the thyroid. Thyroid antibody levels may be detectable and rise during the acute phase of thyroiditis. There may be an underlying genetic predisposition to the condition. Treatment is directed at symptoms and pain relief. Antiinflammatory medications including corticosteroids may be used in more severe cases. Some patients develop a transient hypothyroidism during the recovery phase and thyroidectomy is very rarely indicated.

Struma lymphomatosa (Hashimoto’s thyroiditis) was first described in 1912 and refers to autoimmune thyroiditis. The precise nature and aetiology of autoimmune thyroiditis have not been fully elucidated. Genetic factors are certainly important and defects in antigen-presenting processes are considered central in the pathogenesis. Thyroid antibodies (esp. peroxidase and thyroglobulin) are usually demonstrable in patients with Hashimoto’s thyroiditis. The clinical presentation is variable but may include goiter with pressure symptoms and discomfort in the neck,

thyroiditis (with thyrotoxicosis) or hypothyroidism. Thyroxine supplementation is necessary in all hypothyroid individuals. Anti-inflammatory mediation is generally not needed and similarly surgery has no major role in the treatment of autoimmune thyroiditis.

Guidelines

A number of guidelines exist detailing the diagnosis and management of thyroid disorders including hyperthyroidism. These have been produced by recognized professional bodies in Britain, Europe and the USA.

<http://www.british-thyroid-association.org/Guidelines/>

http://www.eurothyroid.com/guidelines/eta_guidelines.html

<http://www.thyroid.org/thyroid-guidelines/>

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Options of reconstruction following resections for advanced laryngo-pharyngeal carcinoma

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Abstract

Reconstruction of pharyngoesophageal defects is increasingly performed as salvage surgery following failed chemoradiation and is therefore associated with a high peri-operative morbidity. However, successful reconstruction can have a profound impact on quality of life in patients with ultimately a poor long-term prognosis – restoring speech and ability to ingest food orally. Free tissue transfer, particularly ALT flap reconstruction, has become increasingly popular as a means of providing a robust reconstruction that can be tailored to the defect (tube or patch, skin resurfacing) with superior outcomes.

Keywords

Laryngopharyngeal reconstruction; free flap; jejunum; antero-lateral thigh (ALT); salvage; fistula.

J ENT Masterclass 2014; 7 (1): 126 - 130.

Introduction

Pharyngoesophageal defects requiring reconstruction are most commonly the result of tumour ablation (total laryngopharyngectomy) for squamous cell carcinoma in the laryngeal region or hypopharynx. Early stage disease is often treated by primary radiotherapy. Therefore, many pharyngoesophageal defects are the result of salvage surgery following radiation failure or late presentation, making reconstruction more challenging. Post-operative complications are common (up to 70%) in this group due to both patient factors (poor nutritional status, high prevalence of systemic comorbidity) and disease factors (neck involvement, previous radiotherapy)¹.

The hypopharynx is a thin-walled muscular tube lined by squamous mucosa that provides a continuum from the oropharynx to the cervical oesophagus. It acts in a coordinated manner to permit transit of the food bolus and oral secretions. The goals of reconstruction are to deliver

a well-vascularised circumferential tissue construct that provides a watertight closure in the short-term and allows functional rehabilitation of speech and swallowing in the medium to long-term. Reconstructive techniques are aimed at restoring continuity of the hypopharynx but cannot reproduce the coordinated muscular movement. However, as the major contributor to the propagation of the food bolus is the tongue rather than the constrictor muscles, continuity is sufficient to enable adequate restoration of function.

Quality of life is of paramount importance in patients with hypopharyngeal malignancy as prognosis is very poor²⁻⁴. Restoration of adequate speech is difficult due to the need for permanent tracheostomy, however, the ability to take food orally can have a profound impact on a patient's psychological and physical well-being.

Early surgical techniques relied on the placement of rigid stents or primary closure, which resulted in prolonged periods of hospitalization and high mortality. Local flaps were then popularized although they were associated with high postoperative complications and poor functional outcomes.

With the advent of microvascular reconstruction, free tissue transfer has proved to be the most effective and reliable method of pharyngoesophageal reconstruction allowing a single-staged reconstruction with improved quality of life and reduced peri-operative complications⁴. Pedicled flaps still have an important role in salvage cases and management of complications.

Classification

Pharyngoesophageal defects are classified as partial (non-circumferential) or circumferential. Further subclassification systems have been developed for partial

Case vignette – partial pharynx reconstruction using an alt flap

A 57-year old male presented with a recurrent laryngeal SCC following primary treatment with chemoradiotherapy. His treatment was a pharyngo-laryngectomy with bilateral modified neck dissection. A 2cm wide strip of posterior pharyngeal wall remained with a defect length of 7cm (Figure 1).

Flap Elevation

An ALT flap was harvested from the left thigh. Flap elevation was performed simultaneous with tumour ablation, using a two-team approach. The main pedicle runs in the intermuscular septum between vastus lateralis (laterally) and rectus femoris (medially). The position of the septum is identified by a line drawn from the anterior superior iliac spine to the supero-lateral corner of the patella. Perforators can reliably be found in the region of the mid-point of this line. In this case, the flap was raised on 2 musculo-cutaneous perforators to enable reconstruction with 2 skin paddles – one for the pharynx and one to partially resurface the anterior neck skin as skin closure in the irradiated neck was tight (Figure 2).

Flap Design

The reconstructed neopharynx should have a diameter of 3cm. Circumferential defects should therefore have a width of 9.4cm ($2\pi r$). In this case, the flap width was determined to be 7.4cm (9.4cm – 2cm residual posterior pharyngeal wall). The skin paddle should be elliptical at the proximal anastomosis to accommodate the wide opening in the pharyngeal inlet and spatulated distally to prevent stricture formation at the distal anastomosis.

Flap Inset

The pedicle is the ligated and transposed to the neck. The flap is inset with inverted mattress absorbable sutures into the neoesophagus prior to microvascular anastomosis to prevent traction injury to the vascular pedicle. A second layer of closure involving ALT fascia to posterior pharyngeal wall is performed to provide an extra water-proofing layer and therefore reduce the chance of anastomotic leak (Figure 3). The second skin paddle was inset into the anterior neck forming the posterior wall of the neolarynx (Figure 4).

defects although none is widely used⁴. Reconstruction of partial defects rarely results in anastomotic strictures and therefore, partial defects should not be converted to circumferential defects as was commonly done for jejunal flap reconstruction.

Reconstruction

When at least two thirds of the posterior pharyngeal wall is preserved, direct closure is feasible and associated with a good functional outcome⁵. When the defect is larger than one third of the pharyngeal wall, tissue reconstruction using either pedicled or free flaps is best advised.

The common free flaps include both fascio-cutaneous flaps (radial forearm flap, anterolateral thigh flap) and



Figure 1: Photograph illustrating defect post tumour resection. A 2cm strip of posterior pharyngeal wall remained extending from the base of tongue to distal hypopharynx (NG tube running along wall).

intestinal flaps (free jejunum, colon, gastro-omental). Although free flaps have largely replaced pedicled flaps due to their increased reliability and reduced donor site morbidity, the pedicled pectoralis major flap remains a solid choice in patients with a very poor performance status or for salvage reconstruction of partial defects following failed free flap surgery. Gastric pull-up flaps are also described for cervical oesophageal defects as well as distal hypopharyngeal reconstructions.

Anterolateral Thigh Flap (ALT)

The ALT flap is a fascio-cutaneous flap supplied by perforators from the descending branch of the lateral

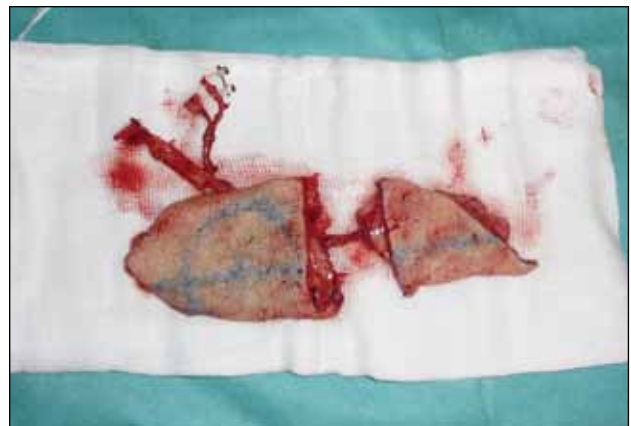


Figure 2: ALT flap raised on two perforators to supply two skin paddles.



Figure 3: Pharyngeal reconstruction complete including extra layer of fascial closure.

circumflex artery. The ALT has emerged as the most popular choice in reconstruction of circumferential pharyngo-esophageal defects due to its reliability, long vascular pedicle, minimal donor site morbidity and robust functional outcomes^{2,3}. In addition, it is distant from the site of radiotherapy in cases of salvage reconstruction and does not violate the abdominal or thoracic cavities.

Radial Forearm Flap

The radial forearm flap is a workhorse flap for Head and Neck reconstruction due to its ease of harvest, robust blood supply and thin pliable skin yielding an excellent substitute for mucosa of the upper aerodigestive tract. However, its limitations include a relatively modest skin paddle size and poor donor site morbidity due to the need for skin grafting and sacrifice of a major upper limb vessel.

Free Jejunal Flap

The concept of replacing 'like for like' is a popular concept in reconstructive surgery. Therefore, the possibility of replacing resected pharyngeal wall with intestinal mucosa through free jejunal transfer was intrinsically appealing⁶. However, the popularity of free jejunal flaps has waned in favour of fascio-cutaneous flaps, principally due to the perceived reduced donor site morbidity and



Figure 4: Closure complete with second skin paddle inset into anterior neck skin.

absence of any conclusive proof of difference in functional outcomes⁷.

OUTCOME

Circumferential Defects

There is a general consensus that free tissue transfer is superior to pedicled flaps in terms of functional outcome and donor site morbidity^{7,8}. Free flap reconstruction delivers tissue with a more reliable vascular supply, allows inset without tension and provides a greater variety of flap compositions, shapes and sizes to conform to defects more accurately. It is less well established which free flap provides the optimal reconstruction. There have been few comparative studies and most case series are small, therefore there is a real lack of evidence to guide best practice.

Fistula and anastomotic stricture

Fistula formation is an early failure of wound healing. Stricture formation is a later event that often follows failed primary wound healing. Many authors report similar complication rates in terms of fistula and anastomotic stricture rate between free ALT and jejunal flaps^{9,10}. One large observational study demonstrated a benefit of free jejunal flaps although this has not been widely reproduced¹¹. In their study, Chan and colleagues assessed outcomes in 202 patients undergoing reconstruction for total circumferential pharyngeal reconstructions¹¹. Fistula development occurred more frequently in the ALT group (12.5%) compared with patients undergoing free jejunal reconstruction (4.6%) although the difference was not significant. In their study, flap failure was higher in jejunal flaps and donor site complications more severe (two required emergency laparotomies). Indeed, the donor site morbidity from the additional laparotomy in jejunal flaps

has been shown to increase ITU and overall hospital stay compared with patients undergoing ALT flap reconstruction¹⁰.

