Acta Otorhinolaryngologica Italica, XXXVII/5, 355-446, 2017

POSTE ITALIANE SPA - Spedizione in Abbonamento Postale - D.L. 353/2003 conv. in L. 27/02/2004 n° 46 art. 1, comma 1, DCB PISA - Iscrizione al tribunale di Pisa al n. 10 del 30-07-93 - Finito di stampare presso EGP Pisa - Ottobre 2017 - ISSN: 0392-100X (Print) - ISSN: 1827-675X (Online)

ACTA

Otorhinolaryngologica Italica

Official Journal of the Italian Society of Otorhinolaryngology Head and Neck Surgery

Organo Ufficiale della Società Italiana di Otorinolaringologia e Chirurgia Cervico-Facciale

Volume 37

5

October 2017

PACINI EDITORE MEDICINA

www.actaitalica.it

S.I.O.E.C.H.C.F.

Volume 37 – Number 5 – October 2017

ACTA Otorhinolaryngologica Italica

Official Journal of the Italian Society of Otorhinolaryngology - Head and Neck Surgery
Organo Ufficiale della Società Italiana di Otorinolaringologia e Chirurgia Cervico-Facciale

Publisher
Pacini Editore Srl
Via Gherardesca, 1
56121 Pisa, Italy
Tel. +39 050 313011
Fax +39 050 3130300
info@pacinieditore.it
www.pacinimedicina.it

Acta Otorhinolaryngologica Italica is cited in Index Medicus, MEDLINE, PubMed Central, Science Citation Index Expanded, Scopus, DOAJ, Open-J Gate, Free Medical Journals, Index Copernicus, Socolar

Journal Citation Reports:
Impact Factor 1.530
Acta Otorhinolaryngologica Italica is available on Google Scholar

PACINI EDITORE MEDICINA

www.actaitalica.it

Contents

Information for authors including editorial standards for the preparation of manuscripts available on-line: www.actaitalica.it

ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:355-367; doi: 10.14639/0392-100X-1426

Review

New trends in rehabilitation of children with ENT disorders

Aggiornamenti sulla riabilitazione ORL in età pediatrica

R. BOVO, P. TREVISI, E. ZANOLETTI, D. CAZZADOR, T. VOLO, E. EMANUELLI, A. MARTINI
Department of Neuroscience, Institute of Otorhinolaryngology, University Hospital of Padua, Italy

SUMMARY

In the last 20 years, neonatal survival has progressively increased due to the constant amelioration of neonatal medical treatment and surgical techniques. Thus, the number of children with congenital malformations and severe chronic pathologies who need rehabilitative care has progressively increased. Rehabilitation programs for paediatric patients with disorders of voice, speech and language, communication and hearing, deglutition and breathing are not widely available in hospital settings or in long-term care facilities. In most countries, the number of physicians and technicians is still inadequate; moreover, multidisciplinary teams dedicated to paediatric patients are quite rare. The aim of the present study is to present some new trends in ENT paediatric rehabilitation.

KEY WORDS: Children • Rehabilitation • Sinusitis • Laryngeal paralysis • Choanal atresia • Aural atresia • Music • Voice • Cochlear implant

RIASSUNTO

Negli ultimi 20 anni il miglioramento dell'assistenza neonatale ha determinato un progressivo aumento dei bambini che sopravvivono in presenza di gravi malformazioni o patologie congenite. Questi bambini richiedono una riabilitazione prolungata, talora multidisciplinare e complessa. Purtroppo, un'organizzazione adeguata alla riabilitazione della disfagia, dei disturbi della comunicazione e della respirazione non è sempre disponibile, non è sempre coordinata in equipe multidisciplinari che operino sia negli ospedali che sul territorio e non è facile mantenere tutte le figure professionali coinvolte al passo con le sempre più rapide innovazioni. Scopo del presente lavoro è presentare un aggiornamento su alcuni aspetti tuttora controversi della riabilitazione in età pediatrica.

PAROLE CHIAVE: *Bambini • Riabilitazione • Sinusite • Paralisi laringea • Atresia coanale • Atresia auris • Musica • Voce • Impianto cocleare*

Introduction

In the last 20 years, neonatal survival has progressively increased due to the constant amelioration of neonatal medical treatment and surgical techniques. These aspects have produced an increased incidence of children with congenital malformations and severe chronic pathologies. Moreover, the immigration of children from underdeveloped countries, where perinatal infections or other risk factors are still high, have further increased the number of paediatric patients who need rehabilitative care. It is worth noting that among over 50,000 scientific papers in the literature regarding paediatric rehabilitation, only about 1000 are related to ENT arguments. Thus, rehabilitation of paediatric patients with disorders of voice, speech and language, communication and hearing, deglutition and breathing is generally still inadequate to the real needs and rarely is well organised with multidisciplinary teams, working both in the hospital setting and in long-term care facilities. The aim of the present study is to present some new trends in ENT paediatric rehabilitation.

Chronic rhinosinusitis

Rhinosinusitis is a very common condition and its prevalence has increased in recent years in both children and the adult population. By definition in chronic rhinosinusitis (CRS), symptoms last more than 12 weeks. Antibiotics are the most frequently used therapeutic agents in acute rhinosinusitis (ARS). Uncomplicated ARS, if no allergies exist, can be treated with amoxicillin (40 mg/ kg/day or 80 mg/kg/day). Other reasonable choices are amoxicillin/clavulanate and cephalosporins. If hypersensitivity to any of the above antimicrobials is suspected, alternative choices include trimethoprim/sulfamethoxasole, azithromycin, or clarithromycin [1]. Surgical intervention in the treatment of nasal polyps is considered in patients who fail to improve after a trial of maximal medical treatment or in patients presented at diagnosis with antrochoanal polyp, cystic fibrosis (CF), Kartagener and Churg-Strauss syndromes. Functional endoscopic sinus surgery (FESS) involves the clearance of polyps and polypoid mucosa and opening of the sinuses ostia. If maximum medical therapy is unsuccessful in a

child with chronic or recurrent sinusitis, evaluation for underlying medical disorders (e.g. immunodeficiency, allergic rhinitis, CF and immotile cilia syndrome) is warranted. Surgery consisted of adenoidectomy with or without antral irrigation and balloon sinus dilation, and FESS [2].

Follow-up begins after surgery and can last for years; it is performed with nasal endoscopy and inspection of breathing spaces, eventual nasal secretions, healing of nasal mucosa, natural ostium and sinusotomy patency. In the first visit after FESS, there is removal of nasal packing; it is normally performed one or two days after surgery. Further visits are made at 15 days and one month after surgery: the goal is inspection of nasal cavities and removal of nasal crusting and fibrinous exudate to prevent nasal adhesions. If no complications exist, clinical follow-up visits are scheduled 3-6 and 12 months after surgery and are made to prevent late complications and relapse. Recurrence rates are higher in nasal polyposis stage IV and V (association with CF, Kartagener and Churg-Strauss syndrome). In these cases, there is no definitive treatment for nasal polyposis and long follow-up is necessary. In the youngest patients, endoscopic medications must be scheduled in sedation or under general anaesthesia: parents should be previously informed about this requirement and the fact that these are not new surgical interventions, but are necessary to improve the first result. All children with CRS should be submitted to allergy tests. Tests for immunodeficiency should be done in children with chronic recurrent disease, poor response to medical treatment, a history of other chronic infections (such as recurrent pneumonia or otitis) or when unusual microorganisms are isolated in the nasal secretion. To obtain the best results, surgery in children should be performed by expert surgeon after a skills trial in phlogistic, malformative and neoplastic diseases in adults and using surgical instruments dedicated to the paediatric population.

The health impact of chronic recurrent rhinosinusitis of paediatric patients and their parents is severe. Children with rhinosinusitis are perceived by their parents to have significantly more bodily pain and to be more limited on physical activities than children with asthma, juvenille rheumatoid arthritis and other chronic disorders [3]. The SN-5 is a validated symptom score questionnaire for the evaluation of CRS in children [4]. The self-administered survey is completed by the child's parent using 7-point ordinal response scales for each item. Domains include sinus infection, nasal obstruction, allergy symptoms, medication use, emotional distress and activity limitations.

Choanal atresia rehabilitation in paediatric patients

Choanal atresia is defined as a congenital obstruction of the posterior nasal choanae. It represents one of the most frequently observed congenital nasal defects, with a prevalence of 1:5,000-8,000 live births [5]. In about 50% of cases it occurs bilaterally, thus constituting the main indication for sinonasal surgery in the newborn [6].

The association of choanal atresia with craniofacial and genetic syndromes is well known. In particular, between 7% and 29% of patients with choanal atresia are affected by CHARGE syndrome. In these conditions, the atresia presents often bilaterally (Fig. 1) [5].

Bilateral choanal atresia presents with respiratory distress in the immediate neonatal period. The crises are typically alleviated when the child begins to cry. Surgical intervention is considered the main therapeutic option. Over the decades, various surgical techniques have been described [7-9].

An "ideal" surgical technique should ensure adequate choanal patency and low restenosis rates, should spare the surrounding anatomical structures and provide low rates of morbidity and mortality. It should also ensure the shortest time hospitalisation [8].

Nowadays there is still a lack of randomised controlled studies comparing the efficacy of the different surgical approaches, but it is common expert opinion to consider an endonasal endoscopic approach to be the least invasive and probably the safest in terms of compliance [9].

However, restenosis remains the most frequent complication in choanal atresia surgery, with a prevalence between 9% and 36%. Adjuvant measures have been introduced to reduce the restenosis rate: nasal stenting, mitomycin C and balloon dilatation. The use of nasal stenting is still debated [10].

A stent is generally applied to stabilise postoperative outcomes, but this procedure entails some worrisome complications. Nasal and nasopharyngeal infections, mucosal ulcerations, tissue ischaemia and necrosis and formation of granulation tissue are only some of the possible consequences of long-term use of a nasal stent [10 11].

Recently, some authors performed stentless choanal endoscopic surgery repair. To date, a total of 42 procedures have been carried out, with a restenosis rate of only 38% [11-13]. Nasal irrigation in the postoperative period is crucial for maintaining neo-choanal patency, in association to endoscopic medications according to a precise follow-up schema. In our centre, nasal packing is removed 24 hours after the surgical procedure, the first postopera-

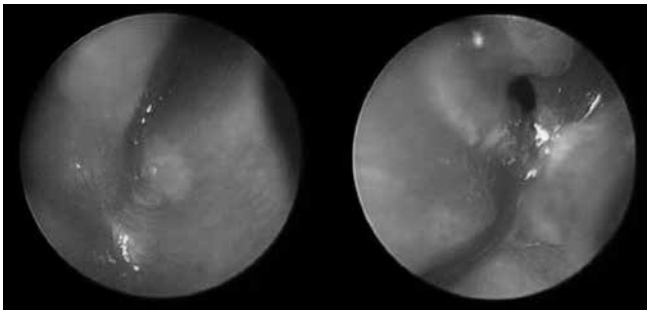


Fig. 1. Endoscopic view of a bilateral choanal atresia.

tive visit is generally performed after 7 days, under sedation. Further visits take place after 15, 45 and 90 days, and then at 6 and 12 months.
Anti-reflux agents are helpful in avoiding granulation tissue formation, since gastro-oesophageal reflux is a negative predictive factor for restenosis, with incorrect postoperative management and an early age at surgery (> 10 years) [14].

Obstructive sleep apnoea

Sleep disorders include different conditions ranging from primary snoring to obstructive sleep apnoea (OSA). OSA is characterised by both partial and complete airway obstruction, which induce hypoxaemia with a relevant decrease in quality of the sleep and day life.
OSA in children has a prevalence between 1.1% and 2.9% [15]. The diagnostic gold standard in OSA syndrome is overnight polysomnography, but home pulse oximetry has also been proposed as a screening test [16]. Adenotonsillar hypertrophy is the most important aetiologic factor for OSA in paediatric patients: nearly 45% of OSA children are affected by lymphatic Waldeyer's ring hypertrophy [17]. Adeno-tonsillectomy is therefore indicated as a first therapeutic option in OSA children without other important comorbidities and has shown good efficacy in improving the patients' quality of life [18]. However, the degree of adenotonsillar hypertrophy is not strictly related to the severity of respiratory sleep disorder. Predictors for a persistent elevated postoperative apnoea-hypopnoea index (AHI) are: age > 7 years, BMI increase, preoperative AHI > 20 and asthma.
As reported by Albera et al. in a large cohort of paediatric patients, more OSA children presented with impaired swallowing function and impaired speech articulation in comparison to non-OSA patients. Interestingly, adeno-tonsillectomy improved obstructive respiratory function in the first group of patients, but did not modify secondary dysfunctions such as atypical swallowing, oral breathing, or dyslalia [19].
A rehabilitative programme is necessary in addition to surgical or medical therapy for OSA. No standardised protocols are reported to date [20]. The speech therapy centre in Rome has proposed a valid rehabilitation scheme, which consists of neuromuscular and myofunctional therapy for oro-facial musculature [21].

Laryngeal paralysis

Laryngeal paralysis (LP) is the second most common laryngeal congenital malformation after laryngomalacia. Of all laryngeal malformations, its prevalence is about 15-20%. Unilateral LP (48%) may cause swallowing impairments and chronic food inhalation; depending on the position of fixation of the vocal cords, bilateral LP (52%) may present with respiratory symptoms varying from inspiratory stridor to acute respiratory distress with cyanosis. The latter condition requires emergent tracheal intubation [22].
A flexible fiberscope is routinely used in the diagnostic workup of LP. It is performed without anesthesia, thus allowing direct visualisation of laryngeal motility. Possible underlying associated malformation, which is present in about 45% of LP cases, is investigated with a rigid laryngo-tracheo-bronchoscope under general anaesthesia. Only after both central and peripheral causes of vocal fold paralysis have been excluded, the condition can be defined as idiopathic. In severe cases of LP, when the risk of liquid inhalation occurs, it is necessary to place a nasal-feeding tube. In addition, tracheostomy is required in 8% and 53% of cases of unilateral and bilateral LP, respectively [22].
Above all, idiopathic LP may partially spontaneously resolve within the 6th-12th month of life. When there is no evidence of improvement in laryngeal motility after the age of 2 years, the lesion could be defined persistent. At this point, surgical intervention is required to create adequate respiratory space. A posterior cordectomy is generally performed [23].
Logopaedic rehabilitation (LR) is indicated in unilateral LP with the aim of inducing a spontaneous compensation of vocal fold motility. The earlier LR is begun, the better the functional results that might be obtained. Moreover, LR finds application in children who underwent tracheal tube or nasal-feeding tube placement. Long lasting tracheal intubation (> 48 h), as well as nasal-feeding tube application, can provoke vocal and swallowing dysfunctions when removed. Tracheostomy, moreover, affects laryngeal motility in indirect ways, determining deafferentation of the proprioceptive innervation in the transglottic area and progressive muscular atrophy [24]. A LR programme is defined on the basis of symptoms. Plurisensorial stimulation touches all the structures involved in respiratory, vocal and deglutition functions.

Juvenille laryngeal papillomatosis

Juvenille laryngeal recurrent papillomatosis (JRRP) is a rare viral disease caused by HPV-6 and HPV-11 infection. Both single and multiple lesions of JRRP affect especially the glottic region but, in 5-28 % of cases, may also extend caudally into the tracheobronchial three and lungs [25]. The papillomatosis glottic involvement entails important functional and vocal consequences, with significant impact on the emotional and behavioural sphere of children, and consequently their quality of life.
Although in JRRP the goal of treatment is obtaining adequate respiratory airway patency to avoid tracheostomy, it is also of utmost importance to define suitable surgical treatment protocols to reduce the incidence of iatrogenic vocal damage.
The intensity of voice function alteration correlates with the number of surgical procedures per person, and not with age at diagnosis [26]. Consequently, voice function preservation surgery should preserve as much healthy la-

ryngeal mucosal tissue as possible, without reaching radical excision.
The gold standard treatment is a mini-invasive approach with CO_2 laser or microdebrider surgical excision of lesions, associated or not to adjuvant virostatics [27]. Only one prospective cohort study in 11 patients compared vocal function outcomes of the two surgical techniques. Main vocal outcomes included overall severity rating, jitter, shimmer and noise-to-harmonic ratio. "Cold" dissection with a microdebrider resulted in better immediate and early postoperative voice outcomes in children. Additionally, increased exposure to CO_2 laser correlated with worsening voice quality. This can be explained by the potential thermal injuries of the surrounding and deeper tissues induced by the laser [28].
Long-term soft tissue complications including scarring, stenosis and web formation can also lead to voice disorders. The total number of repeated microsurgical interventions performed per patient and the lesion site influences the rate of these complications. The most frequent laser-induced soft tissue complication is anterior glottic web [25]. The rate of soft tissue complications is influenced not only by the total number of repeated surgical interventions per patient, lesion site, surgical technique, age at diagnosis and advanced stage of disease, but it also correlates with the presence of gastro-oesophageal reflux [29].
The main functional aim in JRRP surgery is therefore avoiding soft tissue deep laryngeal damage in order to prevent voice function injuries in children. A "cold" dissection of the glottic lesions sparing the lamina propria, healthy surrounding tissue and glottal deeper laryngeal structures seems to be the right direction. The use of a microdebrider is reaching increasing consent in this field. However, in literature there are no prospective randomised studies to support the superiority of the microdebrider surgical technique. In the future, the use of tetravalent HPV vaccine might represent a promising option.

Breathing rehabilitation in patients with laryngo-tracheal axis stenosis

The most frequent diseases causing laryngo-tracheal stenosis in the paediatric population and requiring breathing rehabilitation are: laryngomalacia, vocal cord paralysis (monolateral or bilateral), hypoglottic stenosis, tracheal stenosis and tracheomalacia.
Laryngomalacia is a congenital abnormality of the laryngeal cartilage. It is a dynamic lesion resulting in collapse of the supraglottic structures during inspiration, leading to airway obstruction. It is thought to represent a delay of maturation of the supporting structures of the larynx [30]. If present, reflux can worse breath symptoms [31]. Laryngomalacia is the most common cause of congenital stridor and is the most common congenital lesion of the larynx.
Diagnosis is made by flexible naso-pharyngo-laryngoscope under topical or no anaesthesia, followed by direct laryngoscopy under general anaesthesia (without muscle relaxant). In order to complete the staging, pulmonary function tests (PFTs) and polysomnography (PSG) are mandatory [31]. Spontaneous resolution of symptoms is the rule; it usually occurs by the age of 2-5 years, so the main treatment consists in antireflux drugs and follow-up. Surgical intervention is indicated only in severe cases (10-12% of all cases) of laryngomalacia and consists in endoscopic approaches, namely supraglottoplasty. The aim of surgery is to correct the anatomical cause with minimal tissue damage. A cold steel technique is recommended. Other instruments have been used including laser and microdebriders.
In recent years, paediatric breathing physiotherapy uses various techniques to help removal of mucus from the airways and improvement of pulmonary function. These are: cough, compressions/vibrations, forced expiratory technique (FET), autogenic drainage (AD), prolonged slow expiration (PSE), positive expiratory pressure (PEP), positive continuous periodic pressure (PCPAP), continuous positive airway pressure (CPAP), physical exercise, aerosol and nasal unblocking.
Evaluation of patient posture is another important issue: chest conformation, postural alignment (chin, shoulder, thorax position) and spine alignment on frontal and sagittal plane. The main goal of breathing treatment is removal of airway secretions, where physiological clearance mechanisms (cough, cilia, ventilation) are ineffective.

Paediatric tracheostomy: a changing trend

In the last 30 years, the role and the indications for tracheostomy have remarkably changed. The most common indications for paediatric tracheostomy have passed from infective causes (epiglottitis, croup, diphtheria) to airway obstruction and anomalies [32], long-term ventilation requirement and underlying neuromuscular or respiratory problems [33].
Long-term intubation is now the first indication for tracheostomy; in the absence of guidelines, the majority of authors agree to perform a tracheostomy after 2-3 weeks of intubation to avoid hypoglottic or tracheal stenosis [34].
A literature review shows that 50% of patients with tracheostomy is less than one year old. This is related to the improvement of the Paediatric Intensive Care Unit (PICU) that allows more premature babies survive, but at the same time it entails greater risk of complications for the smaller diameter and the lower stiffness of the trachea. More generally, there has been in recent years an increase of late complications of trachestomy, related to the prolonged presence of the tracheostomy tube.
These late complications are peristomal granulomas, tracheal stenosis, trachea-innominate fistula, trachea-oesophageal fistula and trachea-cutaneous fistula.
The surgical procedure is more complicated in the paediatric population. Open surgical tracheostomy and percutaneous dilatational tracheostomy, described by Ciaglia in 1985 [35], are two possible approaches in the adult population.

