Paediatric reinnervation update

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Abstract
The management of unilateral or bilateral vocal fold palsy is challenging for otorhinolaryngologists. The ideal treatment should aim to restore the respiratory, phonatory, sphincteric and swallowing function without disruption of the laryngeal framework. After encouraging results for both unilateral and bilateral reinnervation in adults, these procedures have been performed in select paediatric patients, with the purpose of offering a long lasting treatment option in comparison with traditional procedures. With this review we hope to encourage further international collaborations and investigation in this field, since the benefits of the techniques appear to be particularly promising in paediatric patients.


Key words
Vocal fold palsy, laryngeal electromyography, laryngeal reinnervation

Introduction
The availability of the paediatric flexible nasolaryngoscopes has made the diagnosis of vocal fold palsy (VFP) easier among children. Consequently an increased prevalence of paediatric unilateral VFP has been shown1. This data is also reinforced by the higher survival rates among pre-term, very low birth weight infants, who frequently require surgical treatments including patent ductus arteriosus (PDA) ligation with an associated high risk of recurrent laryngeal nerve injury resulting in a unilateral vocal fold paralysis.

In the past congenital or acquired infections represented a large share of the aetiologies, but the implementation of vaccination programs and antibiotic treatments has drastically decreased their incidence2,3,4. Nowadays iatrogenic left VFP seems to be mainly related to cardiovascular disease5 with the estimated incidence of iatrogenic palsy following PDA ligation in babies under <1 kg ranging from 22.7 to 67%6,7. Right VFP is usually neoplastic or subsequent to a central lesion8.

Bilateral vocal fold palsy (BVFP) is mainly neurological or idiopathic. Arnold Chiari Malformations are the most frequently associated condition in children diagnosed with BVFP9,10.

Both unilateral VFP (UVFP) and BVFP are also complications following surgery for congenital tracheo-oesophageal malformations11. The early diagnosis of VFP is vital to improve morbidity and mortality in children with long-term respiratory complications following tracheo-oesophageal fistula (TOF) repairs.

However, despite all the heterogeneous information about the aetiology available in literature, the real incidence of VFP in children remains unknown and is therefore probably underestimated.

The management of VFP is challenging for otorhinolaryngologists, since the larynx is one of the main tools for human social interaction and therefore its functional impairment during growth can have dramatic consequences. The ideal treatment should aim to restore the respiratory, phonatory, sphincteric and swallowing function without disruption of the laryngeal framework.

The concept of laryngeal reanimation was developed in the early 1900s, but only in recent decades has reinnervation been applied in humans12. After encouraging results from both unilateral and bilateral reinnervation in adults, these procedures have been performed in selected paediatric patients, with the purpose of providing a more permanent treatment option in comparison with traditional procedures. It must be recognised however that the most common causes of unilateral and bilateral VFP in children differ to
those in adults; in adults usually the cause of laryngeal nerve injury is iatrogenic.

**Pre-operative work up**

In order to consider the option of laryngeal reinnervation, a comprehensive preoperative work up is crucial.

Direct dynamic and static evaluation of the larynx helps to define possible anatomical alterations or structural defects such as crico-arytenoid joint ankylosis, interarytenoid scars, interarytenoid webs or posterior glottic stenosis. A dynamic evaluation also helps to elucidate whether there is a breathing pattern coordinate with respiration and any paradoxical vocal fold movements. These conditions can be related to traumatic or prolonged endotracheal intubation, laryngeal trauma, inflammatory processes, radiation or caustic damage. Magnetic Resonance Imaging, and in select cases Computed Tomography, may be necessary to investigate the aetiology and associated pathologies, particularly in cases of bilateral vocal fold palsy. Assessment of cardiorespiratory function is fundamental to plan the treatment and includes specialist paediatric respiratory and cardiac opinion. Chest radiography is important to assess the extent of any pre-existing lung injury and also to assess the diaphragm in cases suitable for bilateral selective reinnervation techniques.