Other authors have demonstrated ALT flaps to provide reliable and predictable functional outcomes. In one study, Yu et al. from MD Anderson, USA reported both the fistula and stricture rate in circumferential ALT reconstructions to be just 9%, similar to free jejunal flaps^{10,12}. In cases of ALT reconstruction for salvage pharyngo-laryngectomy, the reported fistula rates have been predictably higher, up to 42%¹³. The incidence of pharyngo-cutaneous fistula development in tubed fascio-cutaneous flaps may be reduced by use of a Montgomery Salivary Bypass Tube®, which bridges the anastomotic sites reducing contact of the suture line with saliva^{3,14}. Similarly, a double layer closure involving an inner layer of skin closure and outer fascia to postvertebral fascia may similarly reduce fistula formation.

A significant advantage of the ALT flap is that multiple skin paddles can be taken on different perforators so that anterior neck skin can be resurfaced in addition to restoration of pharyngeal continuity. There is often a skin deficit in previously irradiated necks that cannot be addressed by a free intestinal flap (see case vignette), which may require an additional flap (eg pectoralis major flap) to resurface the skin. ALT flaps are therefore often considered the first choice fascio-cutaneous flap. The radial forearm flaps is a good second-line flap in patients with a thick thigh envelope⁵.

Speech and swallowing

Speech and swallowing are of paramount importance to a patient's quality of life. It is well recognised that many patients who undergo pharyngo-laryngectomy will ultimately not have trachea-esophageal prosthesis (TEP) voice restoration¹⁵. Most agree fascio-cutaneous flaps are more likely to result in improved speech production compared with free jejunal flaps, which are often associated with a wet sound¹⁶. Studies report similar quality of TEP voice production between radial forearm and ALT flaps¹⁷.

Comparative studies have generally shown equivocal results between fascio-cutaneous flaps and free intestinal flaps in terms of achieving a normal oral diet postoperatively^{10,11}. Some authors have reported that dysphagia from late stricture formation can be problematic in ALT free flap reconstructions, occurring in up to 30% of cases^{18,19}. However, most studies report that the majority of patients ultimately achieve sufficient oral intake to allow removal of the feeding jejunostomy tube^{3,18}.

Another consideration is that intestinal flaps are more intolerant of radiotherapy leading some oncologists to reduce post-operative radiotherapy dosage in patients after jejunal flap reconstruction, whereas a full dose can be given in tubed fascio-cutaneous flaps²⁰. This suggests a potential oncological benefit in ALT flap reconstruction although there is no data to support an actual advantage in terms of survival or loco-regional control.

Partial defects

Reconstruction of partial hypopharyngeal defects rarely results in anastomotic strictures and therefore, they should not be converted to circumferential defects. Hence, there is no place for free jejunal flaps in partial hypopharyngeal reconstruction.

Partial defects are reconstructed using a patch, which is commonly either a free fascio-cutaneous flap (ALT or RFF) or pectoralis major myo-cutaneous flap (PPMF). PPMF have traditionally been the workhorse flap but compared with fascio-cutaneous flaps are bulky and associated with poor deglutition. However, they can provide good soft tissue cover of vital structures in heavily irradiated necks and are useful in salvage cases (failed free flap reconstruction, fistula repair, carotid artery or jugular blow-out)²¹. Good functional outcomes have been also reported with RFF patch reconstructions where less than 3cm of native posterior pharyngeal wall has been left in situ although the donor site morbidity is less favourable than ALT flaps²².

Summary points

- Patients undergoing laryngo-pharyngectomy involving extensive pharyngeal mucosal resection or in salvage cases following failed chemoradiation protocols are best reconstructed with free tissue transfer.
- Early postoperative complications are frequent in this patient population.
- Both fascio-cutaneous and free intestinal flaps can deliver the possibility of successful reconstruction in terms of restoration of swallowing with acceptable fistula and stricture rates. Free flap choice is therefore best determined by individual expertise and preference.
- ALT flaps are becoming increasingly popular due to their increased versatility (eg anterior neck skin resurfacing), improved speech outcomes and reduced donor site morbidity.
- Partial Hypopharyngeal defects are best reconstructed are best reconstructed using a free fasciocutaneous patch flap or a PPMF.

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Facial nerve neoplasms

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Acknowledgements

We would like to thank Dr Gillian Potter and Dr Rekha Siripurapu, Consultant Neuroradiologists at Salford Royal Hospital for their assistance in preparing the radiological images.

Key words

Facial nerve neoplasms.

J ENT Masterclass 2014; 7 (1): 131 - 136.

Facial nerve neoplasms

The facial nerve is predominantly concerned with innervation of the muscles of facial expression but is also responsible for carrying afferent taste fibres from the anterior two thirds of the tongue (via the chorda tympani) and for parasympathetic innervation of several glands within the head and neck including the submandibular, sublingual and lacrimal glands. It originates from the pons as two roots, a large motor root and a smaller sensory root, the latter becoming the nervus intermedius. It then follows a complex course through the internal auditory canal (IAC), where the two roots merge, entering the Fallopian canal to pass through the temporal bone and into the parotid gland.

It consists of approximately 10,000 neurons that, in their extracranial course, are enveloped by Schwann cells. The neurons are surrounded by a fibrous sheath making up the nerve. The blood supply of the nerve is from three sources. The labyrinthine branch of the Anterior Inferior Cerebellar Artery (AICA) supplies the proximal nerve and passes through the internal auditory canal. The superficial petrosal branch of the middle meningeal artery supplies the nerve at the level of the geniculate ganglion. Finally the stylomastoid branch of the posterior auricular nerve supplies the nerve in its more distal portion.

In this paper, neoplasms that involve the facial nerve and their management are described. Primary tumours of the facial nerve are predominantly schwannomas or hemangiomas, the former being the most common, comprising around 64% of facial nerve tumours¹. However, other types of neoplasm can also involve the nerve. The table below shows a general classification and overview of tumours that can involve the facial nerve (Table 1).

Table 1 Summary of tumours of the facial nerve

Benign	Schwannoma Haemangioma
Primary Malignant	MPNST* Skip lesions from parotid malignancies
Metastatic (haematogenous spread)	Breast, kidney, lung, stomach

*MPNST: Malignant Peripheral Nerve Sheath Tumour

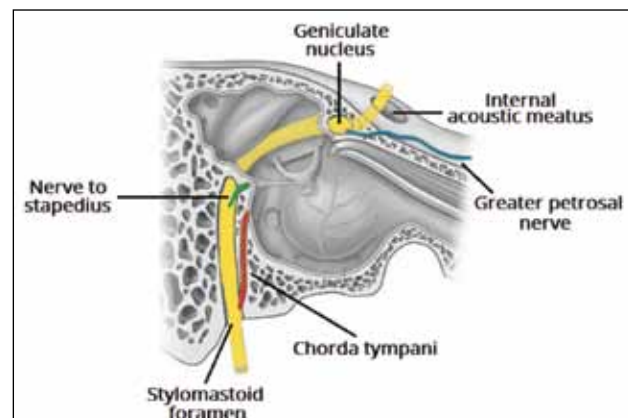


Figure 1: Drawing illustrating the intra-temporal course of the facial nerve.

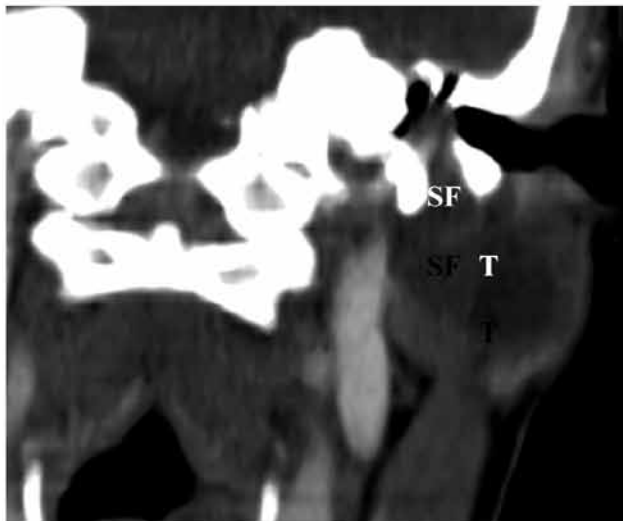
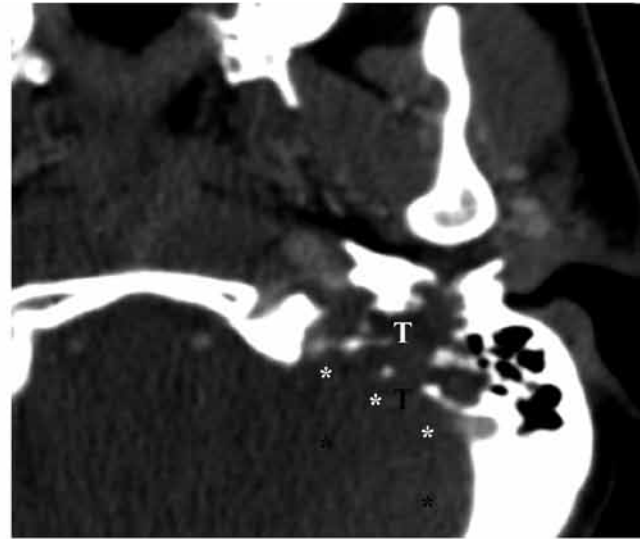


Figure 2: CT scan in patient with facial nerve schwannoma presenting with a parotid mass.

Top: Axial CT neck following IV contrast showing hypodense tumour (T) centred in the left parotid gland, with normal surrounding parotid tissue (P), extending superiorly into left temporal bone producing erosion of the posterior petrous face (***) .

Bottom: Coronal CT showing hypodense left parotid gland tumour (T) extending superiorly through the stylomastoid foramen (SF) into the left temporal bone. Intraoperatively, the lesion was closely adherent to the facial nerve nerve. Histology confirmed facial nerve schwannoma.

Facial nerve schwannomas

Facial nerve schwannomas (FNS) are rare benign tumours, and may occur at any point along the course of the facial nerve, from the cerebellopontine angle (CPA) cistern intracranially to the extracranial branches innervating the muscles of facial expression and salivary glands. FNS tend to present in the 5th decade of life and do not have a side preponderance. They present with a range of clinical features depending on anatomical location^{2,3}. Like schwannomas in other anatomical sites, FNS tend to be slow-growing, although the rate of growth may vary between individuals.

FNS were first described in 1930 and initial reports were sporadic^{4,5}. The introduction of high-resolution computerized tomography (CT) and magnetic resonance imaging (MRI) in the 1970s and 1980s led to a dramatic improvement in the ability to diagnose FNS with an associated rise in the number of cases reported.

Presenting symptoms

Facial weakness and/or hearing loss are the commonest presenting symptoms – a meta-analysis of 427 patients with FNS showed presenting symptoms of facial nerve palsy and hearing loss as 63% and 51% respectively⁶.

The segment involved may also influence presentation. For example, CPA and IAC tumours more frequently affect audiovestibular function. A study by Mowry et al recently reported a series of 16 patients exclusively with a CPA and/or IAC FNS and found that unilateral hearing loss was the most common presenting complaint followed by tinnitus and imbalance/vertigo⁷. Similarly, tumours of the labyrinthine portion of the nerve most commonly result in facial weakness. They may also present as a parotid mass (Figure 2). Although facial paresis is the most common presenting symptom, it can be of variable severity and may be transient or progressive⁸. Recurrent episodes of transient weakness and hemifacial spasm may also occur⁹.