There are different types of tracheostomy tubes that vary in certain features for different purposes; they can be made in plastic, silicon, PVC and metal. For the first application, it is generally suggested to use a plastic tube. The length and angle of the tube should be such as to maintain its end portion in axis with the trachea. The American Thoracic Society suggests selecting a tube of such a length as to extend to 2 cm below the stoma and at least 1-2 cm from the carina [36]. The National Guideline Clearinghouse (NGC) [37] recommend that skin care of the stoma and under the tracheostomy ties be provided at least daily, and more often if indicated, to prevent pressure necrosis and to maintain intact, clean and dry skin. Tracheostomy tube suctioning should be performed at least twice daily and as needed, based on clinical assessment to assure tracheostomy tube patency (ATS). It is recommended that tracheostomy tube changes are performed routinely by institutional standards to maintain airway patency; the first change is made within 5-7 days for surgical tracheostomy and within 10-14 days for percutaneous tracheostomy. The further changes are routinely made every 2-4 weeks according to the Cincinnati Children's Hospital Center (CCHMC) guidelines [38]. There is insufficient evidence and a lack of consensus to make a recommendation on the use of heated versus cool humidification in prevention of mucous plugging (ATS). According to AAO-HNSF decannulation can be made if clinically there is resolution of the primary disease, no active infection, tolerance of the speaking valve, endoscopically there is a clear tracheobronchial tree without suprastomal granuloma and functionally if there is an adequate cough reflex. The process of decannulation needs observation for 24-48 in a monitored setting [36]. Every child with tracheostomy should be referred to a phoniatric clinic for evaluation of the phonation and deglutition. Rehabilitation of speech relies on phonatory valves, signs language, laryngophone and fenestrated tracheotomy tubes. Evaluation of the deglutition to rehabilitate the patient for feeding is made with administration of methylene blue solution under videolaryngoscopy and with scintigraphic study of deglutition.

Dysphagia following laryngo-tracheal reconstruction

The laryngeal anatomical structures involved in swallowing are epiglottis, laryngeal vestibule and vocal folds [39 40]. Anatomical alterations of upper airways causing stenosis may prevent coordinated process of swallowing, affecting its efficiency and safety [41]. Surgery designed to restore the airway in laryngo-tracheal anomalies can cause or exacerbate the alterations of swallowing mechanisms and interfere transiently or permanently on airway protection mechanisms causing dysphagia. Surgery of the airway include both endoscopic (epiglottoplasty, dilatations and balloon surgery, vocal fold lateralisation, partial aryteno-idectomy, closure of laryngo-tracheo-esophageal cleft, posterior cordotomy) and open surgery (laryngotracheoplasty for airway dilatation, laryngotracheal reconstructions, cricotracheal resection with removal of stenotic tract and termino-terminal anastomosis).

The difficulties in feeding and swallowing after laryngo-tracheal reconstruction are multifactorial and to be able to make a rehabilitative project is mandatory understand the reason of these difficulties. There are specific and non-specific factors that contribute to the disease. Non-specific factors are basic diagnosis, health status of the baby and type of surgery which has undergone. Specific factors can be further divided in immediate and delayed. The immediate factors are anatomical structure transformation, altered protection of airway and presence or absence of the tracheostomal tube. The delayed factors are development of sensory skills, acceptance of feeding aids, acceptance of food more consistent, development of oral motor skills like chewing, adjusting meal times and appropriate eating behaviour.

Considering the importance of swallowing and breathing for general health and in the quality of life of the child, it is very important to manage these diseases with a multidisciplinary approach involving surgical, medical and rehabilitative features [42].

In the literature, there are many studies that stress the importance of evaluating feeding and swallowing skills of the child before and after surgery; this is done to better understand the functional ability of the child and understand if the swallowing problems are related to the basic diagnosis or a consequence of the surgery on anatomical structures [43-45].

The evaluation protocol includes the presence of alternative nutrition; evaluation of the different mechanisms of sensory and motor parts of deglutition; assessment of the management of oral secretions; the evaluation of the mechanisms of sucking/chewing and swallowing; breathing during the meal; and the amount of food administered. If swallowing function will be evaluated with instrumental tests, the child may undergo a video-fluoroscopic swallowing exam.

The goal of preoperative evaluation is to understand the anatomical and physiological factors that determine any difficulty feeding in order to react appropriately and quickly in the postoperative period. After intervention, assessment will be carried out to evaluate the results and make a rehabilitation plan with the objective of recovering the best features. The rehabilitation project must be customised and targeted, and should not only take into account swallowing function, but also respiratory function, and must include weaning from tracheal cannula if de-cannulation is possible, or use of speech valve.

Voice rehabilitation in children: two different possible protocols

The Voice Craft method (Estill Voice Training) was established in 1988 by American singing voice specialist Jo Estill and is characterised by a series of vocal manoeuvers to develop specific control over individual muscle

groups within the vocal mechanism [46]. Training comprises 13 vocal exercises or compulsory figures. Each 'figure' establishes control over a specific structure of the vocal mechanism, in isolation, by moving the structure through a number of positions. The most important compulsory figure is probably the false vocal folds control, which identifies three possible positions of the false vocal folds: *constricted*, *mid* and *retracted*. Moreover, Estill Voice Training incorporates six 'voice qualities' as mechanisms for demonstration of voice production control. The six voice qualities are speech, sob, twang, opera, belting and falsetto. A protocol of 12 training sessions for the voice rehabilitation in children has been described by Fussi and Turlà [47]. In the first session, children and parents cooperate in collecting clinical history and receiving together initial and simple counseling about vocal hygiene and possible consequences of voice disorders. Children receive a diary to note correct or un-correct vocal use during the day every evening. During the second session, several relaxing and stretching exercises are carried out. Perceptive training (starting from the intensity parameter) is taught during the third session, using specific games and exercises. The fourth and fifth sessions are dedicated to correct breathing and pneumo-phonic coordination. These aspects are generally boring to children and need to be taught through different games (soap balls, wind imitation, etc.). The sixth session is dedicated to control of the correct acquisition of breathing and to further auditory perception training on intensity and pitch. In the seventh session exercises of articulation and exercises to experiment and perceive vocal tract resonance are proposed. Several nasalisation and chewing movements are explained. During the eighth session, children are invited to sing a simple tune using different modalities of voice productions, correct breathing and coordination, hyperarticulation etc. The basic vocal qualities described in the Estill method are explained in the ninth lesson: speech, sob, belting and twang. During the 10th and 11th lessons, children must produce the different voice qualities by imitating several cartoon characters. Finally, during the last session participants are involved in dramatising a simple story by using different voice qualities and productions, depending on the specific context of the story. Post-treatment evaluation generally demonstrates that children have acquired better consciousness of their voice instrument, use different voice modalities depending on the specific situation, significantly reduce vocal abuse and enjoy in playing with their voice.

The aim of the "Proprioceptive-Elastic Voice Rehabilitation Program" (PROEL) (Fig. 2) [48] is to achieve a relaxation of muscle stiffness and to obtain elasticity through facilitating postures, unstable balance, and body movement. The method of work is "experimental": a hoarse patient compares his/her voice before and after exercise, and thus makes an "impression" on the brain that allows them to internalise a "phonatory pattern" correctly. Perception

Fig. 2. Proprioceptive-elastic therapy (PROEL).

training is thus fundamental even in the PROEL method: children should become conscious of their voice qualities, of the mechanisms of voice production, how to use the voice in the different daily situations and how to avoid voice fatigue. Rehabilitative training should be considered completed when the child has perfectly consolidated the correct use of voice in relation to total body, is able to recognise the possible risk factors for his/her voice and is able to self-correct voice misuse or abuse without an external guide. The PROEL method has been modified by De Maio et al. [49] for optimal use in paediatric dysphonic patients. Ludic activities, on several occasions chosen by the young participants themselves, have demonstrated to be useful in improving voice production and enjoyable by the children.

A new instrument for the evaluation of the benefits obtained with different treatments for the voice disorders in children is the Children Voice Handicap Index 10 questionnaire (CVHI-10). This questionnaire is easily administered, highly reproducible, with good clinical validity and responsiveness to treatment [50].

Aural atresia rehabilitation

Patients with *bilateral* atresia should have either a softband BAHI (Bone Anchored Hearing Implant) or a conventional headband bone conduction hearing aid in early life to provide adequate stimulation for development of the central nervous system. When the child grows older, percutaneous BAHI becomes an option [51], usually by 5 years old. The surgical technique has been recently simplified with the linear incision (Fig. 3), instead of the skin flap technique [52].

Canalplasty is a choice for selected candidates after the age of 8. The anatomy of the temporal bone is a major confounding factor in the approach of hearing rehabilitation. Patients with good middle ear anatomy (Jahrsdoerfer score 7 or above) [53] may be suitable for canal reconstructions, although this kind of surgery is less frequently carried out than in the past. In most studies comparing BAHI and patients with EAC recon-

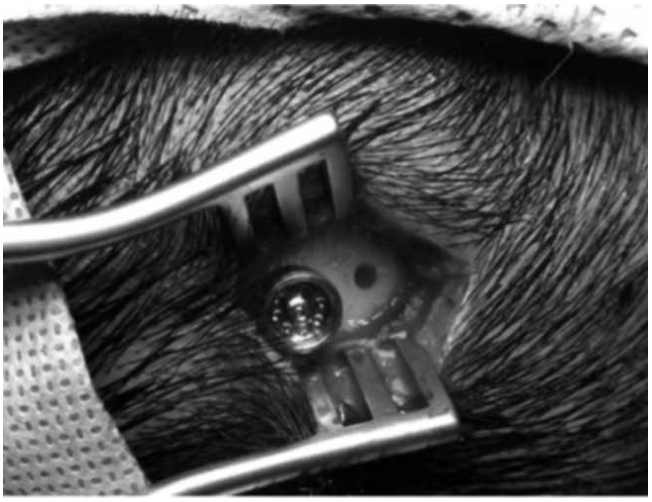


Fig. 3. The linear incision and the insertion of a new-profiled abutment.

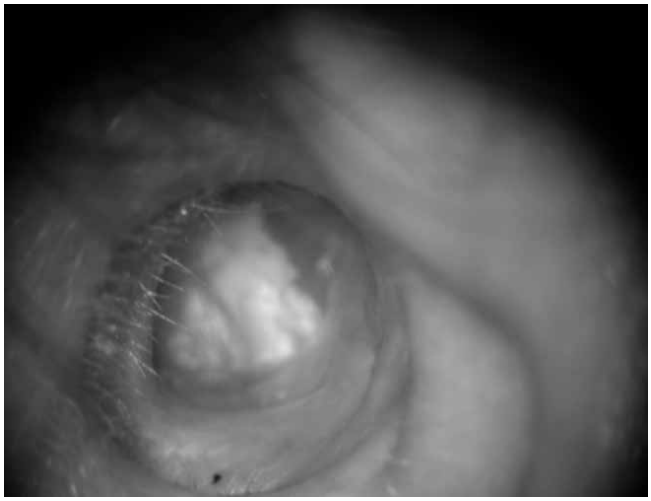


Fig. 4. Apparent good surgical outcomes of atresiaplasty. However, recurrent external otitis exacerbated by whatever kind of ear moulds required the implantation of BAHI.

struction, BAHI has generally resulted in significant hearing gain vs. reconstruction [54]. The mean postoperative speech reception threshold is 25-35 dB HL, which is the range of mild hearing loss and around 30% of patients still need a conventional hearing aid to assist with hearing after surgery [54]. In addition, otologists are often frustrated with the relatively common occurrence of restenosis and recurrent infections of the canal (Fig. 4). The reported rate of restenosis ranges from 5 to 29% and around 26% of the population requires reoperation. Serious complications may also occur during this surgery, such as worsening of hearing loss and facial nerve palsy in 1% of cases, as up to 30% of this group of patients have an anomaly in the course of their facial nerve [55 56].

Vibrant sound bridge (VSB), on the other hand, is implanted inside one middle ear, which provides unilateral stimulation to the inner ear system. This unilateral direct inner ear stimulation completely removes the possibility of signal confusion. VSB is a middle ear implant consisting of two parts, the external audio processor (EAP) and the implantable vibrating ossicular prosthesis (VORP). The EAP picks up sound signals, amplifies them and transmits them to the VORP. The floating mass transducer (FMT), in the distal part of the VORP, vibrates the attached middle ear structure through a single point of attachment and thereby stimulates the cochlea.

In aural atresia patients, the FMT can either be attached to the stapes, if it is functioning, or to the round window, in which case the procedure is known as round window vibroplasty. During VSB implantation, the usually malformed middle ear cleft has to be entered to insert the FMT. It carries a risk of injury to facial nerves and the inner ear, while no such complications occur in BAHI.

Bonebridge (BB) was initially designed for patients over 18 years old because a certain thickness of the cortical bone is required. Despite some reports of successfully implanted paediatric patients, this procedure requires a great deal of caution.

For those with *unilateral* disease, time is allowed for a thorough discussion and consideration of treatment options. In fact, it has been well established that patients with unilateral hearing loss may have difficulties in communication and at least 25% of the patients' parents and teachers report behavioural problems and academic performance issues [57].

There is still controversy about how much we should do for patients with unilateral congenital aural atresia. Restoring binaural hearing can avoid the development of an ear dominance syndrome and numerous studies have shown that it brings more benefits than harm, including better hearing in noise, improved distance hearing and elimination of head-shadowing [58]. However, to avoid a dominant syndrome, binaural hearing should be promptly restored, most probably in the first years of life. As every patient's needs and expectations vary, detailed discussion should take place to achieve the best solution for each individual case.

In some patients who need repeated magnetic resonance imaging (MRI), for example in patients with neurological diseases, the method of hearing rehabilitation has to be carefully considered. This is because MRI is generally not recommended for patients with implantable hearing aids, like VSB. BB can tolerate MRI scanning up to 1.5 tesla and BAHI up to 3 Tesla. These implants also produce artifacts in images of the brain. BAHI is the least disturbing due to its small implant size.

In summary, most patients with aural atresia benefit from hearing rehabilitation. The choices are conventional headband bone conduction hearing aid, softband BAHI, canalplasty, percutaneous BAHI, VSB and BB. Each option has its strengths and weaknesses. Early identification and referral for further management are key to obtain a successful long-term outcome.

Cochlear implant

Cochlear implant in children is a safe procedure with a low risk of complications as largely reported in recent literature [59-61]. Immediate and late complications are not significantly different when surgery is carried out before one year of age, with respect to 12-18 months (P = 1). Moreover, anaesthesiological complications are rare, probably ranging from 0 to 1.5 %, even in syndromic patients [62]. Early implantation is believed to enable the maximal development of communication skills, social exchange and cognitive abilities. The lower age limit of implantation is therefore not related to surgical or anaesthesiological considerations, but to the consideration that very early audiological diagnosis is not always reliable, even when established at tertiary centres, and not all children identified as suffering from sensorineural hearing loss (SNHL) will have permanently impaired threshold levels. The absence of any electrophysiological or behavioural reaction to sound does not always reflect SNHL. Bovo et al. [61] have recently described a case series of 23 newborns with a diagnosis of severe-to-profound hearing loss at three months, who significantly improved even reaching a normal auditory threshold during the first year of life. All the full term neonates showed a significant improvement in their initial threshold within 6 months of age. On the other hand, in most of the premature newborns the initial signs of threshold amelioration occurred beyond 70 weeks of gestational age, and even beyond 85 weeks in one case. The authors assumed that when severe-to-profound SNHL is confirmed and persistent after appropriate follow-up tests for 6-8 months, cochlear implantation can be carried out with no risk of diagnostic error in term-born infants. On the contrary, follow-up for severely pre-term babies should last up until no less than 80 weeks of gestational age. The lower limit of age must not be respected in all cases of post-meningitic deafness or in other causes of cochlear fibrosis and calcification.

Music rehabilitation in children with hearing aid and cochlear implant

According to Ford [63], "the capacity to perceive and assimilate music resides in the brain, and although hearing loss may impose certain limitations upon the extent to which musical potential is realised, it does not negate the presence of innate musicality". Furthermore, Darrow [64] stated that "for the deaf or hard of hearing children, music can be in some ways more aurally accessible than speech". There is today a general agreement that these children can enjoy and participate in music activities and can increase their aesthetic sensitivity [65-67].

Nevertheless, it is to be considered that among the three cardinal elements of music, i.e. rhythm, melody and timbre, in most hearing aided or implanted deaf children only rhythm perception is reported to be similar to that of listeners with normal hearing.

In fact, even with technically sophisticated multiple-channel sound processors, recognition of melodies is poor, with performance at little better than chance levels for many implant users. This can also be observed when the tunes are familiar and are played as a sequence of isolated notes without accompaniment or harmony. Thus, discrimination of music interval, tone sequences with ascending or descending notes, or simple melodic structures are greatly deteriorated abilities in profound deaf children. On the other hand, one should consider that often the concepts of high and low are difficult even for hearing students who confuse the term with loud and soft. Nevertheless, the ability to differentiate between notes is necessary to study and learn melodies. Perception of timbre, which is usually evaluated by experimental procedures that require subjects to identify musical instrument sounds, is also generally unsatisfactory [65 68]. Only the discrimination of the different groups of musical instruments is generally possible (i.e. string-, wood-, brass-, percussion- instruments), while recognising a single instrument among its group is very difficult. Despite all these limitations, Hash [68] stated, "Considering an 'average' profound hearing loss, the motivated student is capable of learning to play an instrument to at least an intermediate level". Some instruments will be easier for the student who is deaf or hard of hearing to learn, but under the right conditions nearly all are audible over most of their ranges [65 69]. Generally, instruments with fixed pitches, such as clarinet, saxophone, flute, piano and organ are recommended. Some instruments produce strong vibration that can be felt on the lips, on the chest or by touching them. Percussion instruments, particularly the bass drum, are great producers of vibration and can therefore provide a very tactile experience. On the other hand, whenever the student is still having difficulties sensing vibrations, instrument selection should include one that is capable of producing sustained rather than percussive sounds, as these may be easier to perceive via residual hearing. The xylophone, with its clear and short sounds, is considered one of the easiest instrument to be perceived by the cochlear implanted child. For further details about the instrument selection for a deaf child, see Hash [69].

Singing activities are also strongly recommended for these children. Cochlear implanted children are generally able to sing familiar songs from memory, though their performance is significantly poorer than in children with normal hearing on almost all pitch-based assessment of singing [70].

Musical involvement can help a child to develop a positive self-image with opportunities for self-expression and can improve social interactions. Moreover, music can serve as motivational tool for positive behavior and can relieve the tension and struggle that some children experience during language training. The music classroom can play an important role in promoting acceptance and understanding. Musical activity can aid in breaking down any social barriers, thus helping to diminish misconceptions and fear related to hearing loss.

Darrow [64] affirms that almost any aural concept can be visually reinforced. The use of Windows Media Player visuals has been recommended because of their colourful representation of music elements such as rhythm, tempo, and melodic direction. In fact, visual representation of music can help to clarify what children perceive. Moreover, body rhythms can be implemented to symbolise rhythmic structure. Pitch can also be illustrated using the body. For example, younger students can crouch down for low notes and stand on their tiptoes with arms above their heads for higher notes.

It has been found that music combined with speech therapy can have positive effects on the development of both good listening habits and auditory skills, and on the development of the suprasegmental elements of language, auditory figure-ground discrimination, sequential memory, voice quality and rhythm of speech [69 71].

Nevertheless, it should be noted that only studies that carried out a long and intensive musical training with deaf children were able to demonstrate a significant benefit on language perception and productions [72 73]. For example, Rouchette et al. [74] used training that lasted from 1.5 to 4 years conducted by music teachers with a consolidated experience. In contrast, shorter training carried out by parents or caregivers failed to demonstrated significant positive results [75]. Training benefits were evaluated by using the instrument "Sound in Hands" (Fig. 5). Evaluation included four aspects of auditory perception: discrimination, identification, auditory scene analysis and auditory working memory.

In conclusion, it is still debatable whether music training might have a benefit on language perception and production in deaf children. On the other hand, there is a general agreement that musical involvement can help a child to develop a positive self-image with opportunities for self-expression and can improve social interactions. Moreover, hard of hearing children may enjoy music and motivated students are capable of learning to play an instrument to at least an intermediate level.

Fig. 5. The instrument "Sound in Hands" designed by McAdams and Bigand in 1993, composed of two speakers, a response platform and a computer.

Neurofibromatosis 2. Hearing-related management strategies

Neurofibromatosis 2 (NF2) is a genetic disease (autosomal dominant) with a variable expression due to the different kinds of mutations, mosaicism being the less serious condition. It involves benign tumours of the central nervous system, schwannoma on nerves, or meningiomas. Other tumours are glioma, ependymoma and posterior subcapsular lenticular opacity. Schwannomas on the nerves involve the unavoidable loss of function of the nerve of origin. The incidence is about 1 new case/every year/over 100,000 inhabitants. The mutations are on chromosome 22 in a protein named *merlin*, which acts as a growth factor regulating (inhibiting) growth.