Evaluation of swallowing together with the involvement of speech and language specialists and with videofluoroscopy is helpful to investigate feeding difficulties and aspiration. The assessment of voice is fundamental and should include a thorough assessment working together with paediatric speech and language therapists, to use the most appropriate, accurate tests for each child. Videos are obtained of voice, cough and maximum phonatory times. Paediatric voice related quality of life scores and paediatric voice handicap index scores should also be documented for all children with VFP.

Genetic investigations help to characterise clinical features and diagnose mutations related to neuropathy that can affect possible donor nerves which is especially important when reinnervation is to be contemplated.

Laryngeal Electromyography (LEMG), further developed for use in clinical practice by Hirano and Ohala in 1969, is a useful examination in children with vocal fold immobility. It can help to determine the degree/extent of denervation, spontaneous reinnervation, synkinesis and muscle atrophy, and in cases where the differential diagnosis between paralysis and fixation is challenging. The examination of both thyroarytenoid muscles and posterior cricoarytenoids (PCA) is needed for a precise diagnosis, in particular in iatrogenic nerve damage, since it has been found that the recurrent laryngeal nerve (RLN) branch to the PCA is more frequently damaged during surgery.

Recent studies have shown that in iatrogenic VFP a waiting time of 6 to 9 months since the onset of the palsy may be more appropriate to establish the diagnosis, and confirm whether recovery is likely or unlikely.

The data obtained from these investigations is not only crucial in understanding the dramatic impact of vocal fold palsy in children but when considering treatment options. Therefore an early diagnosis of permanent nerve damage is key to plan an adequate management strategy or avoid unnecessary treatment if a possible recovery is expected.

LEMG can be carried out using total Intravenous Anaesthesia (TIVA) and also spontaneous respiration anaesthetic techniques. Simultaneous evaluation and palpation of the larynx can also be performed. Laryngotraechobronchoscopy during the same procedure allows other pathologies to be excluded, including not only the previously mentioned crico-arytenoid joint issues, but also laryngeal clefts which may be associated with TOF, subglottic cysts and stenosis in premature babies who may have had repeated intubations and tracheomalacia in babies with cardiac co-morbidities.

Self-assessment validated parental questionnaires in younger children such as the paediatric voice handicap index, paediatric voice related quality of life, Pediatric Eating Assessment Tool or STEP-CHILD are useful to evaluate the impact of voice and feeding difficulties on quality of life for children and their carers and provide an additional method for evaluating post-operative outcomes.

When the child’s cooperation is possible voice analysis and a more accurate maximum phonation time should be recorded.

**UVFP**

UVFP is characterised by loss of glottic competence and secondary impairment of the actions for which it is necessary, such as voice and cough production, straining and Valsalva’s manoeuvre.

Dysphonia is the leading symptom of UVFP, although neonates following PDA ligation may present with a weak cry and aspiration. Efforts to talk may be compromised by
a loss of air volume through the glottic gap. In children and teenagers UVFP can represent a risk for social and emotional disturbance and isolation as well as physical and functional impairment23.

Aspiration pneumonia may result in possible life threatening consequences particularly in pre-term infants with UVFP.

Surgery should be considered when conservative management has not been successful or when there is significant aspiration and dysphonia.

Injection mediatisation24 should be carefully performed. In newborn infants and children, the vocal fold mucosa is thinner and the different layers are not developed. In addition the ligament is not clearly detectable in children under 4 years. A correct choice of the material (ideally short lasting) and meticulous injection are essential to avoid scarring, granulation or disruption of a growing vocal fold25.

Type I thyroplasty26 does not provide adequate permanent results. As the larynx grows, the implant may be displaced or the size may be inadequate. Moreover procedures under local anaesthesia and where patient cooperation is necessary to make fine adjustments, and especially on the larynx are likely to prove exceptionally difficult in a child.

Currently the most widely used and well accepted reinnervation technique for UVFP is based on ansa cervicalis to RLN neurorrhaphy.