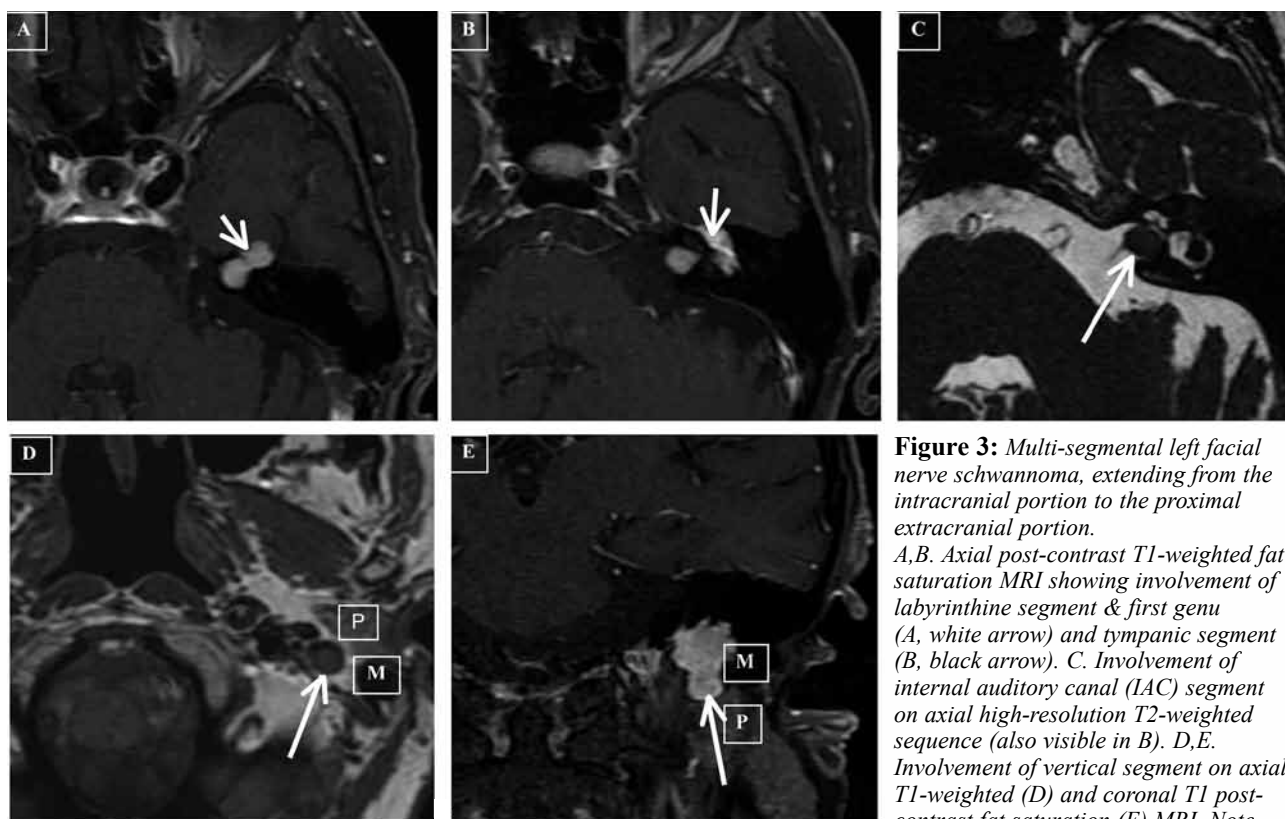


Figure 3: Multi-segmental left facial nerve schwannoma, extending from the intracranial portion to the proximal extracranial portion.

A,B. Axial post-contrast T1-weighted fat saturation MRI showing involvement of labyrinthine segment & first genu (A, white arrow) and tympanic segment (B, black arrow). C. Involvement of internal auditory canal (IAC) segment on axial high-resolution T2-weighted sequence (also visible in B). D,E.

Involvement of vertical segment on axial T1-weighted (D) and coronal T1 post-contrast fat saturation (E) MRI. Note 'waisting' of the schwannoma as it exits

the stylomastoid foramen towards its proximal extracranial segment in the parotid space. P, parotid gland; M, mastoid tip.

The natural disease progression of FNS is variable. Perez et al reported a series of 24 patients with FNS (mean age 44, range 18-65), of whom 11 underwent surgery for symptomatic tumors and 13 (54%) were enrolled in ongoing monitoring only¹⁰. In this latter group, 3 patients had a facial nerve paresis (HB 2 or 3) whereas the remainder had normal facial nerve function. During a mean follow up of 5 years, facial function remained unchanged for 8 patients (62%) and deteriorated in 5 patients (38%). During this interval, 4/13 patients (31%) demonstrated tumour growth on serial MRI (mean 1.4mm/year, range 0.7-2.6mm/year) and 3 had subsequent surgery. In our series of 28 patients from Manchester, 14 patients were initially managed conservatively and the remainder had primary surgical intervention. Two patients in the conservative managed group had growth of their FNS however their facial function remained stable (HB1 and HB3 respectively) and three patients had a deterioration in their facial nerve function (beyond HB3) and were offered surgery (2 patients accepted and 1 patient declined)¹¹.

Diagnosis

The gold standard diagnostic tool for the identification of a FNS is T1 weighted MRI with gadolinium enhancement. This allows identification of multiple segments of the facial nerve, a feature that is highly suggestive of FNS (Figure 3). Nevertheless, it may be extremely difficult to

differentiate FNS from other pathologies, particularly if the radiological changes are confined to the CPA or the IAC as the appearance can be identical to that of a vestibular schwannoma. It may also be difficult to differentiate FNS from other rarer pathologies such as haemangiomas. All presumed VS should therefore have at least one scan with gadolinium to ensure that there is no adjacent VII nerve enhancement to suggest a FNS rather than a VS.

Classification of facial schwannomas

There is no widely used classification of FNS. Because of the multi-segmental nature of FNS it is often not particularly helpful to discuss these tumors in terms of size. A more useful method of classification is by the segment (s) involved. Such a classification also relates to symptoms to some extent. It may also be useful to classify the tumor according to the segments that have displayed significant expansion as it is common for segments adjacent to expanded segments to enhance with gadolinium.

Management

Currently, there are no widely accepted guidelines for the management of FNS.

The philosophy of the majority of skull base units in managing FNS is to preserve facial function wherever possible. The only indications for intervention are significant tumour growth, significant brainstem compression or deterioration of facial function to grade 4 or worse. It has been shown that, apart from an end to end anastomosis, no type of facial nerve graft can reliably produce a final HB Grade of 3 or better. End to end anastomosis is rarely possible in these cases. This knowledge dictates that unless there is a neurological indication to the contrary, a tumour presenting with facial function Grade 3 or better should be observed¹². Bony decompression of the tumour may also be considered under certain circumstances if it is likely to avoid deterioration in facial function and is unlikely to have a detrimental effect on the patient e.g. their audiovestibular function will not be compromised (figure 4).

There is weak evidence to suggest that early resection following deterioration of facial function is associated with better facial outcomes¹³⁻¹⁵. There are, however, some authors that suggest that outcomes are better if the tumor is removed at the first sign of facial weakness¹⁶. It is likely, however, that this will result in additional unnecessary facial weakness as some patients may not develop facial weakness beyond grade 3. It is possible that facial function may improve spontaneously in these tumors¹¹. Similarly, decompression without resection may result in improvement of facial function although there is no significant evidence base for this.

Stereotactic radiosurgery is also a treatment option for those patients with growing tumors and good facial function (Grade 1 to 3). This approach may also allow

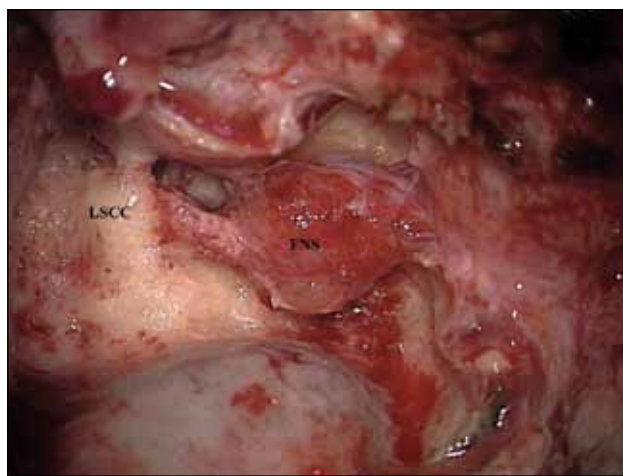


Figure 4: Intra-operative photograph of a right facial nerve schwannoma involving the vertical portion and the intraparotid portion of the facial nerve following facial nerve decompression (LSSC – Lateral semi-circular canal, FNS – Facial nerve schwannoma).

preservation of audiovestibular function, at least in the short to medium term.

Haemangiomas

Hemangiomas of the temporal bone are very rare benign vascular tumours that most often arise in the area of the geniculate ganglion where the blood supply of the nerve is particularly rich. They arise from the perineural vascular plexus¹⁷. They grow very slowly and are most commonly found in middle-aged adults. They tend to cause compressive symptoms even when very small in size. This distinguishes them from schwannomas which despite being larger in size often have few symptoms.

Presentation

Like FNS, symptoms depend on which segment of the facial nerve is affected although haemangiomas do not tend to involve multiple segments of the nerve. Hemangiomas at the geniculate ganglion usually present with facial palsy or hemifacial spasm and a conductive hearing loss may occur once the middle ear cavity is affected¹⁸. Facial palsy can occur even with very small haemangiomas. This may be because the haemangioma shunts blood away from the nerve and therefore causes ischaemia. Haemangiomas affecting the IAM tend to present with audiovestibular symptoms rather than facial nerve palsy^{19,20}.

Diagnosis

Diagnosis is made by imaging. Hemangiomas have indistinct bony margins as they do not have a capsule. This is in contrast to a FNS, which has a well defined remodeled bony margin. Occasionally haemangiomas may invade the bony trabecula or may form intra-tumour bony spicules which have been termed ossifying hemangiomas²¹. MRI signal characteristics include T1 (iso or slightly hypo intense), T2 (hyper intense) and intense contrast enhancement with gadolinium.

Treatment

Complete excision of the haemangioma with preservation of the facial nerve is the treatment of choice. If the facial nerve is directly infiltrated or adherent to the tumour, primary grafting with the greater auricular nerve or sural nerve (depending on site of tumour and length of graft needed) should be performed.