The crucial aspect of the management of NF2 cases is both the decision of what to do and, not less important, when to do something, in the frame of a balance between the natural history of the disease and the consequences of active therapy. The goal of therapy cannot be the cure of the disease, but the setting of pro-active therapy to improve quality of life and prevent the early fate of the disease. When proactive therapy is not successful, functional rehabilitation is feasible, provided early therapy is performed. The role of radiotherapy is limited, for the young age of the patient, the low success of long-term preservation of function and the risk of radio-induced tumours. Clinical observation, radiology and genetics support the diagnosis. The disease is evident in 20% of cases before 15 years with the bilateral schwannoma, the majority of cases after 18 years presentation [76].

The new frontiers in the management of NF2 patient account for: 1) the awareness of the importance of early-stage surgery conceived as functional surgery; and 2) the possibility of rehabilitation, especially of the VIII cranial nerve.

The most frequent condition in NF2 is bilateral acoustic schwannoma. This involves a relentless growth of the tumour and an unavoidable loss of hearing over the years, which may be progressive or sudden but is the functional endpoint. Tumour growth in NF2 schwannoma is more aggressive and rapid than the sporadic and is often characterised by multiple growing lobules of tumours. The natural history of the tumour is also more associated with facial palsy than in sporadic schwannoma.

The treatment involves two different attitudes: a "conservative" attitude, which means watchful observation of tumour growth, in which treatment is delayed until function is lost (hearing) and tumour growth is no more tolerated due to size and impending risk of brain compression. When surgery is performed, the size of tumour is such to put facial nerve preservation at risk, not differently from what is the rule in the sporadic tumour. Late surgery with a large tumour prevents the possibility of hearing preservation (which is feasible and advisable only at a very early stage of tumour,) and of the cochlear nerve (which may anatomically be preserved only in small-medium size tumours and its possibility of

functioning with a cochlear implant seems to be inversely related to the preoperative loss of hearing). The advantage of this "conservative" attitude is to leave natural function to patients (hearing and facial nerve) as long as this is possible. The consequences of a delayed surgical treatment are higher intraoperative surgical risks, higher morbidity on the facial nerve and no possibility of hearing preservation/hearing rehabilitation with cochlear implant. Why should we adopt a conservative strategy, which prevents any possibility of preservation/rehabilitation of function? The answer is in the complexity of the disease, where every choice pays a price and has to be balanced very carefully. Sometimes it may be reasonable, for severe NF2 patients, to leave hearing functions intact (on one side at least) as long as this is feasible in the so-called crucial years, when education takes its course and postpone the problem of the management of bilateral acoustic neuroma at a later age. It is evident that this "conservative" attitude, though the most adopted till the 2000's, has limited value nowadays, or rather it is still an option but has to be balanced in the frame of a more updated programme of management of the NF2 patient. The "proactive" attitude involves an early therapy at an early stage tumour. When good function is still present (hearing) it may be preserved with hearing preservation surgery [77] and, if not, may be rehabilitated with cochlear implant [78].

In our experience in sporadic and NF2 acoustic neuromas, we observed better results in hearing rehabilitation with cochlear implant when: 1) the tumour was small and the cochlear nerve did not suffer longtime from the presence of tumour; 2) hearing was preoperatively good and a functioning cochlear nerve could be preserved. The rationale of this proactive surgery is not to rehabilitate function straightforward, but to cure the disease at an early stage with the attempt to preserve natural hearing in the best preoperative conditions and rehabilitate it only in case of failure.

We summarise our guidelines in Table I for sporadic tumours.

In NF2 patients, the choice is more difficult and should be balanced in the frame of the severity of the disease and the expectations of the patient and family.

Some considerations are preliminary to any decision-making process in the NF2 patient.

A multidisciplinary nature of the approach (neuro-otologist, neurosurgery, genetics, radiotherapy, oncologist); the high rates of success of hearing preservation surgery in sporadic acoustic neuroma are probably less reproducible in the NF2 patient [69]. The inexorable growth, the multilobular pattern of presentation of the tumour relate to more aggressive involvement of the cochlear nerve and, to a lesser extent, of the facial nerve; bilateral acoustic neuroma is often not an isolated condition, but in the NF2 patient it is associated with other sites as meningioma, schwannoma, gliomas. Surgery may involve higher morbidity due to the presence of other adjacent tumours (i.e. lower posterior fossa, jugular foramen, foramen magnum) that may affect the function of other cranial nerves and the CSF pathways; hearing rehabilitation with ABI, though always feasible, should be the last option after any attempt of hearing preservation/hearing rehabilitation with cochlear implant. Similarly, good facial nerve preservation should be the goal in small-medium size tumours. When not feasible, intraoperative reconstruction of the facial nerve with a graft should be the option.

In conclusion, the new trend in NF2 management involves proactive therapy in the attempt to preserve function or rehabilitate it in case of failure. The attitude of leaving the disease at its fate leads to the unavoidable condition where it is too late to spare function or rehabilitate it. The crucial step of when active therapy should begin to interfere with the natural course of the disease is the main aspect of any choice, as well

Table I. Treatment algorithm of sporadic vestibular schwannoma in our centre.

T size (mm)	Decision factors	Treatment
Intrameatal or T < 10 in CPA	Good hearing class A (B)	Hearing preservation surgery (observation)
	Good hearing class A (B) + risk	Observation*
	Bad hearing	Observation* or hearing rehabilitation
T 10-15	No growth	Observation* or surgery
	Growth	Surgery
	Growth + risk	Radiotherapy
T 15-25	-	Surgery or Radiotherapy
T > 25	-	Surgery
	Risk	Partial surgery + radiotherapy
Any size	Cystic tumour	Surgery

* Active treatment is planned in case of vertigo or new onset of 7the c.n. defect or C.I. rehabilitation.

as the awareness of the updated surgical procedures of sparing function and rehabilitate it, such as in bilateral schwannoma. When the tumours affect the mixed nerves (i.e. in the jugular foramen, IX-XII cranial nerves), preservation or surgical rehabilitation of function is, at present, still not feasible.

Conclusions

Rehabilitation programs for paediatric patients with disorders of voice, speech and language, communication and hearing, deglutition and breathing are not widely available in either hospital settings or in long-term care facilities. In most countries, the number of physicians and technicians is still inadequate.

The goal for the future will be establishment of highly specialised third level centres, where multidisciplinary teams dedicated to paediatric patients can collaborate.

Acknowledgments

Thanks to all the authors and coauthors of the Official Report of XXIII Conference of Italian Society of Pediatric Otorhinolaryngology (Rome, November, 05-07th 2015) for their meaningful contributions: Claudia Aimoni; Roberto Albera; Paolo Aluffi Valletti, Pasqualina Apisa; Gennaro Auletta; Cristiano Balzanelli; Eugenio Baraldi; Maria Rosaria Barillari; Umberto Barillari; Giovanni Bastanza; Stefano Berettini; Daniele Borsetto; Sergio Bottero; Elona Cama; Elena Cantone; Eleonora Capolongo; Federico Caranzano; Laura Carrabba; Claudia Cassandro; Alessandro Castiglione; Michele Cavaliere; Antonella Cerchiari; Francesca Cianfrone; Giancarlo Cianfrone; Andrea Ciorba; Guido Conti; Virginia Corazzi; Erika Crosetti; Domenico Cuda; Cesare Cutrone; Concetta D'adamo; Wladimiro De Colle;-Cosimo De Filippis; Gessica Della Bella; Antonio Della Volpe; Antonietta De Lucia; Vincenzo De Maio; Giovanni Carlo De Vincentiis; Marco De Vincentiis; Andrea De Vito; Daniele Farneti; Anna Rita Fetoni; Francesca Forli; Andrea Franchella; Sebastiano Franchella; Annamaria Franze'; Stefano Fusetti; Franco Fussi; Giovanna Gaggero; Samanta Gallo; Roberto Gallus; Elisabetta Genovese; Sara Giannantonio; Daniela Ginocchio; Pamela Giordano; Marta Gisolo; Cristina Gondiu; Massimo Grassi; Francesca Graziani; Antonio Greco; Maria Consolazione Guarnaccia; Maurizio Iengo; Alessandro Incognito; Sabina Iozzino; Carla Laria; Paola Leone; Marco Lionello; Lucia Lora; Rita Malesci; Nicola Mansi; Raffaella Marchi; Giulia Marini; Pasquale Marsella; Antonio Mazzoni; Massimo Mesolella; Carla Morando; Laura Moschino; Francesco Mozzanica; Alessandra Murri; Enrico Muzzi; Flavia Nardi; Cristina Nicole'; Ciro Niri; Eva Orzan; Concettina Pacifico; Silvia Palma; Gaetano Paludetti; Annalisa Panarese; Maria Laura Panatta; Claudio Parrilla; Desiderio Passali; Francesco Maria Passali; Sara Penco; Francesco Pia; Alessandro Piacente; Pasqualina Maria Picciotti; Federica Pizzoli; Luca Oscar Redaelli De Zinis; Andrea Ricci Maccarini; Lara Righetto; Sergio Ronfini; Gianni Ruoppolo; Roberto Saetti; Rosamaria Santarelli; Athanasios Saratziotis; Marianna Sari; Letizia Scarponi; Franco Schiavi; Antonio Schindler; Emanuele Scarano; Alessandro Scorpecci; Pietro Scimemi; Marina Silvestrini; Emanuela Sitzia; Lucrezia Spadera; Irma Spahiu; Giacomo Spinato; Roberto Spinato; Giovanni Succo; Fausto Taranto; Valeria Testugini; Stefano Tiglie'; Giancarlo Tirelli; Rosaria Turchetta; Laura Travan; Maria Luisa Tropiano; Marilena Trozzi; Alfonso M.Varricchio; Irene Vernero.

References

1 Sobol SE, Samadi DS, Kazahaya K, et al. *Trends in the management of pediatric chronic sinusitis: survey of the American Society of Pediatric Otolaryngology*. Laryngoscope 2005;115:78-80.

2 Fokkens WJ, Lund VJ, Mullol J, et al. *EPOS 2012: European position paper on rhinosinusitis and nasal polyps. A summary for otorhinolaryngologists.* Rhinology 2012;50:1-12.

3 Cunningham MJ, Chiu EJ, Landgraf JM, et al. *The health impact of chronic recurrent rhinosinusitis in children*. Arch Otolaryngol Head Neck Surg 2000;126:1363-8.

4 Terrell AM, Ramadan HH. *Correlation between SN-5 and computed tomography in children with chronic rhinosinusitis*. Laryngoscope 2009;119:1394-8.

5 Corrales CE, Koltai PJ. *Choanal atresia: current concepts and controversies*. Curr Opin Otolaryngol Head Neck Surg 2009;17:466-70.

6 Friedman NR, Mitchell RB, Bailey CM, et al. *Management and outcome of choanal atresia correction*. Int J Pediatr Otorhinolaryngol 2000;52:45-51.

7 Saetti R, Emanuelli E, Cutrone C, et al. *The treatment of choanal atresia*. Acta Otorhinolaryngol Ital 1998;18:307-12.

8 Pirsig W. *Surgery of choanal atresia in infants and children: historical notes and updated review*. Int J Pediatr Otorhinolaryngol 1986;11:153-70.

9 Cedin AC, Atallah AN, Andriolo RB, et al. *Surgery for congenital choanal atresia*. Cochrane Database Syst Rev 2012;2:CD008993.

10 Bedwell JR, Choi SS. *Are stents necessary after choanal atresia repair?* Laryngoscope 2012;122:2365-6.

11 Zuckerman JD, Zapata S, Sobol SE. *Single-stage choanal atresia repair in the neonate*. Arch Otolaryngol Head Neck Surg 2008;134:1090-3.

12 Ibrahim AA, Magdy EA, Hassab MH. *Endoscopic choanoplasty without stenting for congenital choanal atresia repair*. Int J Pediatr Otorhinolaryngol 2010;74:144-50.

13 Strychowsky JE, Kawai K, Moritz E, et al. *To stent or not to stent? A meta-analysis of endonasal congenital bilateral choanal atresia repair*. Laryngoscope 2015;126:218-27.

14 Teissier N, Kaguelidou F, Couloigner V, et al. *Predictive factors for success after transnasal endoscopic treatment of choanal atresia*. Arch Otolaryngol Head Neck Surg 2008;134:57-61.

[15] Carroll JL, McColley SA, Marcus CL, et al. *Inability of clinical history to distinguish primary snoring from obstructive sleep apnea syndrome in children*. Chest 1995;108:610-8.

[16] Piumetto E, Sammartano AM, Meinardi G, et al. *Diagnostic and therapeutic iter in paediatric OSAS: personal experience*. Acta Otorhinolaryngol Ital 2011;31:149-53.

[17] Friedman M, Wilson M, Lin HC, et al. *Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome*. Otolaryngol Head Neck Surg 2009;140:800-8.

[18] Stewart MG, Glaze DG, Friedman EM, et al. *Quality of life and sleep study findings after adenotonsillectomy in children with obstructive sleep apnea*. Arch Otolaryngol Head Neck Surg 2005;131:308-14.

[19] Albera R, Piumetto E, Gervasio FC, et al. *Conseguenze dell'OSAS pediatrica in ambito foniatrico-logopedico*. In: Relazione Ufficiale XXII Congresso Nazionale SIOP. Alba, Sett 2013.

[20] Moeller JL *Orofacial myofunctional therapy: why now?* Cranio 2012;30:235-6.

[21] Cerchiari A, Falbo M. *Il trattamento riabilitativo miofunzionale dell'OSAS*. In: Relazione Ufficiale XXII Congresso Nazionale SIOP. Alba, Sett 2013.

[22] Monnier P. *Pediatric Airway Surgery*. Berlin Heidelberg: Springer-Verlag; 2011. p. 107-117.

[23] Saetti R, Silvestrini M, Galiotto M, et al. *Contact laser surgery in treatment of vocal fold paralysis*. Acta Otorhinolaryngol Ital 2003;23:33-7.

[24] Schwartz SR, Cohen SM, Dailey SH, et al. *Clinical practice guideline: hoarseness (dysphonia)*. Otolaryngol Head Neck Surg 2009;141:S1-S31.

[25] Preuss SF, Klussmann JP, Jungehulsing M, et al. *Long-term results of surgical treatment for recurrent respiratory papillomatosis*. Acta Otolaryngol 2007;127:1196-201.

[26] Ilmarinen T, Nissilä H, Rihkanen H, et al. *Clinical features, health-related quality of life, and adult voice in juvenile-onset recurrent respiratory papillomatosis*. Laryngoscope 2011;121:846-51.

[27] Fusconi M, Grasso M, Greco A, et al. *Recurrent respiratory papillomatosis by HPV: review of the literature and update on the use of cidofovir*. Acta Otorhinolaryngol Ital 2014;34:375-81.

[28] Holler T, Allegro J, Chadha NK, et al. *Voice outcomes following repeated surgical resection of laryngeal papillomata in children*. Otolaryngol Head Neck Surg 2009;141:522-6.

[29] Holland BW, Koufman JA, Postma GN, et al. *Laryngopharyngeal reflux and laryngeal web formation in patients with pediatric recurrent respiratory papillomas*. Laryngoscope 2002;112:1926-9.

[30] Ida JB, Thompson DM. *Pediatric stridor*. Otolaryngol Clin North Am 2014;47:795-819.

[31] Giannoni C, Sulek M, Friedman EM, et al. *Gastroesophageal reflux association with laryngomalacia: a prospective study*. Int J Pediatr Otorhinolaryngol 1998;43:11-20.

[32] Cotton RT, Prescott CA. *Congenital anomalies of the larynx*. P*ractical Pediatric Otolaryngology*. Philadelphia/New York: Lippincott-Raven; 1999. p.497-514.

[33] Butnaru CS, Colreavy MP, Ayari S, et al. *Tracheotomy in children: evolution in indications*. Int J Pediatr Otorhinolaryngol 2006;70:115-9.

[34] Durbin CG Jr. *Tracheostomy: why, when and how?* Respir Care 2010;55:1056-68.

[35] Ciaglia P, Firsching R, Syniec C. *Elective percutaneous dilatational tracheostomy. A new simple bedside procedure; preliminary report*. Chest 1985;87:715-9.

[36] Mitchell RB, Hussey HM, Setzen G, et al. *Clinical consensus statement: tracheostomy care*. Otolaryngol Head Neck Surg 2013;148:6-20.

[37] National Guidelines Clearinghouse. *Best evidence statement (BESt)*. Basic Pediatric Tracheostomy Care; 2011.

[38] Cincinnati Children's Hospital Medical Center: Best evidence statement (BESt). *Basic pediatric tracheostomy care*. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2011.

[39] Curtis DJ, Hudson T. *Laryngotracheal aspiration: analysis of specific neuromuscular factors*. Radiology 1983;149:517-22.

[40] Curtis DJ, Sepulveda GU. *Epiglottic motion: video recording of muscular dysfunction*. Radiology 1983;148:473-7.

[41] Miller CK, Willging JP. *The implications of upper-airway obstruction and successful infant feeding*. Semin Speech Lang 2007;28:190-203.

[42] Williams S. *Pediatric feeding and swallowing problems: an interdisciplinary team approach. Perspectives in practice.* Can J Diet Pract Res 2006;67:185-90.

[43] Willing PJ. *Benefit of feeding assessment before pediatric airway reconstruction*. Laryngoscope 2000;110:826-34.

[44] Smith LP. *Management of oral feeding in children undergoing airway reconstruction*. Laryngoscope 2009;119:967-73.

[45] Andreoli SM. *Feeding status after pediatric laryngotracheal reconstruction*. Otolaryngol Head Neck Surg 2010;143:210-3.

[46] Estill J. *The primer of compulsory figures*. www.evts.com

[47] Fussi F, Turlà E. *Il trattamento delle disfonie. Una prospettiva per il metodo Estill Voicecraft.* Torino: Omega Ed.; 2008

[48] Borragan A, Lucchini E, Agudo M, et al. *Il Metodo Propriocettivo Elastico (PROEL) nella terapia vocale*. Acta Phoniatrica Latina 2008;30:17-50.

[49] De Maio V, Mansi N, Capolongo E, et al. *La riabilitazione delle disfonie organiche infantili con il metodo propriocettivo-elastico adattato ai bambini*. In: Martini A, Trevisi P, editors. *La riabilitazione in ORL Pediatrica.* Torino: Omega Ed.; 2015. p. 195-200.

[50] Schindler A, Tiddia C, Ghidelli C, et al. *Adaptation and validation of the Italian Pediatric Voice Handicap Index*. Folia Phoniatr Logop 2011;63:9-14.

[51] Ricci G, Della Volpe A, Faralli M, et al. *Results and complications of the Baha system (bone-anchored hearing aid)*. Eur Arch Otorhinolaryngol 2010;267:1539-45.

[52] Bovo R. *Simplified technique without skin flap for the bone-anchored hearing aid (BAHA) implant*. Acta Otorhinolaryngol Ital 2008;28:252-5.

[53] Shonka DC Jr, Livingston WJ 3rd, Kesser BW. *The Jahrsdoerfer grading scale in surgery to repair congenital aural atresia*. Arch Otolaryngol Head Neck Surg 2008;134:873-7.

[54] Evans AK, Kazahaya K. *Canal atresia: "surgery or implantable hearing devices? The expert's question is revisited"*. Int J Pediatr Otorhinolaryngol 2007;71:367-74.

[55] Bouhabel S, Arcand P, Saliba I. *Congenital aural atresia: bone-anchored hearing aid vs. external auditory canal reconstruction.* Int J Pediatr Otorhinolaryngol 2012;76:272-7.

[56] Nadaraja GS, Gurgel RK, Kim J, et al. *Hearing outcomes of atresia surgery versus osseointegrated bone conduction device in patients with congenital aural atresia: a systematic review*. Otol Neurotol 2013;34:1394-9.

[57] Bovo R, Martini A, Agnoletto M, et al. *Auditory and academic performance of children with unilateral hearing loss*. Scand Audiol Suppl 1988;30:71-4.

[58] Baguley DM, Bird J, Humphriss RL, et al. *The evidence base for the application of contralateral bone anchored hearing aids in acquired unilateral sensorineural hearing loss in adults*. Clin Otolaryngol 2006;31:6-14.

[59] Paludetti G, Conti G, DI Nardo W, et al. *Infant hearing loss: from diagnosis to therapy*. Official Report of XXI Conference of Italian Society of Pediatric Otorhinolaryngology. Acta Otorhinolaryngol Ital 2012;32:347-70.

[60] Ciorba A, Bovo R, Trevisi P, et al. *Postoperative complications in cochlear implants: a retrospective analysis of 438 consecutive cases*. Eur Arch Otorhinolaryngol 2012;269:1599-603.

[61] Bovo R, Trevisi P, Ghiselli S, et al. *Is very early hearing assessment always reliable in selecting patients for cochlear implants? A case series study*. Int J Pediatr Otorhinolaryngol 2015;79:25-31.

[62] Trevisi P, Ciorba A, Aimoni C, et al. *Outcomes of long-term audiological rehabilitation in charge syndrome*. Acta Otorhinolaryngol Ital 2016;36:206-14.

[63] Ford, T. *The effect of musical experiences and age on the ability of deaf children to discriminate pitch of complex tones*. (Doctoral dissertation, The University of North Carolina at Greensboro 1985) Dissertation Abstracts International 47 (09A), 2921.