This procedure reinnervates the muscles of the hemi-larynx and can restore vocal fold tone, bulk and tension. There is no restoration of movement coordinate with respiration and phonation; hence it is defined as “non-selective”. The first satisfactory reports of this technique were published by Crumley in 198627,28. Positive outcomes have also been described by Olson et al. (1998), Miyauchi et al. (1998), Lee et al. (2007), Lorenz et al. (2008), Marie et al. (2010) and Weng et al. (2011) in larger retrospective case series in adults29,30,31,32,33,34. All of these reports demonstrated that in adults over 17 years of age non-selective reinnervation could restore the physiological laryngeal phonatory function to near normal/normal voice quality.

The application of this unilateral non selective laryngeal reinnervation (NSR) technique has been extended to the paediatric population. The first report was by Smith in 200835, who in 2015 published the largest report, on a cohort of 35 paediatric patients who underwent this surgery. Although the study revealed no significant association between age at time of surgery and outcome, a slight negative correlation was found with the length of denervation (a longer period of denervation resulting in a poorer outcome), though voice improvement was observed in all patients36,37. Zur and her group described their first results in 2012, with promising outcomes in 10 children under 14 years of age38. In 2015 Zur and Carroll published a comparison study between non selective reinnervation and injection laryngoplasty in 33 children with dysphonia. The study confirmed the hypothesis of long-term superior outcomes of NSR compared to injection laryngoplasty39, and thus the group offer NSR as a standard treatment option in appropriately selected children. Furthermore in 2017 the same group reported on three paediatric patients affected by UVFP who underwent successful NSR for aspiration primarily with concomitant dysphonia40. Following comprehensive assessment, multidisciplinary discussion and encouraged by the results in the literature, the indications of dysphonia and aspiration causing significant medical and psychosocial issues resulted in the authors performing the first NSR in the UK in a 6 year old affected by UVFP, with successful outcome41. In all of the documented cases in the literature good outcomes have been reported, with resolution of aspiration and improvement of voice. Our team has successfully embraced this procedure, only recently introduced into the UK, with good preliminary results42. This technique has been offered in a fully evaluated structured way through the development of a management algorithm (Figure 1) with the aim to establish the prognosis and plan best treatment43.

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**Figure 1:** A management algorithm for paediatric unilateral VFP.
Our group has now performed NSR in 5 paediatric patients, 2 male and 3 females, age range 2 to 16 years old, affected by iatrogenic UVFP. The postoperative outcomes in 3 have revealed a significant improvement in both voice and swallowing parameters and quality of life scores. In one case there has been no improvement following NSR and on reflection it is likely that this was due to a modification of the ansa nerve selection, therefore a revision procedure may be considered. We await the results of NSR following the most recent surgery. Table 1 summarises the findings of the recent literature following NSR in children. The procedure is currently offered to carefully selected children at our institution following a thorough multidisciplinary panel assessment and review.

### BVFP

BVFP usually presents with life threatening stridor in neonates and 50% of these children require a tracheostomy. Paediatric and laryngology specialists from our region have developed a prognostic and therapeutic algorithm for children with BVFP (Figure 2), to aid management in this often psychosocially complex group of children.

In addition to tracheostomy other surgical procedures may be considered for BVFP and include glottic widening procedures, such as lateralising sutures, cordotomy or arytenoidectomy. If BVFP is an option these techniques should be avoided as they result in permanent disruption of the laryngeal framework, with voice impairment and preclusion of a possible reinnervation.

Selective Laryngeal Reinnervation (SLR), as described by Professor Jean-Paul Marie, has the aim of restoring vocal fold movement coordinate with breathing and phonation. A root of the phrenic nerve acts as the donor for both posterior cricoarytenoid (PCA) muscles, with the goal of producing an inspiratory trigger on inspiration and consequent abduction of the vocal folds. The adductor muscles are reinnervated from a small branch of the hypoglossal nerve, active on phonation and swallowing. Both the recurrent laryngeal nerve and phrenic nerve are active on inspiration. This specific function can be mutually beneficial in nerve reanimation surgery. This has been supported by a recent report in which the RLN has been successfully employed as a donor nerve in a patient with a diaphragmatic palsy. Other authors have published good outcomes in the adult population.