The difficult question is when to intervene? Should it be when the haemangioma is small and the patient has normal to HB3 facial nerve (HB≤3) with the hope that complete excision can be performed with nerve preservation, which will allow the nerve to recover function? Or should it be when facial nerve function

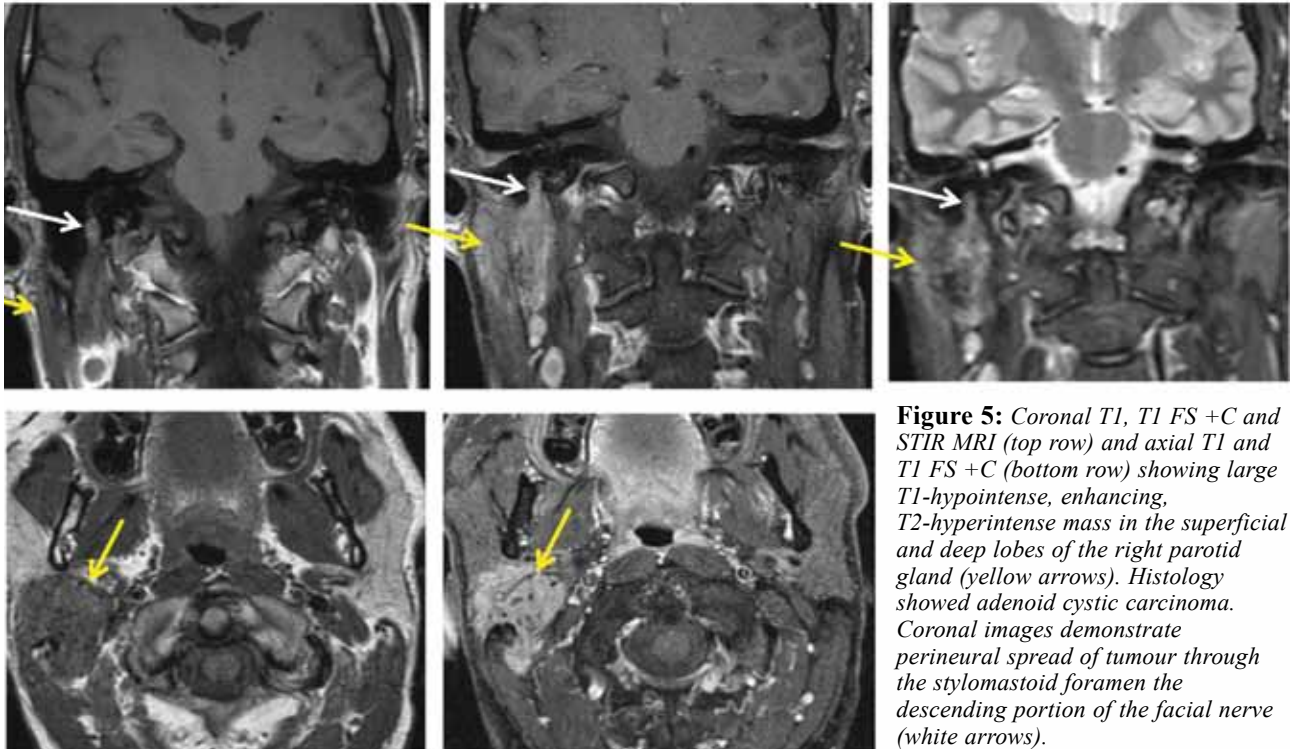


Figure 5: Coronal T1, T1 FS +C and STIR MRI (top row) and axial T1 and T1 FS +C (bottom row) showing large T1-hypointense, enhancing, T2-hyperintense mass in the superficial and deep lobes of the right parotid gland (yellow arrows). Histology showed adenoid cystic carcinoma. Coronal images demonstrate perineural spread of tumour through the stylomastoid foramen the descending portion of the facial nerve (white arrows).

deteriorates beyond HB3 when the tumour may potentially be larger and may have infiltrated the nerve which would necessitate a nerve graft which at best gives facial function of HB3? Some authors have reported that the facial nerve is almost always infiltrated by the tumour therefore advocate surgical intervention only when facial nerve function deteriorates beyond HB3²². This is in contrast to other authors who report good facial nerve outcomes with nerve preservation with a preoperative HB grade >3^{22,23}.

The surgical approach is dependent on tumor location, preoperative hearing level, and tumor size. In patients with normal hearing, tumours at the geniculate ganglion can be accessed via a transmastoid +/- middle fossa approach. Reports have been made of temporarily removing the incus to improve access to the geniculate ganglion to allow tumour removal and then replacing it and securing it with fibrin gel²⁴.

Malignant peripheral nerve sheath tumor (MPNST)

MPSNT are malignant tumours developing from cells present in peripheral nerve tissue. This includes Schwann cells, perineural cells or fibroblasts. The MPNST accounts for approximately 5-10% of all soft-tissue sarcomas and 25-50% occur in the setting of neurofibromatosis type 1 (NF-1)²⁵. MPNSTs are typically a disease of adult life, with most tumours occurring between 20 to 50 years of age.

The most common anatomical sites for MPNST include extremities and the head and neck region. It can arise from the facial nerve and present as a parotid mass however it is very difficult to differentiate from other parotid tumours on clinical examination and investigations such as fine needle aspiration.

Radical surgical excision with or without radiotherapy is the treatment of choice and together they offer a 5 year survival that ranges from 16-52% depending on the series. It is unclear whether the prognosis is worse in MPNST that occur in NF1 compared to sporadic tumours.

Meningioma

Meningiomas of the facial nerve are rare - they most likely arise from the arachnoid villi at the porus acousticus (opening between the CPA cistern and IAC) and Gasserian envelope²⁶. There has been reported associations with progesterone, breast cancer, and radiation therapy²⁷. Treatment principles are similar to that of FNS.

Metastatic disease

Secondary malignant tumours affecting the temporal bone are rare but may involve the facial nerve. They usually originate from the breast, lung and kidney and are a result of haematogenous spread²⁸. The facial nerve can also be involved by perineural spread from the parotid gland; most common pathology is adenoid cystic carcinoma, followed by acinic and mucoepidermoid carcinoma. Radiology is key

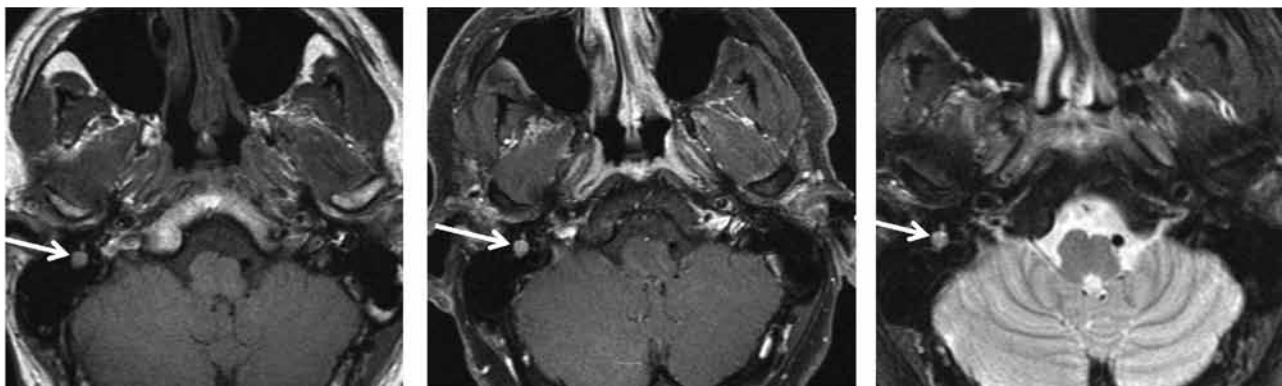


Figure 6: Axial T1, T1 FS +C and STIR MRI showing enlarged descending portion of the right facial nerve, in keeping with perineural spread of adenoid cystic carcinoma arising from the parotid gland.

in assessing for perineural spread; enlargement and enhancement of the facial nerve is seen in the presence of one of the malignant parotid tumours above (Figure 5 & 6).

Summary

FNS and haemangiomas are the two most common facial nerve neoplasms. Imaging is critical in their diagnosis and their treatment involves management dilemmas that need to be tailored to their tumour position, size, hearing, facial nerve functional status and patient expectations.

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Evaluation and management of recurrent laryngeal cancer

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Abstract

Local failure occurs in 10 to 25% of patients treated for early stage laryngeal carcinoma, regardless of the initial treatment. For intermediate stage carcinoma treated with partial laryngectomy, recurrence rates up to 50% have been reported in the literature. Local recurrence rates after (chemo-) radiotherapy for advanced-stage tumours range from 25% to 50%.

Early detection of recurrence in the larynx may allow for function preserving treatment, and may thus be associated with a better prognosis in individual patients. Recurrent laryngeal carcinoma are identified on the basis of patient-reported complaints, or on clinical findings or the results of imaging studies obtained during routine follow-up visits.

Evaluation of the larynx after initial treatment, particularly after previous radiotherapy, remains perplexing despite endoscopy and the availability of modern imaging studies. Both histopathological recognition of squamous cell cancer and determination of the extend of the disease are challenging, particularly in the irradiated larynx.

If initial radiotherapy fails, surgery is the logical option for re-treatment. While total laryngectomy is still considered the safest option in this situation, open or endoscopic partial surgery has the potential to salvage the recurrence while still preserving laryngeal structure and function. Laser resections are oncologically sound procedures in the salvage setting with a moderate larynx preservation rate in patients with limited recurrent disease. However, they provide inferior local control rates compared to open partial laryngectomy techniques. Radiotherapy as a salvage approach to failed partial laryngectomy has not been studied systematically. Salvage laryngectomy is

associated with high morbidity rates, poor overall and disease specific survival, prolonged hospital stays and decreased quality of life compared with primary surgery.

Local recurrence has an adverse impact on survival, on treatment-related morbidity, and on final functional outcome. When planning initial treatment, care should be taken to opt for therapeutic approaches with a low risk of recurrence.

Keywords

Laryngeal cancer, recurrence, salvage surgery.

J ENT Masterclass 2014; 7 (1): 137 - 143.

Introduction:

Recurrences following treatment of laryngeal carcinomas occur locally (in the larynx) or regionally (in the lymph nodes of the neck). Isolated distant metastases in patients with local and regional control are rare events. If distant metastasis occurs, it is most frequently associated with extensive local and regional recurrence, or with second primary tumours.

Local failure occurs in 10 to 25% of patients treated for early stage laryngeal carcinoma, regardless of the initial treatment¹⁻⁴. For intermediate stage carcinoma treated with partial laryngectomy, recurrence rates up to 50% have been reported in the literature⁵. Local recurrence rates after (chemo-) radiotherapy for advanced-stage tumours range from 25% to 50%. Patients with advanced stage head and neck cancer may expect only a 30% to 60% cure rate, and survival among patients with head and neck cancer has only marginally improved over the past 30 years. Depending on site, recurrence rates range from 25% to 50%⁶, and the incidence of additional, subsequent



Figure. 1: Local recurrence of carcinoma in situ following repeat transoral laser surgery for the same condition.

recurrence similarly ranges from 25% to 50%⁷. For the majority of these patients, some kind of salvage treatment will be available if recurrence is detected timely.

Most recurrences occur within two years from the onset of treatment. Smee et al. observed 47.6% of all recurrences following initial radiotherapy for early glottic carcinoma occurring within the first year, 71.8% within 2 years, 96.1% within 5 years, and the last failure occurring at 6.6 years after treatment⁴.

Identification of recurrent laryngeal cancer

Clinical signs and findings associated with local cancer recurrence in the larynx are multifarious. Figures 1 to 5 show some typical clinical aspects of recurrent laryngeal malignancy. Following organ sparing initial treatment, early detection of local treatment failures is essential for a timely initiation of second line treatment. Early detection of recurrence in the larynx may allow for function preserving treatment, and may thus be associated with a better prognosis in individual patients. Recurrent laryngeal carcinoma are identified on the basis of patient-reported



Figure. 3: Paratracheal lymph node metastasis following total laryngectomy for subglottic carcinoma.