[64] Darrow AA. *Sounds in silence. Research in music and deafness.* Update Application of Research in Music Education 2006;25:5-16.

[65] Gfeller K. *Music-based training for pediatric CI recipients: A systematic analysis of published studies*. Eur Ann Otorhinolaryngol Head Neck Dis 2016;133(Suppl 1):S50-6.

[66] Schraer-Joiner L, Chen-Hafteck L. *The responses of preschoolers with cochlear implants to musical activities: a multiple case study*. Early Child Development and Care 2009;179 :785-98.

[67] Vongpaisal T, Trehub SE, Schellenberg EG. *Song recognition by children and adolescents with cochlear implants*. J Speech Lang Hear Res 2006;49:1091-103.

[68] Hash PM. *Teaching Instrumental music to deaf and hard of hearing students*. Research and Issues in Music Education 2003; http://files.eric.ed.gov/fulltext/EJ852403.pdf.

[69] Hash PM. *Instrument Selection*. Research and Issues in Musical Education 2003. www.stthomas.edu/rimeonline.

[70] Xu L, Zhou N, Chen X, et al. *Vocal singing by prelingually-deafened children with cochlear implants*. Hear Res 2009;255:129-34.

[71] Silvestre N, Valero J. *Oral language acquisition by deaf Pupils in primary education: impact of musical education*. Eur J Special Needs Educ 2005;20:195-213.

[72] Torppa R, Faulkner A, Huotilainen M, et al. *The perception of prosody and associated auditory cues in early-implanted children: the role of auditory working memory and musical activities*. Int J Audiol 2014;53:182-91.

[73] Di Nardo W, Schinaia L, Anzivino R, et al. *Musical training software for children with cochlear implants*. Acta Otorhinolaryngol Ital 2015;35:249-57.

[74] Rochette F, Moussard A, Bigand E. *Music lessons improve auditory perceptual and cognitive performance in deaf children*. Front Hum Neurosci 2014;8:488.

[75] Yucel E, Sennaroglu G, Belgin E. *The family oriented musical training for children with cochlear implants: speech and musical perception results of two years follow-up*. Int J Pediatr Otorhinolaryngol 2009;73:1043-52.

[76] Ahn MS, Jackler RK, Lustig LR. *The early history of the neurofibromatosis. Evolution of the concept of neurofibromatosis type 2.* Arch Otolaryngol Head Neck Surg 1996;122:1240-9.

[77] Mazzoni A, Biroli F, Foresti C, et al. *Hearing preservation surgery in acoustic neuroma. Slow progress and new strategies.* Acta Otorhinolaryngol Ital 2011;31:76-84.

[78] Lustig LR, Yeagle J, Driscoll CL, et al. *Cochlear implantation in patients with neurofibromatosis type 2 and bilateral vestibular schwannoma*. Otol Neurotol 2006;27:512-8.

Received: September 7, 2016 - Accepted: December 5, 2016

Address for correspondence: Roberto Bovo. Department of Neuroscience, Institute of Otorhinolaryngology, University Hospital of Padua, Italy. E-mail: roberto.bovo@sanita.padova.it

ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:368-374; doi: 10.14639/0392-100X-844

Head and neck

Spinal accessory nerve preservation in modified neck dissections: surgical and functional outcomes

Preservazione del nervo accessorio spinale nelle dissezioni del collo: outcomes chirurgici e funzionali

V. POPOVSKI[1], A. BENEDETTI[1], D. POPOVIC-MONEVSKA[1], A. GRCEV[1], A. STAMATOSKI[1], J. ZHIVADINOVIK[2]

[1] Clinic for Maxillofacial Surgery, St Cyril and Methodius University, Skopje, R. Macedonia; [2] Institute of Anatomy, Medical Faculty, St Cyril and Methodius University, Skopje, R. Macedonia

SUMMARY

The spinal accessory nerve (SAN) or XI cranial nerve is frequently encountered during neck surgery, and as such is at risk of iatrogenic injury, resulting in "shoulder syndrome". Modified neck dissection (MND) with preservation of the SAN is based on desire to minimise the functional deformity associated with section of the eleventh nerve. The aim of this study was to analyse the intra-operative variations of the spinal accessory nerve pathway and to evaluate shoulder dysfunction postoperatively**.** The cross-sectional demonstration analysis was created through the medical records retrospectively of 165 consecutive patients who underwent neck dissections at our institution in the past 5 years with attention to ultrasound and MRI preoperative findings, type of neck dissection, type of identification and dissection of SAN, postoperative morbidity and survival rate. The safest identification of SAN is in the posterior neck triangle where it may be recognised exiting from the posterior border of the sternocleidomastoid muscle (SCM) at Erb's point. For exact preoperative planning, ultrasound and MRI are superior to determine the position of the eleventh nerve. The mean distance between the greater auricular point and the SAN was 0.90 cm. Average length of the trunk from Erb's point until the penetration in the trapezius muscle was around 5.1 cm, ranging from 4.8 to 5.4 cm. The diversity in the course from the posterior border of the SCM and posterior neck triangle was confirmed in 9 cases (15%), predominantly at the level of entering the posterior neck triangle. The frequency of postoperative morbidity of SAN was 46.7% for radical neck dissections, 42.5% for selective neck dissections and 25% for MND. For each separate type of dissection, different subtypes were included. Identification of the SAN over established landmarks is unconditionally reliant on the exact preoperative mapping of the nerve with imaging diagnostics. MND has similar regional control rates to more comprehensive operations in appropriately selected patients and significantly reduces the risk of functional disability.

KEY WORDS: Posterior neck triangle • Spinal accessory nerve • Neck metastases • Modified neck dissection • Shoulder function

RIASSUNTO

Durante la chirurgia del collo, ci si imbatte frequentemente nel nervo accessorio spinale (SAN) o XI nervo cranico che, pertanto, è a rischio di lesione iatrogena con conseguente "sindrome della spalla". La dissezione del collo modificata con preservazione del SAN è basata sull'intento di minimizzare le deformità funzionali causate dalla sezione dell'undicesimo nervo. L'obiettivo di questo studio è quello di descrivere le varianti intraoperatorie del nervo accessorio spinale e valutare la disfunzione della spalla nel postoperatorio. Lo studio osservazionale trasversale è stato creato analizzando retrospettivamente 165 pazienti consecutivi che sono stati sottoposti a dissezione del collo presso il nostro istituto negli ultimi 5 anni, ponendo particolare attenzione ai reperti preoperatori derivanti da ecografia e risonanza magnetica, al tipo di dissezione del collo, al tipo di identificazione e dissezione del SAN, ai dati postoperatori di morbilità e sopravvivenza. La più sicura identificazione del SAN avviene nel triangolo posteriore del collo, dove potrebbe essere riconosciuto in quanto emerge dal margine posteriore del muscolo sternocleidomastoideo, a livello del cosiddetto punto di Erb. Per un corretto planning preoperatorio, ecografia e risonanza magnetica sono superiori nel determinare l'esatta posizione dell'undicesimo nervo cranico. La distanza media tra il nervo grande auricolare e il SAN è stata di circa 0,90 cm. La lunghezza media del tronco nervoso dal punto di Erb fino al punto in cui esso penetra nel muscolo trapezio è stata di circa 5,1 cm, con un range da 4,8 e 5,4 cm. La diversità nel decorso dal bordo posteriore dello muscolo sternocleidomastoideo attraverso il triangolo posteriore del collo è stata riscontrata in 9 casi (15%), soprattutto a livello dell'ingresso nel triangolo posteriore del collo. La frequenza di lesione postoperatoria del SAN è stata del 46,7% per le dissezioni radicali del collo, del 42,5% per le dissezioni selettive, e del 25% per le dissezioni modificate. Per ciascun tipo di svuotamento, sono stati inclusi differenti sottotipi. L'identificazione del SAN, step fondamentale nella chirurgia del collo, è assolutamente dipendente da un corretto studio preoperatorio attraverso la diagnostica per immagini. La dissezione del collo modificata ha percentuali di controllo regionale simili a quelle di operazioni più demolitive in pazienti accuratamente selezionati, e riduce significativamente il rischio di disturbi funzionali.

PAROLE CHIAVE: *Triangolo posteriore del collo • Nervo accessorio spinale • Metastasi cervicali • Dissezione del collo modificata • Funzione della spalla*

Introduction

While radical neck dissection (RND) had a principal role in the treatment of cervical neck metastasis for many years, the oncological requirement for RND became disputable upon the definition of "shoulder syndrome" in the second half of the last century [1 2]. Consequently, modified radical neck dissection (mRND) with preservation of the spinal accessory nerve (SAN) and removal of lymphatic tissues with similar oncological results was described. However, identification of the spinal accessory nerve even in the correct anatomical position is not always easy during different types of neck dissections. The surgical anatomy of the spinal accessory nerve has been properly acknowledged in the literature with evidence of significant variations [1-4]. The eleventh cranial nerve topography consists of two parts, a cranial part and a main cervical part. The nerve descends in the neck through jugular foramen and near the jugular vein exits in the posterior neck triangle and supplies the sternocleidomastoid and trapezius muscles. These muscles have the functions of: elevation of the shoulder by the trapezius, rotation and tilting of the head toward and away from the side of the contracting sternocleidomastoid muscle and flexion of the neck by both sternocleidomastoid muscles. This cervical part is associated by motor or sensory contributions from the upper cervical nerves. These functions are decreased or absent of weakness or paralysis. When the lesion is nuclear or infranuclear, there is associated muscle atrophy and fasciculations [5-7].

On the other hand, neck dissection is a principal technique for diagnosis (staging) and treatment of cervical lymph node metastasis in patients with head and neck cancer. In modified neck dissections when indications are raised, a very important part is preservation of the spinal accessory nerve, together with internal jugular vein and sternocleidomastoid muscle [8-10]. The pain and dysfunction associated with loss of innervation on spinal accessory nerve has motivated surgeons to modify the classic neck dissection. The modified neck dissection with preservation of the spinal accessory nerve is based on desire to minimise the functional deformity associated with section of that nerve, combined with the recognition that in many situations the nerve intimately involved in the neck disease and its preservation does not compromise the oncological effectiveness of the more limited procedure [4 11-14].

Since the introduction of functional neck dissection, various modifications have been made to reduce the adverse effects of radical neck dissection and have contributed to improving the quality of life and preventing permanent sequelae and medico-legal actions following neck dissection [4]. Proficient knowledge of posterior neck anatomy is crucial to avoid its accidental injury during selective or modified neck dissection in almost any extensive surgery of the posterior neck. Reasonable speed and safety in identifying and preserving important anatomical structures are of fundamental importance, and for this type of neck dissection special attention must be paid to refined identification of the spinal accessory nerve. The aim of this study was to analyse the intra-operative variations of the spinal accessory nerve pathway and to evaluate shoulder dysfunction postoperatively.

Materials and methods

A comparative, prospective study of surgical alterations of the spinal accessory nerve and trapezius muscle function of patients who underwent distinctive neck surgery was performed. This study was done not only to document the indispensability of the trapezius muscle to shoulder-strap stability, but also to clarify the role of eleventh cranial nerve preservation. The cross-sectional demonstration analysis was created on clinical material from the Clinic for Maxillofacial Surgery in Skopje, where in the last five-year period, unilateral neck dissections were performed in 165 patients, of whom 59 were treated with radical neck dissection, 20 with modified neck dissection and in 86 cases with adequate type of selective neck dissection. Neck dissection with a curative intent was done in 80 patients with squamous cell carcinoma of the upper aerodigestive tract (naso- and oro-pharynx), in 26 patients with skin squamous cell carcinoma, 17 with salivary gland carcinoma, 11 with malignant melanoma and 31 with hidden primary.

We evaluated clinical records for this study in 20 patients with modified neck dissection (type I, II, III) and 40 patients with selective neck dissections (supra-omohyoid, lateral, posterolateral, anterior compartment), comparing preoperative diagnostic work-up, intraoperative findings and relationship of the dissected and preserved eleventh nerve with tumour masses and postoperative complications. T1-weighted high-resolution isotropic volume examination for the preoperative assessment of head and neck cancer, by comparison with spin-echo, T1-weighted sequences and the pathology specimen. Bland-Altman plots to assess measurement agreement, Shoulder Disability Questionnaire (SDQ), and Constant-Murley Shoulder Score were used to detect differences between the normal and abnormal sides.

In selected cases, an intraoperative mapping study was done to obtain the exact anatomical data by drawing the exposed accessory nerve in life size during the modified neck dissection. All measurements were made at the end of the procedure by using a Vernier Caliper with 1/64'' in classic anatomic position of the supine body with turned the patient's head about 45°. After the completeness of lymph node and metastases removal from the posterior neck triangle, evaluation was performed over extensive exposure of the spinal accessory nerve. Towards the end of the dissection, the correct location of the nerve was corroborated by enlarging the exposure to confirm the position and integrity of the preserved nerve.

Clinical, electrophysiological and neurologic evaluations of the trapezius and sternocleidomastoid muscles (fibril-

lation and positive sharp waves) were performed at 3 months postoperatively for 20 mRND and 40 SND patients, and 6 months postoperatively only for 20 mRND patients. Stimulus intensity and duration were increased until the maximal amplitude level was achieved. Latency was defined as the time from the application of stimulus to the initial negative deflection of the amplitude. Statistical analysis was performed using IBM SPSS statistics ver. 20. P values lower than 0.05 were considered significant.

Results

Intraoperatively we found significant variances in the positioning of the spinal accessory nerve. Particular attention was paid to identification of spinal accessory nerve positioning and its relationship with the internal jugular vein. Our findings confirmed that the spinal accessory nerve almost always crosses the internal jugular vein anteriorly in the upper neck, with exclusion in 4 cases (6.7%), with posterior crossing at the level of posterior belly of the digastric muscle and one case with rare anomaly where accessory nerve passing through the fenestrated internal jugular vein was observed. In 20 cases we measured the distance from the jugular foramen (skull base) to crossing of internal jugular vein with a mean value of 2.34 cm (ranging from 2.27 to 2.43 cm) (Fig.1).

The diversity in the course from the posterior border of the sternocleidomastoid muscle and posterior neck triangle were confirmed in 9 cases (15%), predominantly at the level of entering the posterior neck triangle. The hypoplastic nerve was apparent in 8.3% (5 cases), generally after removal of neck masses with greater proportions. Hyperplastic nerve was evident in only 3.3% (2 cases). In almost every case we found that the spinal accessory nerve had a typical coiled appearance in its course through the posterior cervical triangle of the neck (Fig. 2).

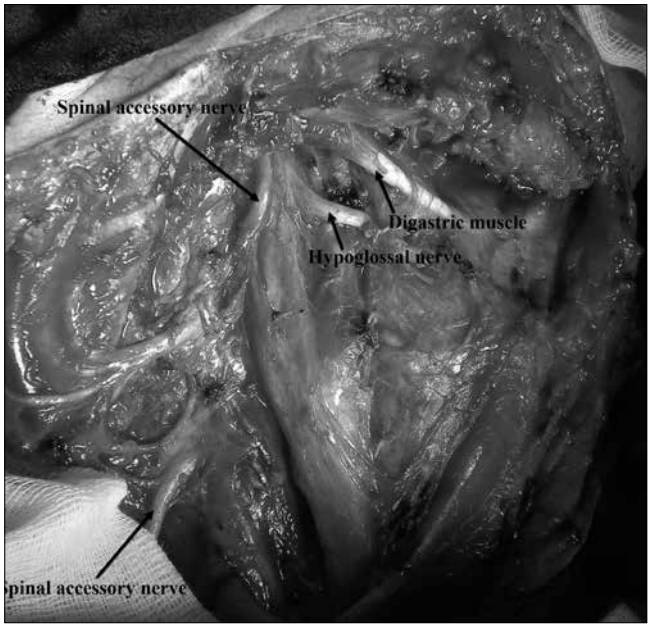


Fig. 1. Identification of spinal accessory nerve in radical neck dissection.

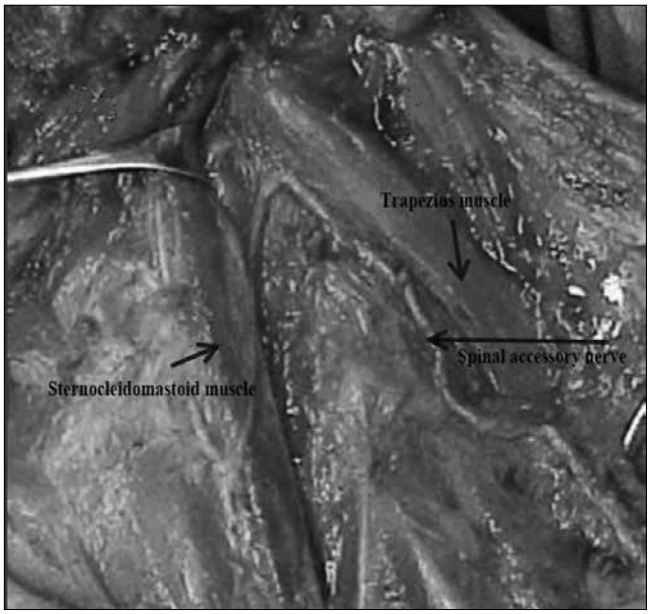


Fig. 2. Modified neck dissection with preserved spinal accessory nerve.

The mean distance between the greater auricular point and the spinal accessory nerve was 0.90 cm. Average length of the trunk from Erb's point until the penetration in the trapezius muscle was around 5.1 cm, ranging from 4.8 to 5.4 cm. The most significant elongation was found in cases after meticolous preparation of spinal accessory nerve – usually after complete removal of neck metastases at levels III - V. There were 4-8 lymph nodes in the spinal accessory nerve chain (Fig. 3).

Measurements of abduction and electromyographic measurements (monopolar needle electrode) of the study group (modified radical neck dissection) in 3 and 6 months postoperatively were found to be superior to those of the control group (selective neck dissection), although the difference between groups was not significant (Table I) Damage to the motor unit averagely recorded at ranges between 320-540 mV. The mean number of dissected lymph nodes was significantly higher in the study group than in the control group. The frequency of postoperative morbidity of the spinal accessory nerve was the highest in radical neck dissections (46.7%) in 28 cases. There was a reduced function in 17 cases with selective neck dissection (42.5%) comparing to preoperative values, while shoulder drop and scapular winging was confirmed in only 5 cases (25%) of modified neck dissection.

The most significant was correlation after radical neck dissection and modified neck dissection including levels IIb and V (Fig. 4). Statistical significance was obtained between shoulder pain score and EMG fibrillation or positive sharp wave score ($p < 0.05$). The Shoulder Disability

Table I. Comparison of EMG latency values in modified radical neck dissection (mRND) and selective neck dissection (SND) on the operated side (3 months postoperative).

Accessory nerve	mRND	n	SND	n	P
Lower trapezius (mean ± SD)	7.34 ± 2.17	5	8.81 ± 1.82	8	0.257
Middle trapezius	5.75 ± 3.25	6	5.32 ± 1.46	9	0.481
Upper trapezius	4.27 ± 1.36	6	4.29 ± 1.02	11	0.429
Pin, trapezius	6.09 ± 3.57	3	5.24 ± 4.3	12	0.615

**n – number of patients*
P < 0.05

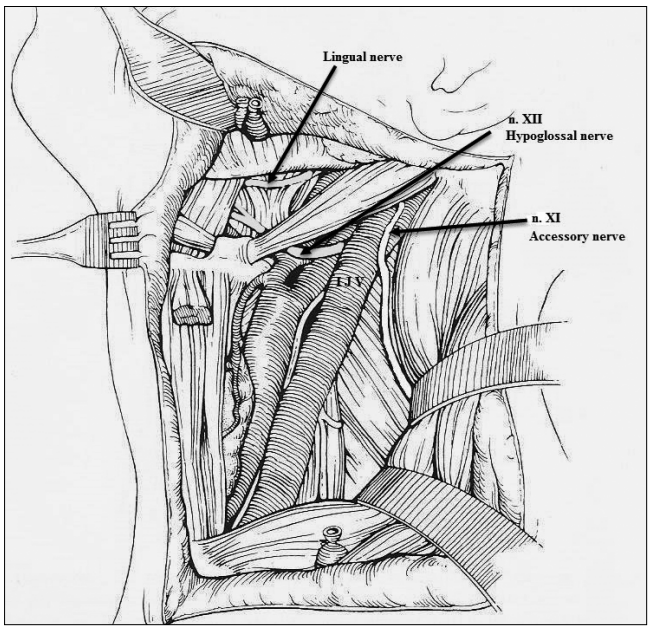


Fig. 3. Cranial nerve XI crossing with internal jugular vein in functional neck dissection (schematic appearance).

Questionnaire score was significantly lower in the spinal accessory nerve preservation group compared to the radical neck dissection group and comparison of active shoulder joint motion ranges on the operated with mRND and the control sides revealed lower EMG discrepancies on operated (abnormal) and control (normal) side (Table II). Visual Analog Scale (VAS) was also used, and 28% of the patients had no pain.