Concerns may be expressed regarding possible permanent damage to the phrenic nerve in a child. As such a comprehensive respiratory assessment is essential prior to proceeding with the surgery. In adults the entire phrenic nerve is commonly used to restore shoulder abduction in brachial plexus injury without major problems. In children there are series that describe the safe use of a phrenic nerve root for the same purpose without significant respiratory impact.

### Table 1. A summary of the available evidence for NSR performed in children for unilateral VFP.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongkasuwan J et al.</td>
<td>2019</td>
<td>32</td>
<td>NSR performed at a younger age may have better voice outcomes compared to NSR performed 1 to 2 decades later.</td>
</tr>
<tr>
<td>Faoury M et al.</td>
<td>2019</td>
<td>1</td>
<td>The use of laryngeal EMG is crucial to predict outcomes and to choose the best treatment option. NSR may provide a permanent solution and should be considered in children as a management option.</td>
</tr>
<tr>
<td>Zur KB et al.</td>
<td>2017</td>
<td>3</td>
<td>NSR is a safe and effective option for the management of chronic aspiration pneumonia and dysphonia in patients with UVFP.</td>
</tr>
<tr>
<td>Farhood Z et al.</td>
<td>2015</td>
<td>3</td>
<td>There was statistically significant improvement in shimmer and Noise to Harmonic Ratio (NHR).</td>
</tr>
<tr>
<td>Smith ME et al.</td>
<td>2015</td>
<td>35</td>
<td>Denervation duration showed a slight negative correlation with postoperative outcomes. Voice improvement was seen in all patients.</td>
</tr>
<tr>
<td>Zur KB et al.</td>
<td>2015</td>
<td>33</td>
<td>The ANSA-RLN group showed better and longer-lasting perceptual and acoustic parameters in comparison with the injection and control groups.</td>
</tr>
<tr>
<td>Marcum KK et al.</td>
<td>2010</td>
<td>2</td>
<td>NSR previously described for older children and adults can be safely adapted for younger children (3 and 6 years old).</td>
</tr>
<tr>
<td>Crumley R et al.</td>
<td>1991</td>
<td>1</td>
<td>Improvement of pitch control in 8 years old patient treated with NSR.</td>
</tr>
</tbody>
</table>
In his case series Marie (2018) described three selective laryngeal reinnervation procedures performed in children under 3 years of age. Two of the children had idiopathic congenital BVFP and one iatrogenic BVFP; secondary to the cervicothoracic removal of a lymphangioma. Postoperatively the first two children have been decannulated and one has greatly improved with only slight stridor on demanding exercise. Selective reinnervation has also been performed in a 17 year old boy. He recovered bilateral inspiratory abduction and is now able to exercise without dyspnoea.

This procedure forms the basis of laryngeal reanimation and hence rehabilitation. In particular the benefits among paediatric patients can be impressive if restoration of physiological respiration and phonation is achieved. Further data and research is required in order to establish the most suitable children and best methods for
reinnervation techniques in order to obtain optimum reproducible outcomes.

Conclusion

VFP when symptomatic is associated with a high morbidity rate and often has a significant negative impact on the lives of children and their families. Therefore the best treatment options are mandatory. Laryngeal reinnervation, unilateral or bilateral, is sophisticated surgery with potential beneficial effects likely to be especially effective in the paediatric population, in particular when taking into account the rate of nerve regeneration in children compared with adults. This technique can be taught and performed by laryngologists and head and neck surgeons with microsurgical skills. However, these techniques have not yet been extensively embraced, and have only recently been introduced into the UK in both adults and children. Further studies in this field are crucial and an increased worldwide interest and collaborations in this approach are desirable, in particular when reporting techniques, data and outcomes.

Acknowledgements

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References


47. Verin E, Morelot-Panzini C, Gonzalez-Bermejo J et al. Reinnervation of the diaphragm by the inferior laryngeal nerve to the phrenic nerve in ventilator-dependent tetraplegic patients with C3-5 damage. ERJ Open Res. 2017;3(4).