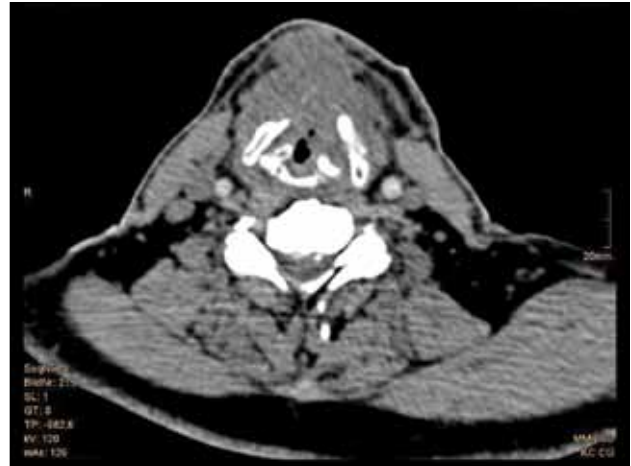


Figure. 2: Local recurrence following vertical partial laryngectomy.

complaints, or on clinical findings or the results of imaging studies obtained during routine follow-up visits. Patient reported complaints associated with recurrent disease frequently include voice changes, progressive swallowing problems, airway obstruction, visible or palpable neck lumps, and pain. All of these symptoms should prompt a rapid endoscopic and radiological assessment.

The differentiation of chondronecrosis versus recurrent cancer may be particularly difficult following radiotherapy or chemo-radiation. If histology fails to detect residual carcinoma, the decision on how to proceed with the patient has to weigh the chances of organ-preserving wound management for suspected chondronecrosis versus salvage total laryngectomy for suspected residual/recurrent disease or a functionless larynx with persistent aspiration and tracheostomy (Figures 6-7).



Figure. 4: Local recurrence following chemo-radiation for supraglottic carcinoma. The lesion was biopsied three times before a histopathological confirmation of recurrence was obtained.



Figure. 5: Peristomal recurrence following total laryngectomy for glottic-subglottic carcinoma.

The value of routine follow-up has been widely disputed in recent years. Kothari et al. studied the yield of routine follow-up visits in 1039 patients treated for head and neck cancer. Only 0.3% ($n = 3/1,039$) of asymptomatic patients attending routine appointments were suspected of having a recurrence, and two (0.2%) were found to have an actual recurrence following investigation. Of the total number of patients reporting a new suspicious symptom, recurrence was suspected in 56% ($n = 152/270$). Patients thus had an 98.1% sensitivity to raising suspicion for a recurrence based on the reporting of new symptoms with a 99.6% negative predictive value⁸.

Early detection of local recurrences may not yield better overall survival rates, but is hoped to allow for less invasive treatment in case of recurrent disease. Therefore, it is accepted that the follow-up of patients with a history of laryngeal cancer is a fundamental part of their care.



Figure. 7: Chondronecrosis of the epiglottis following chemoradiation for supraglottic carcinoma. Repeated biopsies gave no evidence of residual cancer in the larynx, and the condition was finally controlled with repeated microlaryngoscopic debridement and additional hyperbaric oxygenation.



Figure. 6: Chondronecrosis of the larynx following radiotherapy for recurrence of T1b glottic carcinoma treated initially with transoral laser surgery. Laryngectomy was performed, and histopathology confirmed residual cancer in the larynx.

The reasons for post-treatment follow-up include: evaluation of treatment response, early identification of recurrence, early detection of new primary tumours, monitoring and management of complications, optimisation of rehabilitation, promote smoking and excessive alcohol cessation and provision of support to patients and their families. The general structure of follow-up clinics is to have initial high-frequency (monthly to bimonthly) visits, especially in the first 2 years when the risk of loco-regional recurrence is known to be high and then reduce frequency, with follow-up often finishing at 5 years⁹. The main reason to extend follow-up visits beyond that period is to identify late-onset secondary primary tumours of the upper aero-digestive tract. It is generally recognised that apart from local and regional recurrences, patients treated for laryngeal carcinoma bear a significant risk for second primary tumours of the head and neck¹⁰. The risk of developing second primary tumour seems to depend on the intensity of smoking and drinking habits prior to the onset of the first neoplasm in head and neck. In the particular case of LC, the risk for developing a second primary cancer increased according to the number of cigarettes smoked at diagnosis of their laryngeal cancer. In a case-control study of patients with a head and neck cancer, the odds ratio (OR) of a second neoplasm for patients who continued to smoke was 2.9 (95% CI OR 1.8–4.1), and for patients who continued to use alcohol it was 5.2 (95% CI OR 3.3–7.9). According to the attributable risk estimation, persistent tobacco and alcohol consumption would be responsible for one-third of the SPTs in the patients with a head and neck index tumour^{9,10}.

Assessment of recurrent laryngeal cancer

Evaluation of the larynx after initial treatment, particularly after previous radiotherapy, remains perplexing despite

endoscopy and the availability of modern imaging studies. Both histopathological recognition of squamous cell cancer and determination of the extent of the disease are challenging, particularly in the irradiated larynx. Following initial surgery, anatomical changes within the larynx may be difficult to judge, and reconstruction techniques used to close surgical defects may hide recurrent or persistent tumour growth. Actinic changes include fibrosis, oedema, and soft tissue and cartilage necrosis. Oedema of the larynx is a frequent complication of radiotherapy, and even more so of chemo-radiation. An oedematous larynx may harbour recurrence or residual disease, but deep biopsies carry a risk of inducing laryngeal chondritis and chondronecrosis¹¹. The growth pattern of recurrent laryngeal carcinomas is different from that of primary carcinomas. Many recurrences present with multicentric tumour foci, localized below an intact mucosa, and further masked by post-treatment oedema and fibrosis. The identification of a recurrent tumour by endoscopic examination may be difficult with the risk of false-negative biopsies if they are superficial or not in multiple areas. CT and MRI do not allow sufficient differentiation between recurrent tumour and the squeals of (chemo-) radiotherapy. Moreover, after radiotherapy, patient-reported symptoms (hoarseness, odynophagia, and pain) may be similar to those from individuals with cancer recurrence⁶. Laryngeal mobility may be impaired by fibrosis or masked by oedema, as well. Therefore, distinguishing between recurrent carcinoma and the squeals of (chemo) radiotherapy can be a challenging clinical problem. Laryngeal biopsy can exacerbate postradiotherapy changes and can occasionally lead to chondritis, failure to heal, and further oedema. In addition, biopsies in previously treated areas may be falsely negative as a result of sampling error or missed deep residual tumour⁶.

There is evidence that magnetic resonance and positron emission tomography with computerized tomography (PET-CT) scanning are superior at detecting recurrence and second primaries. This is especially true following treatment with radiation or chemo-radiation therapy²⁶. If patients with LC have been treated with CRT or combined modality treatments, the use of PET-CT at 3 months to assess response to treatment should be considered. PET-CT has also the advantage of being a systemic evaluation⁹. However, PET has limited specificity, and radiation-induced inflammation and oedema cannot be reliably distinguished from neoplastic growth.

Treatment options

Recurrent head and neck carcinoma is a clinical challenge. Constrained by previous therapy, salvage modalities impose significant morbidities with potentially little, or

even detrimental, impact on outcome. The lower probability of long-term cancer control, combined with higher toxicity, often makes cure a less central, or unachievable, goal of patient care⁷. Laryngeal cancer, however, reveals distinctly favourable functional and oncological outcomes relative to other sites. This is particularly true following previous treatment for initially early stage carcinoma (stages I to 2 according to UICC). Therefore, it is reasonable to divide treatment options according to the initial stage of the disease and the treatment modality used initially.

In recent years, standard treatment for stage I and II laryngeal carcinoma has been a single modality approach including radiotherapy, transoral laser surgery, or open partial laryngectomy for the vast majority of all patients¹². Radiotherapy has traditionally been used for this condition in Northern Europe, Canada and the United States, but transoral laser surgery has recently gained more acceptance and is now the standard of care for small and accessible vocal cord carcinomas in most parts of the world. The role of open partial surgery for the management of early laryngeal cancer has been greatly diminished during the past decade¹³.

If initial radiotherapy fails, surgery is the logical option for re-treatment. While total laryngectomy is still considered the safest option in this situation, open or endoscopic partial surgery has the potential to salvage the recurrence while still preserving laryngeal structure and function.

In an analysis of 100 recurrent laryngeal carcinoma patients initially treated with (chemo-) radiation at Cleveland Clinic Foundation from 1997 to 2011, 72% of patients required total laryngectomy as a salvage procedure. In patients with early-stage disease (stage I/II) on initial presentation, more than half (51.4%) were diagnosed with advanced-stage cancer at the time of recurrence. The overall post-salvage loco-regional control rate was 70%, and the 5-year disease-specific survival was 70% and 55.2% in the early and advanced group, respectively. The 5-year disease-specific survival was not significantly different between the initially early stage and the initially advanced stage when compared with recurrent staging, initial treatment, salvage treatment, or nodal disease¹⁴. Pellini et al analysed 78 patients treated with supracricoid partial laryngectomy for radiation failure. Disease-free survival at 3 and 5 years were 95.5%. Early and late postoperative complications occurred in 27% and 17.9% of cases. Decannulation and satisfactory swallowing were achieved in 97.4% of cases.

A recent review of the oncologic outcomes of transoral laser microsurgery for radiorecurrent laryngeal cancer

concluded that transoral laser resections are oncologically sound procedures in the salvage setting with a moderate larynx preservation rate. However, they provided inferior local control rates compared to open partial laryngectomy techniques. The pooled mean estimates were: local control rate at 24 months after first transoral laser microsurgery (TLM), 56.9%; local control after repeat TLM, 63.8%; disease free survival, 70.9%; and overall survival, 74.8%. Pooled mean laryngeal preservation was 72.3%. The results from the literature showed that this procedure may primarily be applicable for earlier stage lesions (rT1/2), thus highlighting the selected nature of this group of patients carcinoma.

The authors also trust that conventional margins used during transoral microsurgical resection in the treatment of primary laryngeal cancer may not be applicable in the radiorecurrent setting. The relatively lower mean larynx preservation rate of 72.3% (TLM) versus 84% (open partial laryngectomy) is believed to be a reflection of the higher locoregional failure after TLM and the lower threshold for resorting to a total laryngectomy, partly because of limited surgical experience with open procedures, and the desire for complete oncologic clearance. The better overall survival rates in the partial laryngectomy cohort may be explained by the fact that they are likely to have good pre-treatment performance status, as good pulmonary function being a prerequisite for partial laryngectomy¹⁵.

If initial laser surgery fails, second transoral resections are feasible and may achieve ultimate local control. Radiotherapy as a salvage approach to failed partial laryngectomy has not been studied systematically. Mahler et al. from Norway observed 18 local recurrences following laser surgery for T1a vocal cord cancer in 188 consecutive patients³. Radiotherapy was used as the only salvage treatment in 9 out of these, and in combination with surgical salvage in five. Local control with larynx preservation was achieved in 96.6% of the entire cohort of 188 patients, indicating radiotherapy is a valid salvage option in selected patients.

Salvage following failed open surgery will invariably rest on additional surgery, usually total laryngectomy with or without postoperative radiotherapy.

Stomal recurrence after partial or total laryngectomy is usually considered to be incurable. Early infiltration of skin, trachea and oesophagus precludes surgical salvage in the majority of cases, and radiotherapy or chemo-radiation are seldom curative. Significant risk factors are glottic and subglottic tumour localization and regional tumour spread

at initial diagnosis. Postoperative radiotherapy in all stage III-IV cases can significantly reduce the risk of stomal recurrence. If complete resection can be accomplished, complex reconstructive techniques including myocutaneous flaps and/or microvascular tissue transfer is usually required^{16,17}. Pre-operative tracheostomy to secure a critical airway up to several weeks before definitive laryngectomy in patients with laryngeal cancer has been proposed as a risk factor for poor oncologic outcome. A recent retrospective study found no statistically significant differences in overall survival, disease specific survival, or laryngectomy-free survival between patients undergoing pre-operative tracheostomy and those not¹⁸. Stomal recurrence obviously is not linked to pre-treatment tracheostomy, but to lymphatic spread and subglottic involvement of the tumour, and missed postoperative radiotherapy.