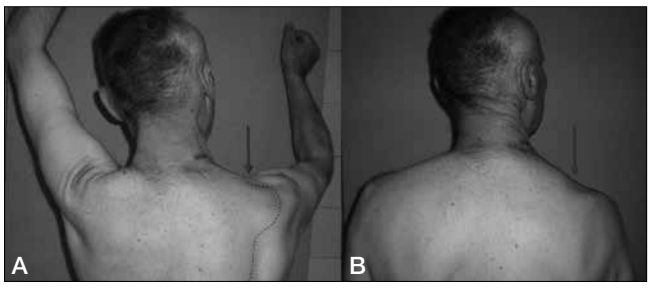


Fig. 4. a. Trapezius muscle disability – right shoulder dropped after radical neck dissection of malignant melanoma; b. Dysfunction of the right shoulder – accessory nerve resected.

The arm abduction test was with score of 4.3 in properly treated cases with preservation of SAN.

Five patients with history of adhesive capsulitis were enrolled who had higher *EMG* ratios of the upper trapezius to lower trapezius during arm elevation.

Patients who underwent supraomohyoid selective neck dissection that involved minimal dissection of the spinal accessory nerve had minimal loss of shoulder function and usually, normal electromyograms in 3 months that documented less injury to the spinal accessory nerve. Again, these patients had improvement with the time. No patient had recurrence of neck disease during at least 3, 6 and 12 months of follow up.

Discussion

The main therapeutic dilemma for the therapy of metastatic carcinoma from head and neck malignancy remains the choice of the type of neck dissection. The probability of metastases to the neck from various sites in the upper aerodigestive tract has been outlined [10 15], so there are data from much of the literature on the technique and indications for functional modifications of the classical radical neck dissection. Conley and Schuller [10] confirmed a large percentage of metastases (42%) in close proximity to the spinal accessory nerve where it comes to lie near the internal jugular vein. Ballantyne, Shah and Bocca's group [10] gave strong support to MRND emphasising that in many situations the spinal accessory nerve is not intimately involved in neck disease and its preservation does not comprise the oncologic effectiveness of the more limited procedure. These and other investigations have designated the introduction of modified neck dissections.

Beneficial surgical intervention in case of posterior neck metastases depends on suitable exposure and preservation of the spinal accessory nerve. This induces a consistent understanding of the anatomy of the posterior neck triangle for performing surgery safely, including the sufficient knowledge of extracranial anatomy of spinal accessory nerve variations [11 16-18].

Patten and Hillei [19] indicated that adhesive capsulitis is a principal component of XI nerve syndrome that can significantly compound the morbidity of a neck dissection even when the accessory nerve recovers.

Table II. Comparison of active shoulder joint motion ranges on the operated with mRND and the control sides.

Shoulder function	Operated (mean ± SD)	Control (mean ± SD)	n	P
Flexion	130.7 ± 24.5	143 ± 15.6	20	<0.002
Abduction	128.3 ± 27.3	144.6 ± 14.3	20	<0.002
Internal rotation	71.2 ± 13.1	72.5 ± 11	20	0.477
External rotation	64.5 ± 11.3	68.7 ± 11.9	20	0.019

Our findings support results in the literature that the spinal accessory nerve is located anterior to the internal jugular vein in the majority of the cases, although it is imperative for the surgeon to be mindful to anatomic variability and possible posterior crossing of the internal jugular vein by the spinal accessory nerve in the neck to avoid injury to the internal jugular vein during the dissection of the nerve. Since the great auricular nerve (Erb's point) represents a constantly identifiable landmark, it allows simple and reliable identification of the course of the spinal accessory nerve. Across the posterior triangle, the nerve was running superficially with either straight (78%) or coiled (22%) pathway. The accessory nerve and the phrenic nerve were similar in terms of anatomic evidence and number of motor nerve fibres. On ultrasound evaluation, the accessory nerve exited the posterior border of sternocleidomastoid at a mean of 6.5 (5.0-8.5) cm below the mastoid process and penetrated the anterior border of trapezius 5.5 (3.0-7.0) cm above the clavicle with mean caliber of 0.75 ± 0.10 mm.

The most common complication of neck dissection is shoulder pain and dysfunction due to manipulation of the spinal accessory nerve, resulting in trapezius muscle atrophy mainly in procedures involving the posterior neck triangle [18].

Lee et al. [20] showed that 22 of 25 (88%) patients had shoulder pain, but that the average pain score was low (2.3 ± 1.3).

Kuntz and Weymuller [21] reported that the modified radical neck dissection group of patients reported greater shoulder disability at 6 months compared with the selective neck dissections group, but at 12 months there was no difference between the two groups.

Giordano et al. [22] analysed shoulder function after selective and superselective neck dissections, and the subjective test showed no significant differences between the two groups even when sublevel IIB is spared.

The findings of Cheng et al. [23] in their prospective study with subjective evaluation of shoulder pain and objective evaluation of shoulder muscle strength suggested that patients who underwent selective neck dissection had the least damage to spinal accessory nerve function and the least shoulder disability after neck dissection.

Cappiello et al. [24] compare the results of clinical and electrophysiological investigations of shoulder function in patients affected by head and neck carcinoma, and a high number of abnormalities was found on electrophysiological testing, only a limited number of patients, mostly in group B (received a selective neck dissection involving clearance of levels II-V), displayed shoulder function disability affecting daily activities.

In a study by Remmler et al. [25] modified nerve sparing dissections were followed on the average by a significant, but temporary and reversible phase of shoulder dysfunction. By comparison, radical neck dissection is followed by profound and permanent trapezius muscle weakness and denervation [25].

Birinci et al. [26] carried out a prospective, double-blind clinical trial where shoulder function deterioration was significantly less for patients with insignificant intraoperative neuromonitoring changes than in patients with significant intraoperative neuromonitoring changes ($P < 0.05$).

Chepeha et al. [27] concluded that patients receiving modified radical neck dissection had significantly worse shoulder function than patients with selective neck dissection ($p = 0.0007$).

Van Wilgen et al. [28] reported that after modified radical neck dissection 33.3% of patients experienced shoulder complaints; after postero-lateral neck dissection 66.7% and after supraomohyoid neck dissection 20% of the patients experienced shoulder complaints. Wilgen et al. [28] indicated that the type of neck dissection was significantly ($P < 0.001$) related to shoulder complaints.

Selcuk et al. [29] showed that in patients who underwent anterolateral neck dissection, the goniometric results were better than with the functional neck dissection.

Macaluso et al. [30] reported that early detection of spinal accessory nerve injuries can be improved through EMG testing.

According to Svenberg et al. [31], an important landmark in the neck is to detect the branches from cervical plexus to potentially provide the surgeon with important intraoperative nerve identification and monitoring following surgical injury to the SAN.

Our study indicates that there may be functional disability associated with any type of neck dissection in which the spinal accessory is dissected and placed in some degree of traction. The finding of significantly lower risk of functional disability in modified neck dissections, and confirmation that the modified neck dissection is as effective as the radical neck dissection for controlling neck disease, extends the indications for modified or selective neck dissections as a more logical approach to surgical treatment

of cervical neck disease. If there is no functional advantage, all other arguments for modified neck dissections become inappropriate.

We proposed that adhesive capsulitis is a principal component of XI nerve syndrome that can significantly compound the morbidity of a neck dissection even when the accessory nerve recovers [32]. The subsequent development of adhesive capsulitis in our patients disappeared after 2 months postoperatively.

The results of this study show that, on average, neck dissection patients with the spinal accessory nerve preserved have less pain in their shoulders, less functional disability and stronger results on physical examination than those with the spinal accessory nerve sacrificed without any difference in local control and survival. This is of importance because any inadvertent injury to the spinal accessory nerve during surgical procedures is a cause of significant morbidity with medicolegal repercussions. The findings in this work are consistent to some previous studies regarding te spinal accessory nerve preservation [1 3 9]. This study has the advantage that it originated from existing operative findings rather than cadaver dissections and, as a result, incorporated functional information and postoperative significance of damage to selected muscle functions.

Conclusions

We can validate that the spinal accessory nerve injury is potentially preventable in most cases of neck surgery. Surface anatomical landmarks are not always a reliable guide to the position and course of the nerve in the posterior triangle. Within modified neck dissections, identification of spinal accessory nerve over established landmarks is unconditionally reliant on the exact preoperative mapping of the nerve with imaging diagnostics, but the sophisticated further eleventh nerve dissection and preservation depends on the inclusive surgical knowledge. Modified neck dissection has similar regional control rates to more comprehensive operations in appropriately selected patients and significantly reduces the risk of functional disability.

Acknowledgements

The presented study has been carried with interdisciplinary assistance of all authors.

References

1 Chen DT, Chen PR, Wen IS, et al. *Surgical anatomy of the spinal accessory nerve: is the great auricular point reliable?* J Otolaryngol Head Neck Surg 2009;38:337-9.

2 Durazzo MD, Furlan JC, Teixeira GV, et al. *Anatomic landmarks for localization of the spinal accessory nerve*. Clin Anat 2009;22:471-5.

3 Lloyd S. *Accessory nerve: anatomy and surgical identification*. J Laryngol Otol 2007;121:1118-25.

4 Shah J, Patel S. *Head and Neck surgery and oncology*. III ed. Edinburgh, London, New York, Toronto: Mosby; 2003. p. 353-394.

5 Saman M, Etebari P, Pakdaman MN, et al. *Anatomic relationship between the spinal accessory nerve and the jugular vein: a cadaveric study*. Surg Radiol Anat 2011;33:175-9.

6 Tubbs RS, Stetler W, Louis RG Jr, et al. *Surgical challenges associated with the morphology of the spinal accessory nerve in the posterior cervical triangle: functional or structural?* J Neurosurg Spine 2010;12:22-4.

7 Veyseller B, Aksoy F, Ozturan O, et al. *Open functional neck dissection: surgical efficacy and electrophysiologic status of the neck and accessory nerve*. J Otolaryngol Head Neck Surg 2010;39:403-9.

8 Aravind R, Kathiresan N. *Radical neck dissection: preserving the distal spinal accessory nerve based on its cervical plexus contribution*. J Surg Oncol 2008;98:200-1.

9 Popovski V. *Massive deep lobe parotid neoplasms and parapharyngeal space-occupying lesions: contemporary diagnostics and surgical approaches*. Sec Biol Med Sci MASA 2007;28:113-27.

10 Thawley SE, Panje WR, Batsakis JG. *Comprehensive Management of Head and Neck Tumors*. Vol. II. Philadelphia: W.B. Saunders Company; 1999. p.1147-1172.

11 Boström D, Dahlin LB. *Iatrogenic injury to the accessory nerve*. Scand J Plast Reconstr Surg Hand Surg 2007;41:82-7.

12 Hashimoto Y, Otsuki N, Morimoto K, et al. *Four cases of spinal accessory nerve passing through the fenestrated internal jugular vein*. Surg Radiol Anat 2012;34:373-5.

13 Lima LP, Amar A, Lehn CN. *Spinal accessory nerve neuropathy following neck dissection*. Braz J Otorhinolaryngol 2011;77:259-62.

14 Salgarelli AC, Landini B, Bellini P, et al. *A simple method of identifying the spinal accessory nerve in modified radical neck dissection: anatomic study and clinical implications for resident training*. Oral Maxillofac Surg 2009;13:69-72.

15 Cummings CW, Fredrickson JM. *Otolaryngology – Head and neck surgery.* II ed. Year Book, St. Louis-Baltimore-Boston: Mosby; 1993. Vol. II, p. 1043-1078.

16 Skinner SA. *Neurophysiologic monitoring of the spinal accessory nerve, hypoglossal nerve, and the spino-medullary region*. J Clin Neurophysiol 2011;28:587-98.

17 Lee SH, Lee JK, Jin SM, et al. *Anatomical variations of the spinal accessory nerve and its relevance to level IIb lymph nodes*. Otolaryngol Head Neck Surg 2009;141:639-44.

18 Watkins JP, Williams GB, Mascioli AA, et al. *Shoulder function in patients undergoing selective neck dissection with or without radiation and chemotherapy.* Head Neck 2011;33:615-9.

19 Patten C, Hillel AD. *The 11th nerve syndrome. Accessory nerve palsy or adhesive capsulitis?* Arch Otolaryngol Head Neck Surg 1993;119:215-20.

20 Lee CH, Huang NC, Chen HC, et al. *Minimizing shoulder syndrome with intra-operative spinal accessory nerve monitoring for neck dissection.* Acta Otorhinolaryngol Ital 2013; 33:93-6.

21 Kuntz AL, Weymuller EA, Jr. *Impact of neck dissection on quality of life*. Laryngoscope 1999;109:1334-8.

[22] Giordano L, Sarandria D, Fabiano B, et al. *Shoulder function after selective and superselective neck dissections: clinical and functional outcomes*. Acta Otorhinolaryngol Ital 2012;32:376-9.

[23] Cheng PT, Hao SP, Lin YH, et al. *Objective comparison of shoulder dysfunction after three neck dissection techniques*. Ann Otol Rhinol Laryngol 2000;109:761-6.

[24] Cappiello J, Piazza C, Giudice M, et al. *Shoulder disability after different selective neck dissections (levels II-IV versus levels II-V): a comparative study*. Laryngoscope 2005;115:259-63.

[25] Remmler D, Byers R, Scheetz J, et al. *A prospective study of shoulder disability resulting from radical and modified neck dissections*. Head Neck Surg 1986;8:280-6.

[26] Birinci Y, Genc A, Ecevit MC, et al. *Spinal accessory nerve monitoring and clinical outcome results of nerve-sparing neck dissections*. Otolaryngol Head Neck Surg 2014;151:253-9.

[27] Chepeha DB, Taylor RJ, Chepeha JC, et al. *Functional assessment using Constant's Shoulder Scale after modified radical and selective neck dissection.* Head Neck 2002;24:432-6.

[28] van Wilgen CP, Dijkstra PU, van der Laan BF, et al. *Shoulder complaints after nerve sparing neck dissections*. Int J Oral Maxillofac Surg 2004;33:253-7.

[29] Selcuk A, Selcuk B, Bahar S, et al. *Shoulder function in various types of neck dissection. Role of spinal accessory nerve and cervical plexus preservation.* Tumori 2008;94:36-9.

[30] Macaluso S, Ross DC, Doherty TJ, et al. *Spinal accessory nerve injury: A potentially missed cause of a painful, droopy shoulder*. J Back Musculoskelet Rehabil 2016;29:899-904.

[31] Svenberg Lind C, Lundberg B, Hammarstedt Nordenvall L, et al. *Quantification of trapezius muscle innervation during neck dissections: cervical plexus versus the spinal accessory nerve*. Ann Otol Rhinol Laryngol 2015;124:881-5.

[32] Patten C, Hillel AD. *The 11th nerve syndrome. Accessory nerve palsy or adhesive capsulitis?* Arch Otolaryngol Head Neck Surg 1993;119:215-20.

Received: September 23, 2016 - Accepted: November 17, 2016

Address for correspondence: Aleksandar Stamatoski, Clinic for Maxillofacial Surgery, St Cyril and Methodius University, Skopje, R. Macedonia. Tel. +389 2 3163371; +38977 55 66 62. Fax +389 2 3238464. E-mail: alexandar.stamatoski5999@gmail.com

ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:375-386; doi: 10.14639/0392-100X-1089

Head and neck

Parotid tumours: clinical and oncologic outcomes after microscope-assisted parotidectomy with intraoperative nerve monitoring

Tumori della parotide: risultati oncologici e clinici dopo parotidectomia effettuata con l'ausilio del microscopio operatorio ed il monitoraggio intraoperatorio del nervo facciale

F. CARTA[1], N. CHUCHUEVA[1], C. GEROSA[2], S. SIONIS[1], R.A. CARIA[1], R. PUXEDDU[1]

[1] Department Otorhinolaryngology, Università degli Studi di Cagliari, Azienda Ospedaliero-Universitaria di Cagliari, Italy; [2] Department of Pathology, Università degli Studi di Cagliari, Azienda Ospedaliero-Universitaria di Cagliari, Italy

SUMMARY

Temporary and permanent facial nerve dysfunctions can be observed after parotidectomy for benign and malignant lesions. Intraoperative nerve monitoring is a recognised tool for the preservation of the nerve, while the efficacy of the operative microscope has been rarely stated. The authors report their experience on 198 consecutive parotidectomies performed on 196 patients with the aid of the operative microscope and intraoperative nerve monitoring. 145 parotidectomies were performed for benign lesions and 53 for malignancies. Thirteen patients treated for benign tumours experienced temporary (11 cases) or permanent facial palsy (2 cases, both of House-Brackmann grade II). Ten patients with malignant tumour presented with preoperative facial nerve weakness that did not improve after treatment. Five and 6 patients with malignant lesion without preoperative facial nerve deficit experienced postoperative temporary and permanent weakness respectively (the sacrifice of a branch of the nerve was decided intraoperatively in 2 cases). Long-term facial nerve weakness after parotidectomy for lesions not directly involving or originating from the facial nerve (n = 185) was 2.7%. Patients treated for benign tumours of the extra facial portion of the gland without inflammatory behaviour (n = 91) had 4.4% facial nerve temporary weakness rate and no permanent palsy. The combined use of the operative microscope and intraoperative nerve monitoring seems to guarantee facial nerve preservation during parotidectomy.

KEY WORDS: Parotid tumours • Facial weakness • Intraoperative nerve monitoring • Microscope-assisted parotidectomy • Salivary glands

RIASSUNTO

I pazienti sottoposti ad intervento chirurgico di parotidectomia per lesioni benigne e maligne possono presentare disfunzioni temporanee o permanenti del nervo facciale. Il monitoraggio intraoperatorio della motilità facciale è uno strumento ampiamente riconosciuto per la sua utilità nella preservazione del nervo, mentre l'efficacia del microscopio operatorio è stata raramente discussa. Gli autori riportano la loro esperienza su 198 parotidectomie consecutive eseguite su 196 pazienti con l'ausilio del microscopio operatorio e del monitoraggio intraoperatorio del nervo facciale. Centoqurantacinque interventi sono stati eseguiti per lesioni benigne e 53 per neoplasie maligne. Tredici pazienti operati per lesioni benigne hanno presentato un deficit della funzionalità del nervo facciale: 11 hanno sofferto di paralisi temporanea e 2 di paralisi permanente (entrambe di secondo grado). Dieci pazienti affetti da patologia maligna presentavano un interessamento preoperatorio del nervo facciale. Cinque e sei pazienti affetti da patologia maligna senza interessamento preoperatorio del nervo hanno presentato un deficit rispettivamente temporaneo e definitivo (in 2 casi il sacrificio di un ramo del nervo macroscopicamente infiltrato dalla neoplasia fu deciso solo durante la procedura chirurgica). L'incidenza di paralisi definitiva di una singola branca del nervo facciale dopo interventi eseguiti per lesioni che non originavano dal nervo facciale o che non lo infiltravano macroscopicamente (n = 185) è stata del 2,7%. I pazienti trattati per tumori benigni non flogistici del lobo superficiale della ghiandola parotide (n = 91) hanno presentato una paralisi facciale postoperatoria temporanea nel 4,4% dei casi e nessun deficit permanente. L'uso combinato del microscopio operatorio e del monitoraggio intraoperatorio del nervo sembra garantire la preservazione del nervo facciale nei pazienti sottoposti a parotidectomia.

PAROLE CHIAVE: *Tumori parotidei • Deficit del nervo facciale • Monitoraggio del nervo facciale • Parotidectomia microscopio-assistita • Ghiandole salivari*

Acta Otorhinolaryngol Ital 2017;37:375-386

Introduction

Salivary gland neoplasms represent 3% of all head and neck tumours, the majority of which originate from the parotid [1]. Surgical treatment of parotid neoplasms is focused on complete removal of the tumour together with the extra-petrosal dissection of the facial nerve. Although parotidectomy is a well-known and safe procedure if correctly performed, immediate postoperative facial nerve weakness may occur in 10% to 40% of patients treated for a benign neoplasm [2], whereas permanent postoperative facial weakness has been described in 1% to 7.1% of patients [2-8]. Malignant lesions are generally related to a higher rate of postoperative palsy.

Intraoperative nerve monitoring (NIM) has been associated with a lower risk of immediate postoperative facial nerve palsy in primary cases of parotidectomy [2], while the efficacy of the operative microscope during the parotidectomy has been rarely evaluated. The authors report their experience on the surgical management of parotid gland tumours with microscope assisted parotidectomy (MAP) combined with NIM, focusing on postoperative facial nerve function and clinical/oncologic outcomes according to histology.

Materials and methods

This is a prospective study involving a consecutive cohort of 196 patients treated at our Department with MAP coupled with NIM from November 2010 to January 2016. Medical history was collected before admission. High-resolution ultrasonography (US), computerised tomography (CT), magnetic resonance imaging (MRI) and fine needle aspiration cytology (FNAC) were used for preoperative evaluation, although not always together. Facial nerve function was evaluated preoperatively, on the first day after surgery, after one month and at least at three months after surgery using the House-Brackmann scale [9] completed with the description of the function of all the facial nerve branches (frontal, zygomatic, buccal, mandibular). Patients underwent superficial (removal of all the parotid tissue above the facial nerve) or total parotidectomy (extended to all parotid tissue including the deep lobe of the gland), according to the extension of the tumour. We never performed enucleations or extra-capsular dissections. Neck dissection (levels II-V) and adjuvant therapies were performed in case of malignant lesions, according to the Oncology Guidelines approved by our Institutional Review Board. Facial nerve dissection was always performed coupling the intraoperative microscope (ZEISS S7, focal length 250 mm) with NIM (Medtronic NIM Response® 3.0-4 channels). Typical parameters used at our institution are: stimulus intensity of 0.5-0.7 mA, duration of the stimulus of 100 μsec, rate of the stimuli of 4 bursts/sec and event threshold of 100 μV. Antibiotic prophylaxis (ceftriaxone 1 g IV/day) was given at least 30 min preoperatively; corticosteroids (dexamethasone, 4 mg/day for 7 days) were used when immediate postoperative facial nerve weakness was present. Patients were reviewed during this study for the purpose of facial nerve dysfunction and oncologic outcome as well as for development of symptomatic Frey's syndrome and numbness of the pinna following the sectioning of the great auricular nerve (GAN). This study also considered the correlation between facial nerve dysfunction, histology and surgical complexity (total parotidectomy and superficial parotidectomy, benign neoplasms of the superficial and deep lobe, inflammatory lesions of the superficial and deep lobe, facial nerve schwannoma, primitive malignant tumours of the superficial and deep lobe, lymphomas, normal parotid gland removed during management of skin malignant neoplasms, metastatic tumours of the parotid without skin infiltration or preoperative facial nerve involvement, metastatic tumours of the parotid with skin infiltration or preoperative facial nerve involvement). Patients with a diagnosis of lymphoma were referred for long-term oncologic follow-up to the Department of Onco-haematology with autonomous follow-up. Survival time was assessed from the date of surgery to the date of the last follow-up visit. 5-year overall survival (OS) and disease-specific survival (DSS) rates were calculated using the Kaplan-Meier method. The statistical significance of the different patient populations was tested with the chi-square test, considering significance when p was less than 0.05.

Results

During the period of the study, 198 parotidectomies were performed on 97 men and 99 women (sex ratio M/F of 0.98, mean age 56.1 years, range 15-88). The procedure was performed on the right side in 95 patients, on the left side in 99 patients and bilateral in 2 cases (1 patient presented a primary benign neoplasm of both the parotid glands and 1 patient underwent bilateral parotidectomy for suspicious bilateral metastasis of skin malignancy of the scalp). 145 parotidectomies (73.2%) were performed for benign lesions and 53 (26.8%) for malignant lesions (Table I). 169 patients were evaluated for a chronic swelling of a parotid mass previously confirmed with US, 6 patients were treated for local recurrence after parotidectomy for benign lesion performed elsewhere, 11 patients were treated for possible parotid involvement of cutaneous tumours, and 10 patients presented with an advanced malignant neoplasm with clinical involvement of the parotid area. 143 patients (73%) were preoperatively evaluated with MRI with contrast medium; 53 patients (27%) were evaluated only with CT with contrast medium (28 patients affected by malignant lesions were investigated only with CT). MRI (41.2%) allowed a preoperative diagnosis in 59 cases: 70.9% (44/62) of MRI for pleomor-

Table I. Parotid tumours.

Histologic types	No. of parotidectomies	%
Pleomorphic adenoma	70	35.4
Warthin's tumour[1]	42	21.2
Salivary cyst	5	2.6
Lymph epithelial cyst	2	1
Epidermoid cyst	2	1
Branchial cyst	1	0.5
Mucopapillary cyst	1	0.5
Inflammatory lymphonode	2	1
Sjogren's syndrome	1	1
Lithiasis	1	0.5
Inflammatory degeneration	1	0.5
Masson's tumour	1	0.5
Cystadenoma	3	1.5
Lymph node	2	1
Basal cell adenoma	1	0.5
Haemangioma	1	0.5
Lymphangioma	1	0.5
Fibrosis	1	0.5
Follicular hyperplasia	1	0.5
Chronic cystic hyperplasia	2	0.5
Schwannoma	1	0.5
Oncocytoma	1	0.5
Lipoma	1	0.5
Connective substitution	1	0.5
TOTAL BENIGN LESIONS	**145**	**73.2**
Metastasis of skin malignancy 15 squamocellular carcinomas 1 melanoma 1 Merkel's tumour	17[2]	8.7
Metastasis of renal malignancy	1	0.5
Adenocarcinomas	11[3]	5.6
Carcinoma on pleomorphic adenoma	3	1.5
Mucoepidermoid carcinoma	4[4]	2
Oncocytic carcinoma	1	0.5
Myoepithelial carcinoma	1	0.5
Neuroendocrine carcinoma	1	0.5
Lymphoma	6	3
Normal parotid gland (associated with neck dissection)	8[5,6,7]	4
TOTAL MALIGNANT LESIONS	**53**	**26.8**
ALL	**198**	**100**

[1] 1 patient underwent bilateral parotidectomy for bilateral Warthin's tumour

[2] Facial nerve neoplastic infiltration was evident preoperatively in 7 cases.

[3] Facial nerve neoplastic infiltration was evident preoperatively in 1 case.

[4] Facial nerve neoplastic infiltration was evident preoperatively in 1 case.

[5] 1 patient was submitted to bilateral parotidectomy for suspicious bilateral metastasis of squamous cell carcinoma; histology revealed the carcinoma in only one parotid gland.

[6] 1 patient was submitted to parotidectomy with radical neck dissection for head and neck melanoma; histology did not reveal the melanoma in the parotid gland.

[7] A facial nerve deficit was preoperatively due to the neoplastic involvement of the nerve from the zygomatic skin malignancy in 1 case.

phic adenomas allowed pre-operative diagnosis, while only 13.3% (4/30) of MRI were reliable in pre-operative diagnosis of Warthin's tumour. CT and/or MRI allowed preoperative diagnosis of malignant lesion of the parotid in 18 cases (34%), in 24 cases (45.3%) it confirmed the parotid lesion but could not predict the benign or malignant nature, and was negative in 11 cases (20.7%) whose definitive histological analysis confirmed the presence of carcinoma. FNAC was performed in 37 patients (18.9%), and was predictive in 22/37 lesions (accuracy of 59.5%). FNAC diagnosis of pleomorphic adenoma was predictive in 100% of cases (n = 9), while FNAC was diagnostic in 50% of cases of Warthin's tumour (2/4 patients). Patients with a cytological diagnosis of benign tumour of the parotid (n = 19) was benign in 18 cases, while 1 was malignant. Patients with FNAC suspicious for malignancy (n = 5) underwent neck dissection during the same procedure after intraoperative histological confirmation (4/5 resulted pN+), patients with non-diagnostic FNAC (n = 13) were submitted in 11 cases to parotidectomy alone (definitive diagnosis showed 2 primary malignancies, 1 lymphoma and 8 benign lesions), in 1 case to a delayed neck dissection after histological diagnosis of primitive parotid malignancy, and in 1 case with obvious clinical malignant behaviour, to parotidectomy with neck dissection performed during the same general anaesthesia after intraoperative histological confirmation of the malignant nature of the lesion. Trans-nasal intubation was always performed to avoid the retrograde move of the angle of the mandible due to the oro-tracheal tube, improving the space for nerve identification. A superficial parotidectomy was performed in 140 cases (70.7%) and a total parotidectomy in 58 cases (29.3%). Thirty-eight tumours (19.2%) involved the deep lobe of the parotid gland (28 benign neoplasms, 3 malignant lesions and 7 inflammatory lesions). The sacrifice of single branches of the nerve involved by the tumour was necessary in 13 cases: in 10 patients, the involvement of the nerve was preoperatively obvious, in 2 cases it was evident only intraoperatively (neural invasion was definitively confirmed by histology as shown in Fig. 1) and in 1 case the tumour was originating from the nerve; in 4 cases GAN grafting was performed in the attempt to restore the nerve continuity. Two parotidectomies were performed during management of a head and neck melanoma. In 28 cases the parotidectomy was associated with a selective or modified radical neck dissection, in 3 cases it was associated with the removal of the pinna, and in 8 cases it was widely extended to the facial skin and required a reconstructive procedure (2 pectoralis major pedicled flaps, 2 platysma pedicled flaps, 3 free flaps of rectus abdominis, and 1 forearm free flap). Three patients underwent delayed neck dissection after histological diagnosis of parotid malignancy.

Average operation time for benign lesion was 221 min (range of 120-350). Mean hospitalisation time was 4.3 days (2.4 days for patients submitted to parotidectomy alone and 7.7 days for patients submitted to more invasive procedures). Postoperative complications occurred in 17 patients (Table II). Bleeding always required surgical revision of the haemostasis, while other complications like seroma, salivary fistula and infection were managed by antibiotics and conservative procedures.

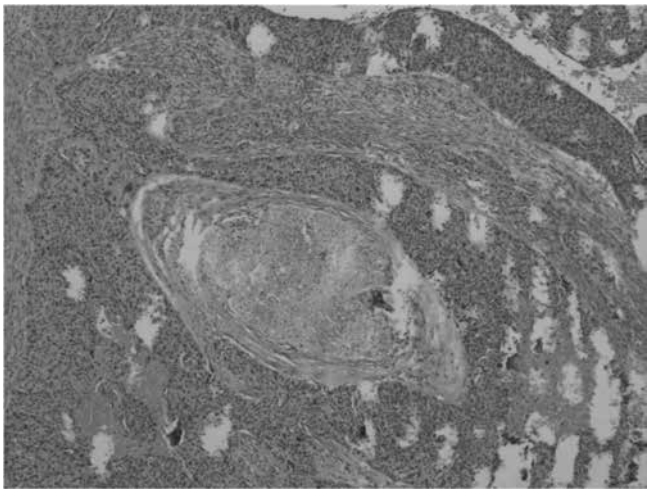


Fig. 1. H&E (20X): squamous cell carcinoma perineural involvement. The patient did not show any preoperative facial weakness, but intraoperatively the mass showed important adherences to a branch of the nerve that was resected.

Among the benign pathologies (n = 145), 11 showed a temporary (7.6%) and 2 a permanent weakness (1.4%) of the facial nerve. The 11 temporary weaknesses were grade II in 8 cases and grade III in 3 cases, with a mean recovery time of 2.3 months (0.2-6 months); in 3/11 cases the tumour involved the deep lobe of the gland and in 4/11 cases the lesion (inflammatory) presented multiple adherences to the nerve. The 2 permanent palsies were of grade II and involved one single branch of the nerve: the first was observed after total parotidectomy for an inflammatory cystic lesion of the para-pharyngeal portion of the parotid gland adhering to the marginal mandibular branch, and the second after superficial parotidectomy for a schwannoma originating from the zygomatic branch of the facial nerve. Among the malignancies, 10/53 procedures were performed in patients with preoperative facial nerve weakness that did not improve after treatment; patients without preoperative facial nerve deficit experienced a temporary weakness in 5/43 cases (11.6%), while in 6/43 cases (14%) presented a permanent deficit (in 2 cases the palsy was due to the surgical removal of a peripheral branch of the nerve macroscopically involved by the tumour, and in 3 cases it was observed after parotidectomy associated with selective neck dissection).

Temporary and permanent facial nerve weakness rates after superficial and total parotidectomy in patients without preoperative deficit were 7.1% (10/140) and 3.6% (5/140)

Table II. Postoperative complications.

Complications	Benign tumour	vs.	Malignant tumour	Superficial parotidectomy	vs.	Total parotidectomy
Bleeding	5		4	6		3
Wound infection	1		-	-		1
Salivary fistula	-		1	1		-
Seroma	5		1	6		-
TOTAL	11		6	13		4

vs. 12.5% (6/48) and 6.25% (3/48) respectively. Patients treated for benign tumours of the extra-facial portion of the gland without inflammatory behaviour (n = 91) had 4.4% facial nerve temporary weakness rate and no permanent palsy. Patients without preoperative facial weakness undergoing superficial or total parotidectomy associated with neck dissection showed a 11.1% rate (2/18) of definitive deficit of the mandibular branch of the nerve; permanent facial nerve weakness after parotidectomy for benign and malignant lesions not directly involving or originating from the facial nerve was 2.7% (5/185). The degrees and branches involved are detailed in Table III. After surgery, 15 patients treated for malignancy underwent adjuvant radiotherapy (50–60 Gy, associated with chemotherapy in 5 patients). Two patients with melanoma underwent adjuvant chemotherapy.

No recurrences have occurred after surgery for benign lesions to date. Among the malignancies, 46 patients were included in regular oncologic follow-up at our Department; mean follow-up period was 20 months (range of 3 month-5 years). Two patients experienced local recurrence and underwent chemoradiotherapy, 2 patients (1 diagnosis of melanoma and 1 Merkel carcinoma) experienced neck skin relapse and underwent salvage surgery followed by chemotherapy and radiotherapy, respectively, 3 patients experienced distant metastasis and underwent chemotherapy. Thirty-five patients were alive with no evidence of parotid tumour-related disease at the last follow-up, while 5 patients died of disease and 6 patients died for other causes. DSS and OS for the cohort of patients followed-up in our Department (n = 46) were 83% and 70.6%; patients with primary malignancy of the parotid (n = 22) showed DSS and OS of 85.6% and 81.3%; patients with metastatic squamous cell carcinoma involving the parotid (n = 15) showed DSS and OS of 90.9% and 53.8%; patients submitted to parotidectomy for suspicious metastasis of squamous cell carcinoma, but negative at histology (n = 6) presented DSS and OS of 100%; patients with preoperative facial nerve weakness/skin infiltration (n = 10) presented DSS and OS of 85.7% and 45%; patients without preoperative facial nerve weakness/skin infiltration (n = 36) presented DSS and OS of 80.3% and 74.6%; patients with node metastasis (n = 17) presented DSS and OS of 76.4% and 54.3%; patients without node metastasis (n = 29) presented DSS and OS of 87% and 80.4% (Fig. 2).

All patients experienced postoperative auricular numbness; at present (or at the last examination for patients died during the follow-up), 133 patients still report numbness in correspondence of the inferior lobe of the pinna: 44.7% who underwent parotidectomy in 2011, 65.9% of those treated in 2012, 67.5% of those treated in 2013, 90.2% of those treated in 2014 and 97.2% of those treated in 2015. Thirty-five patients experienced a Frey's syndrome after parotidectomy performed for benign tumour (n = 145). No patients experienced first bite syndrome.

Discussion

A large variety of benign and malignant tumours can arise from the salivary glands [10], therefore, when a localised parotid mass is detected, it requires a specific diagnostic work-up focusing on evaluating the risk of malignancy, since it changes the prognosis and the attitude toward the facial nerve [11]. High-resolution US, conventional MRI and CT with contrast medium are commonly used for evaluating parotid masses [12 13]. We used, when possible, MRI for preoperative evaluation, but in patients previously evaluated with adequate CT scan images, we did not ask for further imaging. Preoperative diagnostic assessment also takes advantage of FNAC, a minimally invasive technique with a recognised role in cytological diagnosis of patients with salivary gland tumours, with reasonable sensitivity and specificity [14]. Nevertheless, the interpretation of FNAC of salivary gland lesions could be a great challenge for cytologists: the material provided by FNAC may contain poor diagnostic elements and there are some rare tumours that can cause confusion [15 16]. Piccioni et al [17] reported sensitivity and specificity rates of 81% and 99%, respectively, excluding non-diagnostic procedures; however, the analysis of all the procedures of the same study, diagnostic and non-diagnostic, shows an accuracy rate of 77.3% (136 reliable diagnoses in 176 procedures). FNAC has been employed in our Department since 2010, with an accuracy of 59.5%, in preoperative differential diagnosis of benign to malignant neoplasms. The experience of the pathologist is considered fundamental in FNAC [15 18]. According to the literature, we consider that FNAC contribute to, but cannot substitute overall diagnostic assessment [19].

Table III. Postoperative outcomes according to surgical complexity.

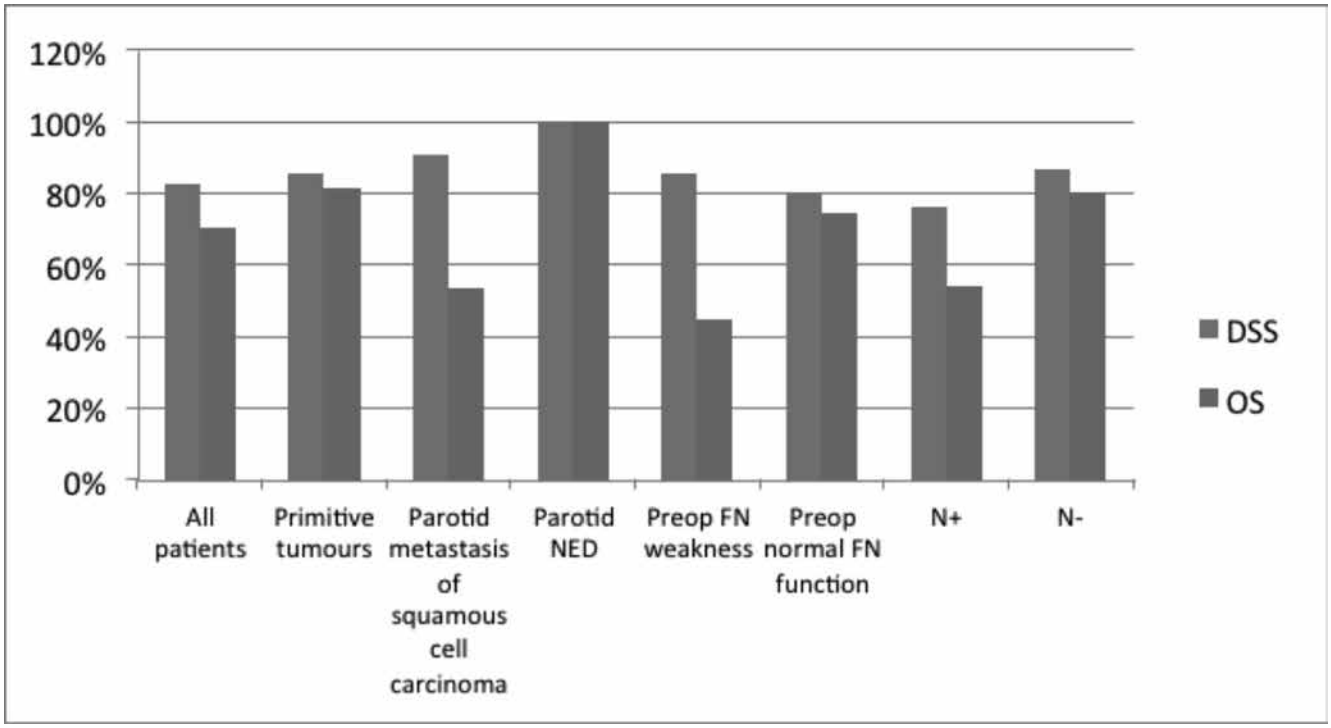
Histological type	Number of procedures	Immediate temporary facial nerve weakness	Permanent facial nerve weakness	Frey's syndrome	Recurrence
Benign neoplasms of the superficial lobe	91	4 1 Grade II – Marginal mandibular 2 Grade II – Buccal 1 Grade III – Marginal mandibular	0	18	0
Benign tumours of the deep lobe	28	3 2 Grade II – Marginal mandibular 1 Grade III – Marginal mandibular	0	7	0
Inflammatory tumours of the superficial lobe	18	2 1 Grade II – Marginal mandibular 1 Grade III – Marginal mandibular	0	7	0
Inflammatory lesions of the deep lobe	7	2 1 Grade II – Marginal mandibular 1 Grade III – Marginal mandibular	1 Grade II – Marginal mandibular	3	0
Schwannoma	1*	0	1 Grade II – Zygomatic	0	0
Primary malignancy of the superficial lobe without pre-operative facial nerve involvement	16**	3 2 Grade II – Marginal mandibular 1 Grade III – Marginal mandibular	3 2 Grade II – Marginal mandibular 1 Grade III – Frontal	3	0
Primitive malignancy of the deep lobe without pre-operative facial nerve involvement	3	0	2 1 Grade III – Marginal mandibular 1 Grade III – Zygomatic	0	0
Lymphomas	6	0	1 Grade III – Zygomatic	1	-
Normal parotid gland removed during the management of skin malignant neoplasms	7	1 Grade II – Marginal mandibular	0	2	0
Parotid metastasis of renal malignancy without skin infiltration or preoperative facial nerve involvement	1	0	0	0	0
Parotid metastasis of skin malignancies without skin infiltration or preoperative facial nerve involvement	10	1 Grade II – Marginal mandibular	0	2	0
Primitive or metastatic parotid malignancies with skin infiltration and preoperative facial nerve weakness	10	-	10	0	2
TOTAL	198	16	18	43	2

**The tumour originated from the nerve and required the sacrifice of a minor branch.*

***2 procedures required sacrifice of a peripheral branch of the nerve that was directly involved by the neoplasm.*

We do not use it systematically when clinical and radiologic evaluations appeared enough to diagnose a benign lesion since the FNAC would not have modified the therapeutic approach. In only one patient with definitive histology showing malignancy, non-diagnostic FNAC was considered responsible for a delayed neck dissection. In the presence of a parotid lesion, it is mandatory that complete removal of the tumour is performed in form of enucleation/extra-capsular dissection (the removal of the entire lesion, without sacrifice of parotid tissue) and superficial or total parotidectomy with the complete excision of the gland including the tumour in healthy margins. Parotid dissection is based on the anatomical knowledge of the extra-temporal facial nerve course and its branches. The classic approach to parotidectomy is anterograde from the main trunk of the VII cranial nerve to the peripheral branches. The main trunk of the nerve is identified and isolated where it emerges from the stylo-mastoid foramen, through the three classical landmarks: mastoid tympanic sulcus, the "pointer" and the posterior belly of the digastric muscle [20]. We routinely perform anterograde dissection with superficial or total parotidectomy, but in three cases of voluminous tumour arising from the superficial lobe of the gland with wide contact between the deepest

Fig. 2. Survival rates according to different risk factors in malignancies.