Initial chemo-radiation has become the standard of care for many patients with advanced laryngeal carcinoma (stages III-IV)¹⁹. Depending on the indication to offer this approach, local, regional and distant site recurrences will occur in some 20 to 50 percent of patients. For these patients, there is a high incidence of distant metastasis. Also, advanced recurrent lymph node metastasis or locoregional tumour extent may preclude the possibility of any surgical salvage. These patients are candidates for palliative chemotherapy or targeted therapy, or supportive care alone. Re-irradiation remains investigational. Its use has been repeatedly described in the literature for patients with recurrent head and neck cancer²⁰. In clinical practice, however, it is hardly ever performed in laryngeal cancer patients due to the high risk of significant morbidity, notably radio-chondronecrosis. In contrast, patients with limited surgical recurrence or residual disease and without evident distant metastasis are candidates for salvage surgery. For these patients, the only feasible treatment is generally total laryngectomy⁶. Salvage laryngectomy, however, is associated with high morbidity rates, poor overall and disease specific survival, prolonged hospital stays and decreased quality of life compared with primary surgery²¹. Given the increased complications associated with neck dissection in the salvage setting, consideration should be given to conservative management of the neck in clinically node-negative patients (staged following primary radiotherapy or chemo-radiotherapy)²².

Involvement of paratracheal lymph nodes, pN-stage, extra-capsular spread, a non-cohesive tumour front, and thyroid cartilage infiltration are significant predictors of disease-specific survival. pN > 1 and the presence of adverse histological features were found to be independent predictors of survival. Around half of patients who

undergo total laryngectomy for stage IV carcinoma will die of disease within 5 years, with most deaths attributable to distant metastasis. Surgery provides excellent loco-regional control but patients, especially those with advanced nodal disease and/or adverse histological features, should be thoroughly screened for occult distant disease²³.

Complications

Salvage laryngectomy carries a high risk of post-operative infection with reported rates of 40-61%^{24,25}. Tissue toxicity resulting from previous irradiation and chemotherapy produces a higher incidence of complications after salvage surgery than after initial surgery performed on healthy tissue. Acute toxicity is an inflammatory response leading to impaired wound healing and increased risk of infections. Complications of salvage surgery are often multiple and interrelated, including infection, bleeding and formation of pharyngo-cutaneous fistula (PCF) resulting in complex and prolonged wound healing phases, and often require additional interventions²¹.

In recent years, numerous surgical modifications and adjuncts have been investigated in order to identify factors that could reduce the incidence of postoperative wound breakdown and salivary fistulae. Obviously, the routine use of introducing fresh “new” tissue to aid with the reconstruct the pharynx or to reinforce the pharyngeal closure is also very helpful^{26,27}. Published data support the use of a pectoralis major myofascial or myocutaneous flap in patients undergoing salvage surgery²⁸. (Figures 8-9). Other publications focused on the use of perioperative antibiotic treatment²⁴, routine use of salivary bypass stents²⁹, and the impact of preoperative haemoglobin and albumin³⁰. In abdominal surgery, there is strong evidence that the using triclosan-coated sutures significantly reduces the risk of surgical site infections³¹. Klein and co-workers, in a large cohort study including 2766 patients, found perioperative diclofenac treatment likely results in an increased proportion of patients with anastomotic leakage after colorectal surgery³². They concluded that cyclo-oxygenase-2 selective non-steroidal anti-inflammatory drugs should be used with caution after colorectal resections with primary anastomosis. While the applicability of these results for clinical practice in head and neck surgery remains to be confirmed, it is evident that operative techniques in laryngeal surgery need to be modified in patients undergoing salvage surgery for recurrent or persistent cancer following chemo-radiation for laryngeal cancer.

Local recurrence has an adverse impact on survival, on treatment-related morbidity, and on final functional



Figure 8: Typical pharyngo-cutaneous fistula following total laryngectomy as a salvage procedure for failed chemo-radiation.

outcome. When planning initial treatment, care should be taken to opt for therapeutic approaches with a low risk of recurrence. Patients wishing to opt for riskier approaches should be well aware of the potential chances but also the possible deleterious consequences of their decision. This equally applies to “minimally invasive” surgery in intermediate size tumours as well as to “organ preservation”



Figure 9: Pectoralis major myofascial flap covered with split thickness skin graft to reinforce pharyngeal closure.

conservative approaches in advanced stages. Avoiding local recurrences is by far superior to second line treatment with respect to survival and quality of life, even if the initial price to pay by the patient in terms of treatment radicality seems high at first sight.

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Outcomes of minimally invasive parathyroidectomy with dual-modality imaging

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Abstract

The success of minimally invasive parathyroidectomy is in the pre-operative dual modality imaging to accurately locate the adenomatous gland and aid a focused approach to gland excision. The accepted modalities are those of ultrasonography and Sestamibi scanning to allow both anatomical and functional information of the gland's position to be determined. Scan concordance results in a high confidence of accurate intra-operative localisation of the gland and resulting minimal surgical time, reduced cost and improved patient outcomes.

Key words

Primary hyperparathyroidism, minimal access surgery, dual modality imaging.

J ENT Masterclass 2014; 7 (1): 144 -148.

Introduction

Minimal access parathyroid surgery is becoming a well-recognised approach for the management of single gland adenomas causing primary hyperparathyroidism and is increasingly being utilised as an alternative to the gold standard of bilateral neck exploration¹⁻³. This approach utilises a smaller incision with shorter operative and recovery time when compared to the traditional bilateral neck exploration¹. It can be performed as a day-case procedure, the challenge being accurate localisation and correct placement of the incision to aid gland excision.

Dual modality imaging provides anatomical localisation of the gland relative to the thyroid lobe and adjacent structures through focused ultrasonography. The anatomical findings are reinforced by performing the Sestamibi (MIBI) scan, which is a functional scan. This also allows us to anticipate other challenges preoperatively, such as the presence of

thyroid nodules or adjacent lymphadenopathy, as well as identification of ectopic adenomas.

Aims

Accurate localisation pre-operatively of the parathyroid adenoma responsible for the primary hyperparathyroidism allows a focused approach and excision of the gland via a minimally invasive incision, without the need for an open four-gland exploration. We aim to share our experience of the benefit of high quality preoperative dual modality imaging (ultrasound and Sestamibi scan) in minimal access parathyroidectomy

Methods

After a diagnosis of primary hyperparathyroidism is established by the endocrinologists, dual modality imaging is organised prior to referral to the otolaryngologists for the one-stop ENT parathyroid clinic. The imaging is then reviewed and if a non-ectopic single-gland adenoma is identified, the patient is listed for a day-case minimally invasive parathyroidectomy.

The success of the operation is determined both biochemically and via an intra-operative frozen section confirming that the excised gland is parathyroid tissue. Biochemical confirmation is achieved by comparison of calcium levels preoperatively and at the 6 weeks outpatient follow-up.

Results:

A retrospective case note review was carried out of 190 single gland parathyroid adenomas for which minimally invasive parathyroidectomies were performed by the senior author in one hospital between 25/04/06 – 15/07/14.

There were 143 females and 47 males, with a mean age of 61.83 years (range 19-87), 88% were referred to ENT via

endocrinology, 21% were referred via other physicians and one case was referred directly from a General Practitioner.

Sixty six percent of patients presented with non-specific symptoms of hypercalcaemia and were diagnosed on serum profiles. Presentations included nephrolithiasis (18%), musculoskeletal pain (16%), abdominal pain (4%), psychic disturbance (4%) and metabolic abnormalities (0.5%). The average pre-operative parathyroid hormone (PTH) level was 23.1pmol/L with a pre-operative calcium of 3.0mmol/L.

The location of the adenoma was determined anatomically via ultrasonography and functionally via sestamibi scan. Comparison of the imaging results found via dual modality had a 77% concordance rate. Successful surgical localisation and biochemical cure was achieved in 100% of cases in this group of concordant scans.

The intra-operative positions of the adenomas were consistent with the imaging (ultrasound and/or MIBI scan). Overall, there was a 96% concordance between intra-operative location of the adenoma with the pre-operative imaging. (Table 1 and Table 2). Utilising ultrasonography alone gave a 97.8% specificity whereas MIBI alone located 82% compared to intra-operative gland position. A comparison of the size of the adenomatous gland shows that there is a good correlation of the ultrasound determined scan pre-operatively with the size measured ex-vivo by histopathology. (Table 3)

The operation was carried out under local anaesthesia in 6.3% of cases with comparable outcomes to general anaesthesia. The overall mean operating time is 59.8 minutes (range 12-135 mins), with 96.3% of specimens confirmed as parathyroid tissue on intra-operative frozen section.

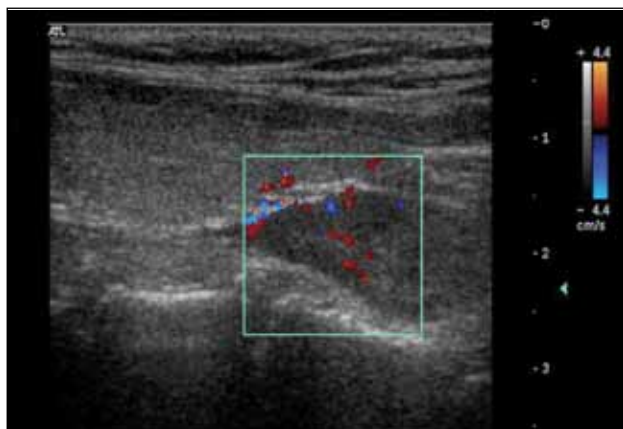


Figure 1: Ultrasound scan with Doppler showing a parathyroid adenoma.

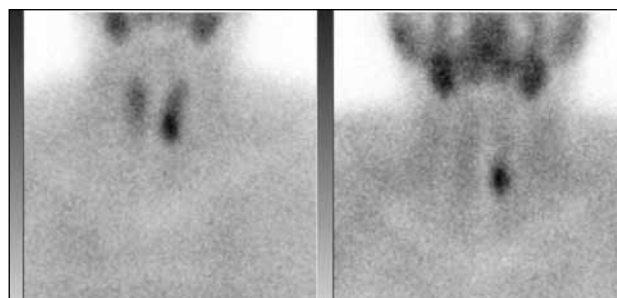


Figure 2: A Sestamibi scan showing a hyperfunctioning parathyroid gland with increased uptake of radioisotope in the left lower zone of the neck.

Post-operative recovery was uneventful with 94% of patients being discharged home within 24 hours and there were no reported complications of bleeding, infection, haematoma or laryngeal nerve palsy in our case series. The remaining had co-morbidity or social circumstances that prevented early discharge. Biochemically, the calcium reduced by an average of 0.55 mmol/L at the outpatient follow up, in comparison to the pre-operative levels.