FN = facial nerve
NED = not evidence of disease

aspect of the tumour and the main trunk of the nerve, we performed a retrograde dissection, starting from the identification of the frontal branch being the most superficial in the close proximity to the incision, and no postoperative facial nerve weakness was observed. Extra-capsular dissection through a standard preauricular approach is reported in the literature, abandoning the concept of formal dissection of the nerve with minimal dissection of parotid tissue [21]. Mantsopopulos et al. [22] suggested that this technique may be applied in cases of a superficially located mobile lesion or in cases of pleomorphic adenoma arising from the pharyngeal portion of the parotid after digastric muscle sectioning (trans cervical approach), while a more radical procedure requiring dissection of the facial nerve and its branches should be reserved only after detection of malignancy in frozen sections of an extra-capsular specimen. He reported a 1.9% rate of postoperative permanent facial palsy after extra-capsular dissection for benign neoplasms of the superficial lobe. We observed a lower incidence of facial palsy (4.4% temporary weakness rate and no permanent palsy) after superficial parotidectomy performed for well-defined benign tumours of the superficial lobe of the parotid gland, and we do not agree with the extra-capsular dissection also on the basis of our personal histological findings of pleomorphic adenomas that lack of a capsule (Fig. 3). Superficial parotidectomy in experienced hands moderately increases surgical time compared to extra-capsular dissection, but we believe that it is rewarding in terms of facial palsy and risk for recurrences, allowing to remove intraparotid lymph nodes, avoiding asymmetry of the parotid region and reducing the chances to leave metachronous Warthin's tumours. Nevertheless, extra-capsular dissection has to be performed in the majority of tumours of the deep lobe of the parotid, where the glandular parenchyma is very limited or, when the tumour of the superficial lobe is in close contact with the nerve;

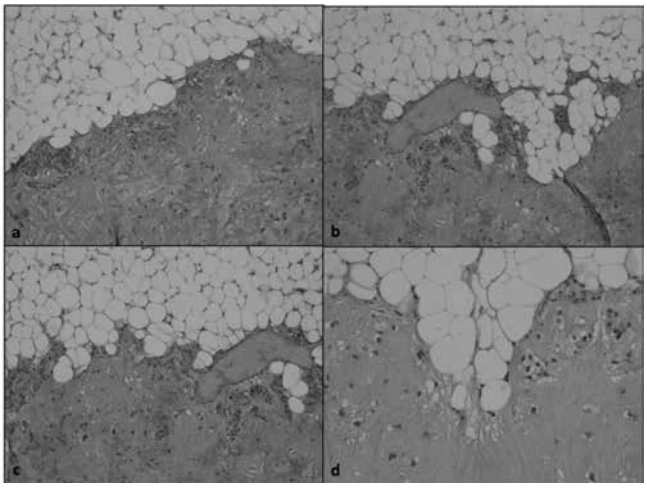


Fig. 3. H&E: microscopic view (a & b 10X, c & d 20X) of a discontinuous capsule of a pleomorphic adenoma. The removal of the lesion by superficial parotidectomy leaving a border of glandular parenchyma along the tumour allowed complete removal of the lesion.

in these cases a blunt dissection, usually performed by the finger of the surgeon, represents the most frequently performed technique. Spillage of the tumour after an accidentally interrupted capsule is indeed the main cause of single or multiple recurrences, while complete removal of the lesion without spillage of the tumour, leaving a boundary of parenchyma along the tumour can be obtained only after the complete visualisation of the facial nerve. Furthermore, the experience of the surgeon arises only from routine careful dissection of the nerve that may be imperative in challenging cases, such as voluminous tumours, recurrences and chronic inflammation. Witt et al. observed a higher tumour recurrence rate after extra-capsular dissection (3%) than after superficial parotidectomy (0.3%) with a $p < 0.05$ [23]. Colella et al. also reported lower recurrence rates after total or superficial parotidectomy (0.01% and 0.02% respectively) compared to those reported after extracapsular/enucleation (0.08%) [24].

On the contrary, Albergotti et al. did not observe difference in tumour recurrence after superficial parotidectomy vs. extra-capsular dissection, with a significantly lower rate of transient facial nerve paresis after extra-capsular dissection and no difference in permanent facial paralysis between the two procedures [25]. In the present series we did not observe spillage of the tumour as a consequence of accidental rupture of the capsule, and we did not observe recurrence of benign tumours. Facial nerve injury is the most significant complication of parotidectomy [2]. Postoperative facial weakness may be due to the section of the nerve, intraoperative trauma (thermal trauma, compression or stretching), or ischaemia, when neoplasms adhere to the nerve and require a dissection with the sacrifice of the "vasa nervorum". Nerve damage is classified as neurapraxia, axonotmesis, and neurotmesis, largely based on the degree of injury, which ranges from microscopic to macroscopic [26]. When the anatomy of the nerve is preserved, the facial deficit should resolve within 12 weeks [27], after this time all deficits could be considered definitive with low chance of regression. House-Brackmann is a common and reproducible tool developed to quantify facial function in six steps from normal (I) to total paralysis (VI). Since it doesn't fully correlate with facial function of each of the branches [28], in our study we added the description of the function of each single branch, with main attention to the marginal mandibular branch.

Intraoperative facial nerve monitoring is widely used in otology, neurotology, and skull base surgery [2 29 30]. The goals of NIM during parotidectomy are the same as those during otology and neurotology: early facial nerve identification, warning the surgeon of unexpected facial nerve stimulation, mapping of the course of the nerve, reduction of mechanical trauma to the nerve and evaluation and prognosis of nerve function at the end of the procedure [31]. Facial nerve monitoring is a safe procedure: facial nerve injury due to voluntary overstimulation is almost impossible, since electrically evoked facial nerve responses during electrophysiological facial nerve monitoring are obtained using a safe pulsed nerve probe, and the intensity of the stimulus is preoperatively established.

In our protocol, the setting of the stimulation was never greater than 0.7 mA. Other complications may be due to nerve electrodes such as skin infection and bleeding, but these are rare with sterile techniques and proper needle electrode placement and removal. There is a statistically significant reduction in postoperative facial nerve weakness in patients treated with the aid of NIM [2 32], and postoperative facial dysfunction can be presumed intraoperatively by an elevated nerve response (> 0.5 mA) [32].

In the present series, NIM was mainly used as a warning of initial stressing of the nerve inducing the surgeon to change the dissection and waiting for the silencing of the spontaneous bursting of the involved branch. We believe that such a policy can play an important role in reducing immediate postoperative facial nerve weakness as described by different authors [2 30].

Microsurgery is a discipline of multiple ENT subspecialties requiring optical magnification and 3D view. The microscope is an important tool for the success of many of the most complex and difficult surgical procedures in medicine today [33]. The interchangeable lenses (200-400 mm) allow a working distance that is appropriate to the depth of the various surgical approaches in otolaryngology [34]. MAP improves the surgeon's view, with better magnification and resolution, and better and more stable light source, allowing for fine discrimination of the terminal branches of the facial nerve from the vessels and the salivary ducts, even when neoplasms deeply adhere to the nerve (Fig. 4). Con-

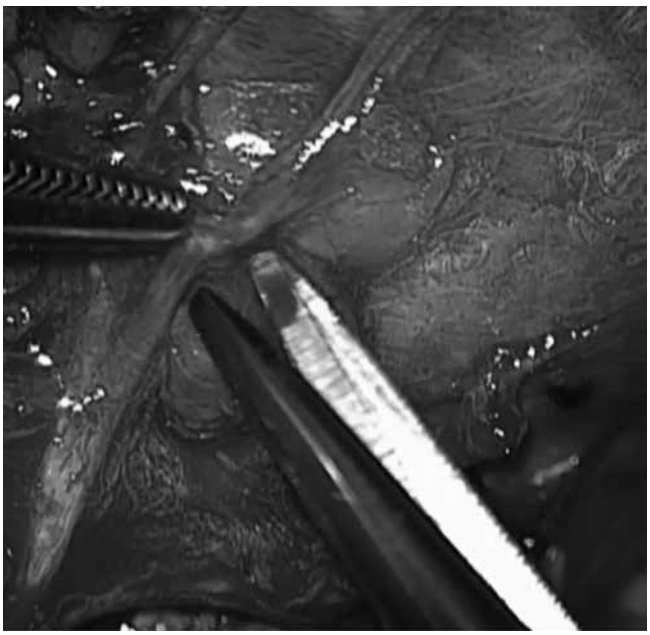


Fig. 4. Microscopic assisted dissection of the perinevrium in a malignancy.

Table IV. Postoperative facial nerve weakness reported in the literature.

Source	No. of cases	Temporary	Permanent
Present work (benign tumours)	145	7.6%	1.4%
Cristofaro (superficial parotidectomy)	45	20%	4.5%
Reza Nouraei	162	40.3%	1.2%
George and McGurk (extracapsular dissection)	156	3%	1%
Ciuman	196	6.5%	2%
Goutinas-Lichius 2006	937	25%	6%
Upton	237	18%	1.2%
Koch	492	32.7%	2.3%
Goutinas-Lichius 2004	295	27%	5%
Yuan	626	23.16%	4.15%
Laccourreye	229	5.7%	3.9%
Greer Albergotti	397	20.4%	1.1%
O'Brien 2003	355	27%	2.5%
ALL SERIES	**4272**	**22.4% (N = 957)**	**3.4% (N = 145)**

sequently a more fine dissection can be performed with precise haemostasis around the vasa nervorum, with reduction of postoperative facial nerve dysfunction rate. Average operation time for benign lesion was 221 minutes (range of 120-350). In our series, the mean operative time also includes procedures in which the identification of the facial nerve was performed by surgeons in training, which explains the longest operative times observed.

Facial nerve preservation rate changes according to different studies (Table IV) [2 6 21 35-42]. Cristofaro et al. reported a transient and definitive facial paralysis rates significantly more frequent after superficial parotidectomy than after extra-capsular dissection (20% versus 4.5%, and 2.2% versus 0%, respectively), involving mainly the mandibular branch in both techniques [35]. In our series, the MAP used together with the NIM was associated with very limited postoperative facial weakness rates: after procedures performed for benign lesions, and all the definitive weaknesses were limited to one peripheral branch and of grade II according to the House-Brackman classification. Patients treated for benign tumours of the extra facial portion of the gland without inflammatory behaviour (n = 91) experienced 4.4% facial nerve temporary weakness rate and no permanent palsy. In the literature, inflammatory lesions adherent to the nerve are associated with postoperative facial weakness [43]. In our study, inflammatory lesions of the deep lobe showed a higher risk of postoperative facial nerve temporary and definitive deficits (p = 0.005); nerve trauma could be due to adherences and fibrosis between the facial nerve and the gland. The 14% rate of postoperative permanent facial nerve weakness of an isolated branch in our patients treated for malignant lesions without symptomatic preoperative facial nerve involvement (see Table III) is strictly related to the following causes: when perineural involvement is intraoperatively demonstrated without preoperative facial nerve palsy, if it is a minor branch, we tend to sacrifice the branch and perform nerve grafting, and, in addition, we observed that parotidectomy associated with neck dissection is related to a higher permanent palsy of the marginal mandibular branch (11.1%), probably due to excessive manipulation of the exposed nerve during neck dissection. In addition, the extensive devascularisation of the nerve may increase the risk of postoperative weakness, as observed in our total parotidectomies.

Abscesses are uncommon complications and rarely require surgical revision [44]; we never observed this complication in our series. Bleeding and haematomas occur after 3-7% of procedures [3]. In the present series, immediate bleeding requiring revision was observed after 4.5% of the parotidectomies, and it was generally due to the accidental cauterisation of the branch of the stylomastoid artery that we think should be constantly ligated. Frey's syndrome after parotidectomy has been reported in 18%-50% of cases [6]. In our series, it was observed in 24.1% of patients treated for benign pathology. Surgical and non-surgical treatments of Frey's syndrome have been proposed, but the outcomes are disappointing since only temporary relief is achieved [45].

The GAN is frequently sacrificed during parotid surgery especially if runs close to the tumour, with consequent numbness around the ear lobe but a modest impact on patient quality of life [46]. Moretti et al. suggest that saving as many branches of the GAN as possible during parotid surgery could be useful in reducing hypo-dysaesthesia [47]. In the present study we noticed that numbness decreases progressively over time and is not reported as a main postoperative problem by patients.

First bite syndrome is facial pain localised in the parotid area and associated with severe cramps or spasms; although it has been estimated to occur after 9.6% of all procedures [48], we did not observe this condition in our series.

Surgical incision and the removal of parotid tissue impact aesthetically on a visible area of the head and neck, but in literature only a small percentage of patients complain of scar and/or depression of the surgical area [34]. In our series, scar was commonly related to the Blair's incision more frequently used in elderly or males, but in females, if requested and possible in relation to the site and size of the tumour, a modified intra-canal facelift incision was performed with optimal results. Nowadays, the facelift approach is considered a cosmetically superior approach to parotid tumours as confirmed by objective data [49].

A long follow-up is recommended even in patients treated for benign neoplasms, since the mean interval between recurrences reported in literature is 7.0 ± 5.3 years for first recurrence [50]. A limit of the present series is a follow-up no longer than 6 years. The most important cause of recurrence is rupture and incomplete removal of the tumour [51]. Facial nerve schwannoma can be conservatively removed keeping facial nerve function intact with an intra-capsular enucleation under the microscope [52]. The schwannoma of the facial nerve of our series originated from a minor branch, as a consequence the surgeon decided to sacrifice the nerve with a subsequent minor deficit that was well accepted by the patient.

Early-stage low-grade malignant parotid gland tumours were cured by surgical resection alone, while more advanced lesions were treated by surgical resection combined with radiotherapy. Surgical management of the facial nerve in patients with parotid cancers presenting with normal facial function is focused on the preservation of the nerve unless it is adherent to, or entrenched in, a malignant tumour, since no statistically significant difference in survival rate is reported between conservative and radical treatment of the seventh cranial nerve [53]. Sacrifice of the nerve could be considered when it is clinically and/or intraoperatively massively involved in a clearly malignant neoplasm [54]. When the margins of resection are close to the facial nerve, adjuvant radiotherapy can improve local control of the disease [51].

Although our survival data should be considered with caution since only 21 patients of 46 had a follow-up longer than 2 years, 5-year DSS and OS rates of our patients with parotid malignancies (83% and 70.6%) were comparable to those reported in the literature (78% and 58%) [55]. As observed by Xiao et al. [56], N+ patients of our series experienced worse survival rates compared to N0 patients (5 years DSS and OS of 76.4% and 54.3% vs. 87% and 80.4%, respectively).

Conclusions

The surgeon's experience is the main guarantee for facial nerve preservation and low recurrence rates during parotidectomy. In our experience, superficial parotidectomy for benign tumours not directly involving the nerve is a safe procedure with minimal risk for facial nerve injury. Inflammatory lesions requiring surgical treatment can be burdened by a moderately higher risk of temporary or permanent facial nerve dysfunction; as a consequence, precise counselling with the patient is mandatory, as well for patients undergoing surgery for malignancy. Minor complications such as numbness of GAN areas and Frey's syndrome do not usually represent major discomfort for patients compared to facial nerve damage.

References

1 Pinkston JA, Cole P. *Incidence rates of salivary gland tumors: results from a population-based study*. Otolaryngol Head Neck Surg 1999;120:834-40.

2 Sood AJ, Houlton JJ, Nguyen SA, et al. *Facial nerve monitoring during parotidectomy: a systematic review and meta-analysis*. Otolaryngol Head Neck Surg 2015;152:631-7.

3 Reza Nouraei SA, Ismail Y, Ferguson MS, et al. *Analysis of complications following surgical treatment of benign parotid disease*. ANZ J Surg 2008;78:134-8.

4 Koch M, Zenk J, Iro H. *Long-term results of morbidity after parotid gland surgery in benign disease*. Laryngoscope 2010;120:724-30.

5 Guntinas-Lichius O, Kick C, Klussmann JP, et al. *Pleomorphic adenoma of the parotid gland: a 13-year experience of consequent management by lateral or total parotidectomy*. Eur Arch Otorhinolaryngol 2004;261:143-6.

6 Guntinas-Lichius O, Klussmann JP, Wittekindt C, Stennert E. *Parotidectomy for benign parotid disease at a University Teaching Hospital: outcome of 963 operations*. Laryngoscope 2006;116:534-50.

7 Yuan X, Gao Z, Jiang H, et al. *Predictors of facial palsy after surgery for benign parotid disease: multivariate analysis of 626 operations*. Head Neck 2009;31:1588-92.

8 Bron LP, O'Brien CJ. *Facial nerve function after parotidectomy*. Arch Otolaryngol Head Neck Surg 1997;123:1091-6.

9 House JW, Brackmann DE. *Facial nerve grading system*. Otolaryngol Head Neck Surg 1985;93:146-7.

10 Barnes LEJ, Reichart P, Sidransky D. *World Health Organization classification of tumors. Pathology and genetics of head and neck tumors.* Lyon, France: IARC Press; 2005.

11 Bussu F, Rigante M, Giglia V, et al. *Clinical history, prognostic factors, and management of facial nerve in malignant tumors of the parotid gland*. Clin Exp Otorhinolaryngol 2014;7:126-32.

12 Bag AK, Curé JK, Chapman PR, et al. *Practical Imaging of the Parotid Gland*. Curr Probl Diagn Radiol 2015;44:167-92.

13 Celebi I, Mahmutoglu AS, Ucgul A, et al. *Quantitative diffusion-weighted magnetic resonance imaging in the evaluation of parotid gland masses: a study with histopathological correlation*. Clinical Imaging 2013;37:232-8.

[14] Layfield LJ, Tan P, Glasgow BJ. *Fine-needle aspiration of salivary gland lesions: comparison with frozen sections and histologic findings*. Arch Pathol Lab Med 1987;111:346-53.

[15] Mukunyadz P. *Review of fine-needle aspiration cytology of salivary gland neoplasms, with emphasis on differential diagnosis*. Am J Clin Pathol 2002;118:S100-S115.

[16] Tyagi R, Dey P. *Diagnostic problems of salivary gland tumors*. Diagn Cytopathol 2015;43:495-509.

[17] Piccioni LO, Fabiano B, Gemma M, et al. *Fine-needle aspiration cytology in the diagnosis of parotid lesions*. Acta Otorhinolaryngol Ital 2011;31:1-4.

[18] Tatomirovic Z, Skuletic V, Bokun R et al. *Fine needle aspiration cytology in the diagnosis of head and neck masses: accuracy and diagnostic problems*. J BUON 2009;14:653-9.

[19] Alphs HH, Eisele DW, Westra WH. *The role of fine needle aspiration in the evaluation of parotid masses*. Curr Opin Otolaryngol Head Neck Surg 2006;14:62-6.

[20] Pia F, Policarpo M, Dosdegani R, et al. *Centripetal approach to the facial nerve in parotid surgery: personal experience*. Acta Otorhinolaryngol Ital 2003;23:111-5.

[21] George KS, McGurk M. *Extracapsular dissection - minimal resection for benign parotid tumors*. Br J Oral Maxillofac Surg 2011;49:451-4.

[22] Mantsopoulos K, Koch M, Klintworth N, et al. *Evolution and changing trends in surgery for benign parotid tumors*. Laryngoscope 2015;125:122-7.

[23] Witt RL, Rejto L. *Pleomorphic adenoma: extracapsular dissection versus partial superficial parotidectomy with facial nerve dissection*. Del Med J 2009;81:119-25.

[24] Colella G, Cannavale R, Chiodini P. *Meta-analysis of surgical approaches to the treatment of parotid pleomorphic adenomas and recurrence rates*. J Craniomaxillofac Surg 2015;43:738-45.