Table 1: Correlation of gland located by ultrasonography, in comparison in intra-operative findings

Location of gland	% correlation
Right upper	100
Right mid	93
Right lower	100
Left upper	100
Left mid	100
Left lower	100

Table 2: Correlation of gland located by Sestamibi scanning, in comparison in intra-operative findings

Location of gland	% correlation
Right upper	100
Right mid	30
Right lower	86
Left upper	82
Left mid	100
Left lower	75

Table 3: Comparison of size between ultrasound imaging and histopathology

	Ultrasound imaged size (mm)	Histopathology size (mm)
Mean	16.19	17.19
Range	5-60	5-60

Table 4: Biochemistry pre-operative and post-operatively				
	Pre-op calcium (mmol/L)	Post-op calcium at follow up (mmol/L)	Preop PTH (pmol/L)	Post op PTH (pmol/L)
Mean	3.0	2.5	23.1	4.6
Range	2.71-4.61	2.19-3.07	7.2-147.5	0.2-16.9

Discussion

Primary hyperparathyroidism is a biochemical diagnosis, which is supplemented by pre-operative imaging to afford increased surgical success via a minimally invasive approach, a significant reduction in operating time and complications. Imaging also aids localisation of ectopic parathyroid glands, which was often the cause of unsuccessful bilateral neck explorations⁴.

Increasingly, the diagnosis is picked up on routine blood tests in primary care and patients are referred for diagnosis in tertiary care centers. This involves pre-operative radiographic evaluation and subsequent surgical exploration via a minimally invasive approach.

First line imaging studies are agreed to be ultra-sonography (US) and Sestamibi scanning^{5,6} due to their cost-effectiveness and diagnostic accuracy. Other modalities may be helpful in revision surgery. These include computerised tomography (CT) scans, 4DCT, MRI and PETCT.

CT scans, although widely available, are costly and involve radiation exposure. They offer no advantage over ultrasound in identifying abnormal parathyroid glands but do have a role in identifying ectopic glands in re-exploration cases⁷. Four-dimensional computed tomography (4D-CT) scans provide anatomical and functional information of the abnormal parathyroid glands useful in localising ectopic or intra-thyroid parathyroid adenomas. It helps for better preoperative planning in revision surgery in a scarred field with poor tissue planes⁸. Magnetic Resonance Imaging (MRI) is less commonly used but demonstrates excellent anatomic detail to localise ectopic glands via a non invasive, radiation free modality with the advantage that images are not degraded by streak artifacts from surgical clips or previous surgery⁹. The use of PET-CT is reserved for patients in whom other imaging modalities have failed to find the abnormal parathyroid gland¹⁰.

In our study, there is a positive correlation between preoperative imaging and surgical findings. The accuracy of localisation is increased further when dual modality imaging is concordant (77%) with this conferring 100% surgical localisation of the adenomatous gland, as confirmed by frozen section and subsequent biochemical analysis.

There have been a number of studies that have supported the success of pre-operative^{1,2,11-13} imaging for parathyroid surgery using dual modality imaging, however there is discordance in the literature with some advising against the routine use of imaging prior to a first time parathyroidectomy⁴ but agree with their use in revision cases.

Contributory to the success of the pre-operative imaging is the participation of a dedicated radiologist with an interest in parathyroid surgery who performs both the US and MIBI scan and is experienced in their interpretation¹². Care is taken to ensure that the ultrasound scans are performed with the patient supine and head extended, akin to the position on the operating table, to further aid the intra-operative localization and placement of the incision¹. The ultrasound scanning field extends from the carotid artery to the midline longitudinally and from the hyoid bone superiorly to the thoracic inlet inferiorly, in a transverse plane⁶. Useful maneuvers may be utilised, such as asking the patient to swallow to reveal inferior parathyroids that are located deep to the clavicles¹⁴ as well as compression of subcutaneous tissue and strap muscles in some patients can delineate the incompressible adenoma relative to other structures⁶. This approach enables us to minimise the biggest drawback of ultrasonography; operator dependence. The literature reports that the success in gland localisation has an intra-operative dependency between 33-79%¹⁵.

According to the literature, the sensitivity of picking up glands >0.5gms is 85% on US¹⁶ and there is no difference in identifying glands based on serum calcium and PTH values¹⁷. Ultrasound however, will not be able to pick up the 5% of adenomas that are in ectopic positions⁵ such as in the mediastinum¹⁸, retro-oesophageal, intra-thyroid¹⁹ or paratracheal areas.

In 3% of our cases, we were unable to locate the adenomatous gland during primary surgical exploration. Well documented causes of false positives on the ultrasound scan are thyroid nodules, lymph nodes¹³ or Hashimoto's thyroiditis^{20,21}. It is particularly challenging to differentiate parathyroid adenomas from thyroid nodules in patients with enlarged multinodular goiters which distort the surrounding anatomy, and especially with intrathyroid parathyroid adenomas⁶.

The typical appearance of a parathyroid adenoma on ultrasound is an ovoid, extra-thyroidal lesion with a connective tissue plane separating it from the thyroid gland and an extra-thyroidal peripheral vascular supply from the poles giving the gland an “arc” of vascularity⁵. In contrast, a lymph node is kidney shaped with parenchymal flow in a central and linear distribution and hence the colour Doppler can be utilised to differentiate between the two⁶.

Ultrasonography (US) allows us to conduct a non-invasive, inexpensive outpatient procedure without radiation to the patient, in order to localise with precision, the relation of the adenomatous gland to adjacent structures. It also allows differentials to be excluded due to key characteristics such as enlarged lymphadenopathy, striated muscle strands of the longus colli muscle as well as features typical of a parathyroid carcinoma such as cystic degeneration, calcification and heterogeneity with local invasion²².

Technetium99m methoxyisobutylisonitrile (Sestamibi) scan is the modality which picks up the hyperfunctioning gland, which retains the Technetium longer than the other parathyroids and thyroid gland due to its increased mitochondrial activity²³. This appears prominent on the 2 hour delayed image, due to prolonged and avid uptake of the radioisotope^{5,6}. Factors that increase the sensitivity of the Sestamibi scan include high serum calcium²⁴, high PTH levels²⁵ and low vitamin D levels²⁶. The literature reports a sensitivity of 95% for parathyroid adenoma location using this method²¹.

A major benefit of the MIBI scan is that it allows ectopic adenomas to be identified, most commonly in the mediastinum²⁰ which are difficult to localise on ultrasonography. There is a subset of patients identified in the literature as posteriorly located upper parathyroid glands (PLUG) that have descended to become located in the tracheo- esophageal groove or retroesophageally, which are difficult to detect on ultrasonography. It is advised that primary hyperparathyroid patients with preoperative positive MIBI and negative US are more likely to have PLUGs. These should not be assumed to be a lower gland adenoma before reviewing the lateral planar MIBI views to exclude an upper parathyroid tumor that has descended into the tracheoesophageal groove²⁷.

The use of further imaging modalities may be useful for patients with persistent or recurrent disease or inconclusive results on Sestamibi. These include Sestamibi-single photon emission computed tomography (SPECT-MIBI) which provides a multi-dimensional higher resolution images with a 92-98% sensitivity compared to 71-79% of using MIBI alone^{28,29}. One study found that the sensitivity of utilising a MIBI-SPECT-CT 30 is 88% compared to CT alone (65%) and MIBI-SPECT alone (55%)³¹.

A comparison of the use of 4D-CT, found that it provides significantly greater sensitivity than Sestamibi imaging and US for precise (quadrant) localization of hyperfunctioning parathyroid glands, both functionally and anatomically³² as it allows distinction of parathyroid lesions from other cervical masses.

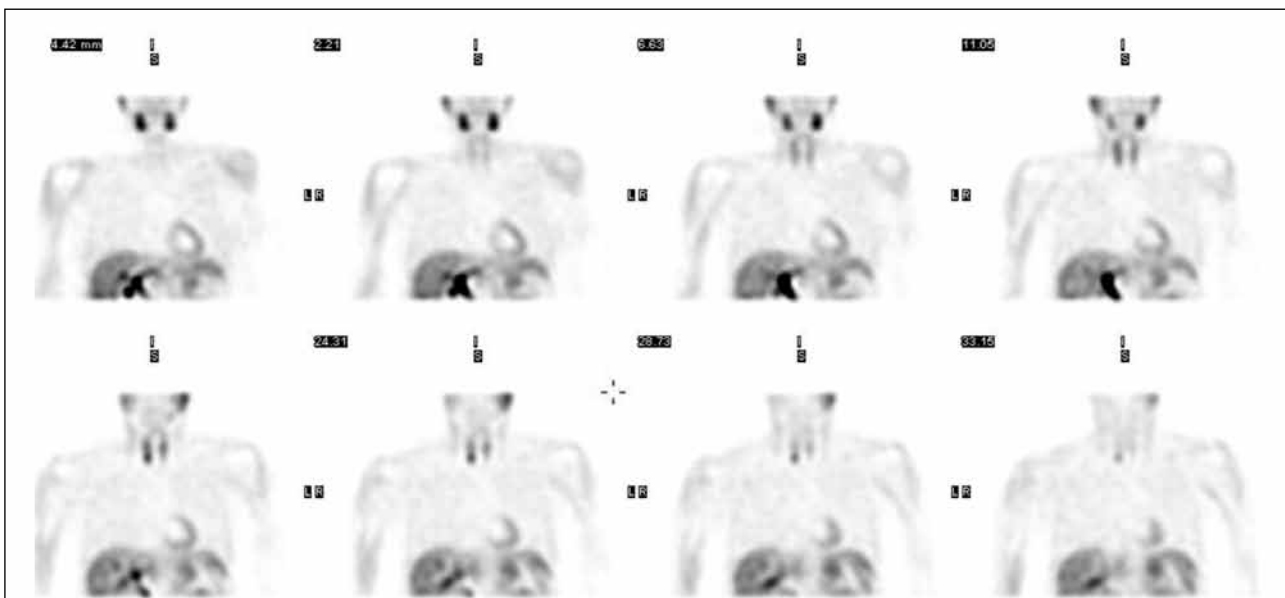


Figure 3: A single photon emission computed tomography (SPECT) Sestamibi Scan showing a right lower zone hyper-functioning parathyroid gland.

One major limitation of the MIBI scan is that it may not light up all adenomatous glands and this can result in difficulty when there is multi-gland disease³³, especially when the scans are not concordant. Additionally this modality also has the drawback of false positives in thyroid nodules³⁴.

The authors would recommend the use of minimally invasive parathyroidectomy for all single gland adenomas when the pre-operative dual modality imaging is concordant. However care should be taken to counsel patients regarding the possibility of more than one adenomatous gland as when scans are not concordant, this may result in more extensive exploration including four-gland exposure.

Conclusion

Pre-operative dual modality imaging utilising ultrasound and Sestamibi scans provides an accurate anatomical and functional location of the adenomatous gland. We have shown that concordance of the scans provides 100% agreement with the surgical site location, as confirmed by intra-operative frozen section. This allows a focused approach to gland excision and management via a day-case minimally invasive parathyroidectomy incision over the location of the gland. Thereby, benefits are conferred for the patients in terms of a smaller scar and quicker healing, with a good subjective satisfaction rate at follow-up.

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Are head bandages really necessary after ear surgery? A systematic review

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Abstract:

Objective:

A systematic review to evaluate the role and effectiveness of the use of head bandage after routine elective ear surgery.

Data Source:

The databases which were searched for this systematic review included OVID (Medline, Embase), EBSCO collections (CINAHL), Cochrane Library, Pub Med (the US National Library of Medicine) and Google Scholar.

Study Selection:

Our review resulted in the selection of randomised controlled trials and case series of studies comparing the effectiveness of the use and absence of head bandage after elective ear middle ear surgery (myringoplasty, mastoidectomy, cochlear implantation etc). Initial search identified 71 articles only. All titles and abstracts were reviewed by two of the authors, and thirteen relevant articles were studied. Out of these 13 studies only 4 met the inclusion criteria for this systematic

review. These included 2 randomised controlled trials (RCTs), 1 retrospective case series and 1 literature review.

Results:

2 RCTS (Level 1b) included the use of head bandage in middle ear surgery, both these studies showed no statistically significant difference in post operative outcomes between the two groups. This finding was also supported by the retrospective case series involving patients undergoing cochlear implantation.

Conclusion:

Current available evidence including two level 1b and one level 2b show no advantage of the use of head bandage after middle ear surgery. This systematic review concludes that head bandages are not required after routine uncomplicated middle ear surgery.

Keywords: head bandage, pressure dressing, ear surgery, middle ear surgery, mastoid surgery.

Stability and survival of bone-anchored hearing aid implant systems in previously irradiated temporal bone

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Introduction:

Bone-anchored hearing aids (BAHA) are based on the principle of osseointegration, which is fundamental to implant stability and survival. Previous exposure to ionising radiation may compromise this, with reports of

reduced survival of dental implants in previously irradiated head and neck cancer patients. No data exist, however, regarding BAHAs in patients with irradiated temporal bone. We sought, therefore, to investigate implant stability and survival in such patients.

Methods:

Patients were identified retrospectively from our electronic BAHA database. Hospital records were reviewed for demographics; operative technique; complications; and details regarding previous irradiation. Implant stability was assessed by resonance frequency analysis (RFA), generating a numerical value – implant stability quotient (ISQ). Extrapolating from dental studies, successfully loaded implants typically have ISQs of ≥ 60 .

Results:

Seven patients were identified for inclusion. Mean time between irradiation and implant insertion was 33 months (range 16-72), and mean time from implant insertion to RFA measurement was 41 months (range 3-96).

Operatively, all patients underwent single-stage procedures under local anaesthesia. One patient suffered a Holger's grade 2 skin reaction, while two suffered significant graft failure, requiring multiple revision procedures. The implant survival rate was 100%. All ISQ values were >60 , with a mean of 66.9 (95% confidence interval: 63.1-70.6).

Conclusions:

Our data support sufficient osseointegration of BAHA implant systems in patients with previously irradiated temporal bone but highlight issues with wound healing. Contemporary soft tissue preservation operative techniques will likely overcome this, facilitating safe and efficacious BAHA insertion in this small but ever-increasing group of patients.

Botulinum toxin for the treatment of pharyngoesophageal spasm in post-laryngectomy patients: the Aintree experience

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Introduction:

Pharyngoesophageal spasm (PES) may cause dysphagia, central valve leak, and is the most common cause of speech failure following transoesophageal puncture in post-laryngectomy patients. Although botulinum toxin has been used effectively for the treatment of PES, data concerning patient-reported outcomes and efficacy for central valve leak is limited. We sought to evaluate results of botox for PES spasm using both subjective and objective measures.

Methods:

Data was collected prospectively (February 2010-August 2013) on thirteen patients undergoing botox injection for PES as identified by videofluoroscopy. We collected digital voice recordings, air pressure measurements (APMs) for speech, and quality of life (QoL) data pre and post-procedure – University of Washington QoL questionnaire, MD Anderson swallowing inventory and Voice Handicap Index (VHI).

Results:

All injections were undertaken in the outpatient setting. APMs for a sustained vowel reduced by 18% following botox injection, while maximum phonatory times increased by 63% (mean increase from 8 -13 seconds). Sustained vowel amplitude dropped (mean 87db- 83db), with an associated reduction in sustained vowel frequency (117Hz-77Hz). Subjectively, symptoms of dysphagia improved, with a 10.5% mean improvement in scores on MD Anderson questionnaires. Overall quality of life scores showed modest improvement, with scores increasing by 7.6%. Mean scores on VHI improved by only 2.0%.

Conclusion:

Our series confirms the safety and objective efficacy of botox injection for PES. Quality of life measurements were less convincing and this disparity between subjective and objective measurements must be considered when treating such patients.

Day case parathyroid surgery: without intra-operative PTH

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Introduction

Parathyroid surgery for single gland adenomas following accurate localisation with dual modality imaging is helpful in focused day case surgery. It is establishing itself as the acceptable definitive treatment of primary Hyperparathyroidism (pHPT) and patients may undergo Minimally Invasive Parathyroidectomy (MIP) with excellent cure rate and minimal morbidity. Accurate localisation is the key to successful MIP.

Aim

1. To demonstrate the safety, efficacy and subjective patient satisfaction of Day Case Parathyroidectomy.
2. To investigate the accuracy of pre-operative radiological localisation in relation to operative findings.

Methods

A retrospective casenotes review of day case parathyroidectomy by a single surgeon, was performed. Data collected included patient demographics, presentation, radiological investigations, operative findings, biochemical outcomes, bed/resource savings and subjective patient satisfaction.

Results

Between 2006-2013, 170 consecutive patients underwent day case parathyroidectomies. Pre-operative Ultrasound scans and MIBI scans were 96.4% accurate with concordance in 78.9%; intra-operative frozen section of 97% confirmed parathyroid tissue.

93.5% of patients who underwent MIP went home within 24 hours. This resulted in a financial gain of 340 bed-days translating into saving of £45570.2, along with theatre efficiency resulting in savings of £217838; a saving per case of £1549.47

Over 95% of patients were subjectively satisfied during follow-up.

Conclusion

Day Case Parathyroid surgery is a safe, effective and well-tolerated procedure in the treatment of single gland pHPT. It confers significant advantages over the traditional gold standard treatment of bilateral neck exploration. It is an efficient use of theatre and hospital resources and beneficial for patient experience.

What's new in rhinomanometry? A comparison of 4-phase rhinomanometry with the classic method using nose models

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Abstract:

Background:

Rhinomanometry is an objective test to measure the nasal patency in the form of nasal airway resistance (NAR). There are various different methods used to measure NAR in rhinomanometry, which include the classic method at fixed pressure of 150Pa or 75Pa, Broms method and the new 4-phase rhinomanometry. The more complex 4-phase

rhinomanometry is now promoted as being superior to the simple classic method despite the long history of use of the classic method in clinical trials on medicines and nasal surgery. Clinicians and researchers may be confused by the choices available between these different parameters. This study aims to determine if there is any difference between the NAR measurements obtained by the classic and 4-phase rhinomanometry methods.

Methodology:

In-vitro study with measurements of NAR using both methods when applied across four artificial nose models of decreasing diameters, representing a wide range of human nasal resistances.

Results:

No statistically significant differences were found between NAR values obtained from both methods ($U > U_{critical}$, $p > 0.05$). Strong, positive correlations were found between NAR measured with both methods, which were statistically significant ($r_s = 1.000$, $p < 0.001$).

Significant correlations were also found between logarithmic transformation of NAR from classic method when compared with logarithmic transformation of vertex resistance and effective resistance from 4-phase rhinomanometry at 150Pa ($r > 0.90$, $p < 0.05$).

Conclusion:

No statistically significant differences were found between the NAR values measured using both methods. The complexity of 4-phase rhinomanometry does not provide any benefit over the simpler classic measurements, as both methods give the same resistance values.

Should we be operating on all thyroid cancers?

George Garas, Ali Qureishi, Imran Khan, Fausto Palazzo, Thanos Athanasiou, Emmanouil Zacharakis, Neil Tolley

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Introduction:

Thyroid cancer is the commonest endocrine malignancy with a rising incidence. Wider access to imaging investigations has increased the detection of asymptomatic thyroid nodules known as “incidentalomas”. This combined with the introduction of thyroid cancer screening programmes in certain countries has led to a surge in the diagnosis of papillary thyroid microcarcinoma (PTMC). PTMC (<1cm in diameter) generally follows an indolent course and carries an excellent prognosis. As a result, the role of surgery for this cohort of patients has been questioned.

Methods:

A systematic review was conducted by searching the Cochrane Controlled Trials Register, Medline and EMBASE databases from 1966 onwards. A total of 506 studies were retrieved. Based on design, number of patients and origin (high volume/specialised centres and

national registries) 8 papers were identified that provided the best evidence to answer the question.

Results:

The clinical behaviour of PTMC tends to be indolent and the associated prognosis excellent. The literature suggests that when PTMC is unifocal, confined to the thyroid parenchyma and with no metastases, the risk of mortality is very low (<0.1%) - even without treatment. Cadaveric studies further confirm the high prevalence (6-36%) of subclinical PTMC in patients dying of other causes.

Conclusions:

Patients diagnosed with incidental PTMC confined to the parenchyma of the thyroid gland and with no metastases, family history of thyroid cancer or history of ionising radiation exposure may opt for conservative management based on the reported findings. Serial ultrasound imaging with regular outpatient review may represent an alternative to surgery.

Epistaxis management: Is there a role for floseal?

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Abstract:

Epistaxis is the most common emergency encountered by otorhinolaryngologists, with more than 27000 patients presenting to emergency departments (ED) in 2009. Most patients with nosebleeds are managed in a stepwise treatment fashion, starting from conservative and escalating to more invasive treatments. In our centre we have previously audited the management of epistaxis, completing multiple audit cycles since 2007. Our data has previously shown that on average patients presenting with epistaxis to our centre had a 38% admission rate and were admitted for an average of 2.6 days.

We introduced the use of floseal, a haemostatic gel that stops arterial bleeding, as an adjunct to manage epistaxis.

We wanted to ascertain if patients could be managed using floseal and discharged on the same day of treatment. In our study we used floseal as an adjunct to our standard practice, to be used if nasal cautery was unsuccessful and rather than proceeding directly to nasal packing. Patients who were treated with floseal were observed for 30-60mins within the ED and discharged directly. We retrospectively reviewed the notes for all patients that presented with epistaxis over a six month period. 320 patients presented to ED, of which 40 were treated with floseal. The admission rate was reduced from 38% to 27%, which was statistically significant. Our results show that floseal is a useful adjunct in the treatment of epistaxis to decrease patient admission rates and has been added to the roster of therapeutic options to manage epistaxis in our centre.



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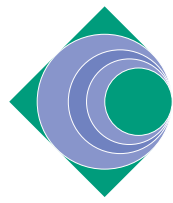


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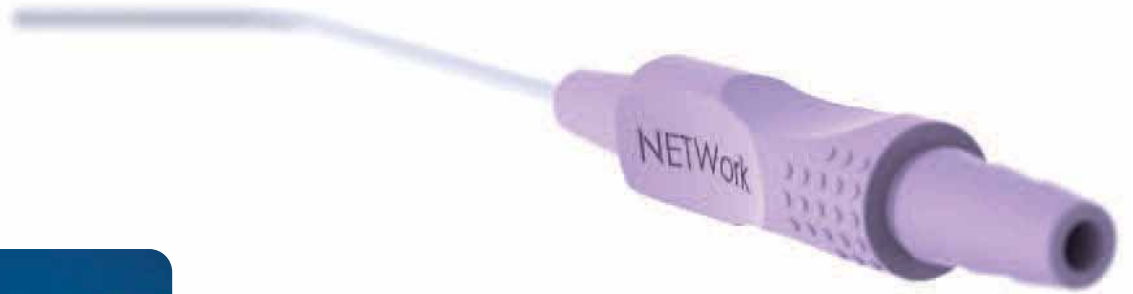
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