[25] Albergotti WG, Nguyen SA, Zenk J, et al. *Extracapsular dissection for benign parotid tumors: a meta-analysis*. Laryngoscope 2012;122:1954-60.

[26] Seddon HJ. *Three types of nerve injury*. Brain 1943;66:237-88.

[27] Dulguerov P, Marchal F, Lehmann W. *Postparotidectomy facial nerve paralysis: possible etiologic factors and results with routine facial nerve monitoring*. Laryngoscope 1999;109:754-62.

[28] Reitzen SD, Babb JS, Lalwani AK. *Significance and reliability of the House-Brackmann grading system for regional facial nerve function*. Otolaryngol Head Neck Surg 2009;140:154-8.

[29] Lowry TR, Gal TJ, Brennan JA. *Patterns of use of facial nerve monitoring during parotid gland surgery*. Otolaryngol Head Neck Surg 2005;133:313-8.

[30] Terrel JE, Kileny PR, Yan C. *Clinical outcome of continuous facial nerve monitoring during primary parotidectomy*. Arch Otolaryngol Head Neck Surg 1997;157:1081-7.

[31] Silverstein H, Rosenberg S. *Intraoperating facial nerve monitoring*. Otolaryngol Clin North Am 1991;24:709-25.

[32] Brennan J, Moore EJ, Shuler KJ. *Prospective analysis of the efficacy of continuous intraoperating nerve monitoring during thyroidectomy, parathyroidectomy, and parotidectomy*. Otolaryngol Head Neck Surg 2001;124:537-43.

[33] Uluç K, Kujoth GC, Başkaya MK. *Operating microscopes: past, present, and future*. Neurosurg Focus 2009;27:E4.

[34] Edwards WG. *The versatility of the basic microscope system in otolaryngology*. J Microsurg 1980;1:387-93.

[35] Cristofaro MG, Allegra E, Giudice A, et al. *Pleomorphic adenoma of the parotid: extracapsular dissection compared with superficial parotidectomy - a 10-year retrospective cohort study*. ScientificWorld Journal 2014;2014:564053.

[36] Laccourreye H, Laccourreye O, Cauchois R, et al. *Total conservative parotidectomy for primary benign pleomorphic adenoma of the parotid gland: a 25-year experience with 229 patients*. Laryngoscope 1994;104:1487-94.

[37] Ciuman RR, Oels W, Jaussi R, et al. *Outcome, general, and symptom-specific quality of live after various types of parotid resection*. Laryngoscope 2012;122:1254-61.

[38] Upton DC, McNamar JP, Connor NP, et al. *Parotidectomy: ten-year review of 237 cases at a single institution*. Otolaryngol Head Neck Surg 2007;136:788-92.

[39] Koch M, Zenk J, Iro H. *Long-term results of morbidity after parotid gland surgery in benign disease*. Laryngoscope 2010;120:724-30.

[40] Yuan X, Gao Z, Jiang H et al. *Predictors of facial palsy after surgery for benign parotid disease: multivariate analysis of 626 operations*. Head Neck 2009;31:1588-92.

[41] Greer Albergotti W, Nguyen SA, Zenk J, Boyd Gillespie M. *Extracapsular dissection for benign parotid tumors: a meta-analysis*. Laryngoscope 2012;122:1954-60.

[42] O'Brien CJ. *Current management of benign parotid tumors--the role of limited superficial parotidectomy*. Head Neck 2003;25:946-52.

[43] Gaillard C, Périé S, Susini B, St Guily JL. *Facial nerve dysfunction after parotidectomy: the role of local factors*. Laryngoscope 2005;115:287-91.

[44] Zanaret M, Brasnu D, Lacau Saint Guily J, Hans S. *Le complications de la chirurgie des tumeurs et affections benignes des glandes salivaires*. In: Laccourreye O, Chabolle F. *Les risqué chirurgicaux en oto-rhino-laryngologie: information, prise en charge et prevention.* SFORL; 2008. p. 399-407.

[45] Bjerkhoel A, Trobbe OJ. *Frey's syndrome: treatment with botulinum toxin*. Laryngol Otol 1997;111:839-44.

[46] Galli J, Pandolfini M, Rigante M, et al. *Sensory dysfunction and quality of life after great auricular nerve sacrifice during parotidectomy: our experience*. J Laryngol Otol 2015;129:1121-7.

[47] Moretti A, Citraro L, Petrucci AG, et al. *Great auricular nerve preservation in parotid surgery: rationale and long-term results insights*. Eur Arch Otorhinolaryngol 2015;272:3515-20.

[48] Linkov G, Morris LGT, Shah JP, Kraus DH. *First bite syndrome: incidence, risk factors, treatment, and outcomes*. Laryngoscope 2012;122:1773-8.

[49] Grover N, D'Souza A. *Facelift approach for parotidectomy: an evolving aesthetic technique*. Otolaryngol Head Neck Surg 2013;148:548-56.

[50] Ghanem YA, Mizrachi A, Popovtzer A, et al. *Recurrent pleomorphic adenoma of the parotid gland: Institutional experience and review of the literature*. J Surg Oncol 2016;114:714-8.

[51] Witt RL, Eisele DW, Morton RP, et al. *Etiology and management of recurrent parotid pleomorphic adenoma*. Laryngoscope 2015;125:888-93.

[52] Rigante M, Petrelli L, DE Corso E, Paludetti G. *Intracapsular microenucleation technique in a case of intraparotid facial nerve schwannoma. Technical notes for a conservative approach.* Acta Otorhinolaryngol Ital 2015;35:49-52.

[53] Magnano M, Gervasio CF, Cravero L et al. *Treatment of malignant neoplasms of the parotid gland*. Otolaryngol Head Neck Surg 1999;121:627-32.

[54] Spiro JD, Spiro RH. *Cancer of the parotid gland: role of 7th nerve preservation*. World J Surg 2003;27:863-7.

[55] Nagliati M, Bolner A, Vanoni V et al. *Surgery and radiotherapy in the treatment of malignant parotid tumors: a retrospective multicenter study*. Tumori 2009; 95:442-8.

[56] Xiao CC, Zhan KY, White-Gilbertson SJ, Day TA. *Predictors of nodal metastasis in parotid malignancies: a national cancer data base study of 22,653 patients*. Otolaryngol Head Neck Surg 2016;154:121-30.

Received: February 3, 2016 - Accepted: January 15, 2017

Address for correspondence: Filippo Carta, Policlinico D. Casula, Department of Otorhinolaryngology, Azienda Ospedaliero-Universitaria, University of Cagliari, School of Medicine, SS 554 km 4,500, 09042 Monserrato (CA), Italy. E-mail: filippocarta@unica.it

ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:387-392; doi: 10.14639/0392-100X-1376

HEAD AND NECK

Management of free flap failure in head and neck surgery

Gestione del fallimento dei lembi liberi in chirurgia testa-collo

C. COPELLI[1], K. TEWFIK[1], L. CASSANO[1], N. PEDERNESCHI[1], S. CATANZARO[1], A. MANFUSO[2], R. COCCHI[1]

[1] Operative Unit of Maxillo-Facial Surgery, Otolaryngology and Dentistry, Hospital Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy; [2] Operative Unit of Maxillo-Facial Surgery, Federico II University, Naples, Italy

SUMMARY

Free flap surgery is overall considered the gold standard in head and neck reconstruction, with a success rate of 95%. The management of a total flap necrosis and which solution, between a pedicled or a second free flap, is safer for a salvage procedure is still controversial. Object of this study is to describe the authors' management of total free flap loss in head and neck reconstruction and compare the choices and results to those reported in the literature. From January 2012 to January 2016, 149 consecutive free flaps were performed at the Maxillo-Facial Operative Unit of the Hospital Casa Sollievo della Sofferenza in San Giovanni Rotondo (Italy) for reconstruction of head and neck defects. Of these, 6 flaps were lost due to a total necrosis. In 5 cases it was decided to harvest a second free flap, and in the remaining patient a temporalis muscle flap was used. All the free salvage flaps were successful, without complications and with a good aesthetic and functional recovery. Analysing the data obtained, and comparing them with those reported in the literature, it can be concluded that a second subsequent free flap can be considered an ideal and safe procedure in salvage surgery.

KEY WORDS: Free flap failure • Salvage free flap • Head and neck reconstruction • Flap loss management

RIASSUNTO

L'utilizzo dei lembi liberi è oggi considerata l'opzione di prima scelta nella ricostruzione dei difetti testa-collo, con una percentuale di successo di circa il 95%. La gestione del fallimento di un lembo libero e quale soluzione, tra un secondo lembo libero e un lembo peduncolato, sia più sicura è ancora controversa. L'obiettivo del presente lavoro è descrivere le opzioni adottate dagli Autori e confrontare le scelte e i risultati ottenuti con quelli riportati in letteratura. Dal Gennaio 2012 al Gennaio 2016, presso l'UO di Chirurgia Maxillo-Facciale dell'Ospedale Casa Sollievo della Sofferenza, sono stati allestiti 149 lembi liberi per la ricostruzione di difetti interessanti il distretto testa-collo. Di questi, 6 lembi sono stati persi a causa della comparsa di una necrosi totale nel post-operatorio. In 5 casi si è scelto di allestire un secondo lembo libero, nel restante paziente invece è stato utilizzato un lembo di muscolo temporale. Tutti i lembi liberi di salvataggio allestiti hanno avuto successo, senza complicanze e con un buon recupero estetico e funzionale dei pazienti. Analizzando i dati ottenuti e confrontandoli con quanto riportato in letteratura, è possibile concludere come l'allestimento di un secondo lembo libero costituisca una procedura sicura e ideale come salvataggio dopo necrosi totale di un precedente lembo.

PAROLE CHIAVE: *Fallimento di un lembo libero • Lembo libero di salvataggio • Ricostruzione di difetti testa-collo • Gestione dopo fallimento di un lembo libero*

Acta Otorhinolaryngol Ital 2017;37:387-392

Introduction

Free flap surgery is overall considered the gold standard in head and neck reconstruction, with a success rate of about 95% [1-3]. The most dreaded complication in this procedure is a total loss of the flap. The management of flap necrosis and which solution between pedicled or a second free flap is safer for a salvage procedure is still controversial. In a comprehensive article, Okazaki [4] described the management of 19 flap losses on 502 free flaps. Although performing a new free flap is the best option if achievable, they observed a success rate of 89% in patients who underwent a second subsequent free flap for total necrosis. Loco-regional flaps may be considered a valid alternative when a second free flap is contraindicated or not ideal, but with some limitations including distal necrosis of the flap, wound healing and increased duration of hospitalization [5]. The object of this pilot study is to evaluate in our experience if a second subsequent free flap can be considered a safe and reliable procedure in salvage surgery.

Materials and methods

From January 2012 to January 2016, 149 consecutive free flaps were performed by the same surgeon at the Operative Unit of Maxillo-Facial Surgery of the Hospital Casa Sollievo della Sofferenza in San Giovanni Rotondo

Table I. Pathology and reconstruction characteristics.

Pathology	No. flaps	Donor sites	No. patients	Area reconstructed	No. flaps
Squamous cell carcinoma	122	ALT	50	Mandible	41
Recurrent squamous cell carcinoma	5	Radial forearm	49	Tongue	34
Ameloblastoma	4	Fibula	30	Maxilla	15
Adenoid cystic carcinoma	2	Scapular+latissimus dorsi	8	Cheek	13
Keratocystic tumour	2	Iliac crest	8	Oropharynx	11
Osteoradionecrosis	3	Latissimus dorsi	2	Floor of the mouth	12
Sarcoma	1	Gracilis	2	Scalp	8
Recurrent pleomorphic adenoma	1			Orbito-nasal	3
Facial paralysis	2			Facial reanimation	2
Osteomyelitis	1				
Secondary reconstruction	1				
Free flap necrosis	5				

(Italy). Our cohort consisted in 139 patients, 102 males and 38 females, with a mean age of 65.4 (36-88). Almost all the reconstructions were secondary to oncological resections. The pathological and reconstructive details are shown in Table I. The most common reconstructive options were the antero-lateral thigh (n = 50) and the radial forearm (n = 49) free flaps. Four patients underwent two free flap reconstructions because of the reoccurrence of the disease. One case had a simultaneous double free-flap transfer (fibula + ALT). In all cases flap vitality was controlled through clinical monitoring.

Functional and aesthetic outcomes were evaluated after 6 months, following the scores listed in Table II, using a questionnaire filled out by patients and as judged by a commission of three colleagues.

Table II. Diet, speech ability and aesthetic scores.

Diet	
1	Poor swallow ability
2	Liquid diet
3	Soft diet
4	Free diet
Speech ability	
1	Not intelligible speech
2	Difficult to understand
3	Acceptable speech
4	Normal speech
Aesthetic results	
1	Poor
2	Acceptable
3	Good
4	Excellent

Results

In a group of 149 consecutive free flaps, there were 6 flap losses in 6 different patients with an overall success rate of 96%. Of these there were 4 males and 2 females, with a mean age of 52 years (range 25 and 69 years). Table III lists the type, aetiology, clinical details of the flaps lost and subsequent treatment. We observed total necrosis of three fibula flaps, used for the reconstruction of mandibular (n = 2) and maxillary (n = 1) defects, one ALT flap, performed after a total glossectomy and two latissimus dorsi/scapular flaps performed to reconstruct maxillary defects.

We did not observe any early necrosis: the first signs of necrosis were detected between the 7th and 13th day after surgery (mean time: 10.6 days). In one case (Patient 4), there was a massive haemorrhage due to the rupture of the common carotid artery: the vascular procedure performed in urgency resulted in a thrombosis of the flap's pedicle. This was the only patient who had undergone previous radiotherapy. In one case, we observed a late infection (Patient 6) that resulted in a total flap loss. The other four cases had unknown causes of necrosis.

In five of the six patients a second subsequent free flap was performed, with a success rate of 100%. In one case, we decided to reconstruct the palate defect using a temporalis muscle flap. The donor sites of the salvage free flaps were the antero-lateral thigh (n = 3: subsequent to 1 ALT flap, 1 fibula flap and 1 combined scapula + latissimus dorsi flap), the fibula (n = 1: secondary to a fibula flap loss) and the latissimus dorsi (n = 1: after a combined latissimus-scapula free flap necrosis). The microvascular anastomoses were made on the same side in four cases (Table IV). In one patient, there was the necessity to use the contralateral neck vessels. No vessel grafts were required.

The salvage procedure was made during the same hospitalisation in four patients, within 26 days after the first surgery (mean time: 20 days). Two patients were discharged and after a mean of 44 days they were readmitted and underwent the salvage procedure with a new free flap. The mean hospitalisation time after the second surgery was 15.3 days (range: 1-20 days).

Table III. Characteristics of failed free flaps.

	Sex	Age	Pathology	Pre-RT	Failed flap	Timing of loss (days)	Causes	Salvage procedure	Timing after first surgery (days)	Hospitalisation after salvage procedure (days)
1	M	48	Maxillary squamous cell carcinoma	No	Scapolar +latissimus dorsi free flap	10	Unknown	ALT	26	16
2	M	25	Mandibular ameloblastoma	No	Fibular free flap	10	Unknown	Fibular flap	48	11
3	M	67	Tongue squamous cell carcinoma	No	ALT	12	Unknown	ALT	40	18
4	F	45	Mandibular squamous cell carcinoma	Yes	Fibular free flap	13	Common carotid artery haemorrhage	ALT	26	20
5	M	69	Maxillary squamous cell carcinoma	No	Fibular free flap	7	Unknown	Temporal flap	13	15
6	F	58	Maxillary adenoidcystic carcinoma	No	Scapolar +latissimus dorsi flap	12	Infection	Latissimus dorsi flap	15	12

Table IV. Failed free flaps: vascular pedicle details.

	Sex	Age	Pathology	Failed flap	Artery pedicle 1st surgery	Vein pedicle 1st surgery	Salvage procedure	Artery pedicle 2nd surgery	Vein pedicle 2nd surgery
1	M	48	Maxillary squamous cell carcinoma	Scapolar +latissimus dorsi free flap	Superior thyroyd artery	Internal giugular vein	ALT	External carotid artery	Internal giugular vein
2	M	25	Mandibular ameloblastoma	Fibular free flap	Facial artery	Anterior giugular vein	Fibular flap	External carotid artery	Thyreo-lingual-facial trunk
3	M	67	Tongue squamous cell carcinoma	ALT	Facial artery	Thyreo-lingual-facial trunk	ALT	Lingual artery	Thyreo-lingual-facial trunk
4	F	45	Mandibular squamous cell carcinoma	Fibular free flap	External carotid artery	Inferior thyroid vein	ALT	Contralateral transverse cervical artery	Contralateral thyreo-lingual-facial trunk
5	M	69	Maxillary squamous cell carcinoma	Fibular free flap	Facial Artery	External giugular vein	Temporal flap		
6	F	58	Maxillary adenoidcystic carcinoma	Scapolar +latissimus dorsi flap	Facial Artery	Facial vein	Latissimus dorsi flap	Lingual artery	Thyreo-lingual-facial trunk

No local or systemic major complications were observed. Functional and aesthetic outcomes are shown in Table V. Speech ability was normal in three patients and acceptable in two cases. In only one patient was speech described as difficult to understand. Considering diet and swallowing ability, four patients expressed the capacity of eating a soft diet, one patient can only feed himself with a liquid diet and one patient achieved the possibility of a normal diet after implants. The commission of colleagues who assigned an aesthetic score observed excellent aesthetic results in two patients, good results in one patient and acceptable results in three cases.

Discussion

Free flap surgery is considered a reliable and safe procedure for head and neck reconstruction. The success rate of a free flap described in the literature is about 95% [1-3]. In our cohort, we observed a rate of 96% in 149 consecutive procedures. Despite the high success rates, free flap losses still occur at a rate of about 1% to 6% [6].

The risk factors for a total flap loss are still unclear. Preoperative or previous radiotherapy is reported to be associated with a higher risk of free flap failure and complications [7]. Radiotherapy produces, in fact, macro and microscopic alterations on vascular structures [8-10]. In our

Table V. Aesthetic and functional results.

Sex	Age	Pathology	Failed flap	Salvage procedure	Aesthethic results	Speech	Diet
M	48	Maxillary squamous cell carcinoma	Scapolar +latissimus dorsi free flap	ALT	3	3	3
M	25	Mandibular ameloblastoma	Fibular free flap	Fibular free flap	4	4	4
M	67	Tongue squamous cell carcinoma	ALT	ALT	4	3	3
F	45	Mandibular squamous cell carcinoma	Fibular free flap	ALT	2	2	2
M	69	Maxillary squamous cell carcinoma	Fibular free flap	Temporal flap	2	4	3
F	58	Maxillary adenoidcystic carcinoma	Scapolar +latissimus dorsi free flap	Latissimus dorsi flap	2	4	3

series, only one patient had previously undergone RT and had a common carotid artery rupture.

Anatomic limitations such as vessel depletion can make the search for reliable recipient vessels challenging and increase operation time. However, some authors [11] observed no correlation between the rates of flap necrosis and the choice of recipient vessels, the method of arterial or venous anastomosis, the use of an interposition vein graft, or the timing of reconstruction. According to the literature, in our cohort of 6 patients that experienced a total flap loss we did not observe any primary vessel depletion during the first procedure.

Several authors [12 13] have reported that age alone should not be considered as a contraindication or an independent risk factor when considering free-tissue transfer. Ferrari [12] observed a successful free-flap rate of 98.2% in 54 flaps harvested in patients over 75 years of age and a successful rate of 96.2% in 306 of the 318 flaps performed in those under 75 years. Tarsitano [13] described a similar success rate in patients aged ≥ 75 years compared to the general population. Considering our limited series of total flap loss, we observed a mean age of 52 years (range from 25 to 69) with no patient over 75 years.

Hypercoagulable states, the development of severe infection, external compression and errors in flap harvesting and management of the pedicle can be further causes of flap loss.

In 5 of our 6 cases, the aetiology of the flap loss could not be determined. According to Corbitt [14], who reported similar findings, both the artery and vein were thrombosed and the detection of flap compromise occurred late (mean: 10.6 days; range: 7th-13th day after surgery).

Thrombosis on postoperative day 5 or later after microvascular reconstruction (late thrombosis) is reported to account for 10% to 28% of all thromboses [15]. Even if free flaps are believed to undergo revascularisation via the surrounding tissue and are able to survive without pedicle flow for several days after surgery, compromised recipient beds (such as irradiated tissue), chronically infected wounds and ischaemic vascular disease can interfere with free flap revascularisation, making the flap dependent on the pedicle for a longer period of time [15 16].

Probably in our group of patients the reduced or absent revascularization via the surrounding tissues added to late impairment of the pedicle (kinking, compression, misdiagnosed infections, etc.), which was the cause of the delayed loss of the flap.

Few studies have been published about the best way to manage the loss of a free flap, and the use of a subsequent salvage free flap is still a controversial issue. The hesitation is due to concerns regarding lack of recipient vessels, as well as increased risk of a second flap loss and postoperative complications. Different authors, in fact, have described higher rates of failure of a second free flap reconstruction, with success rates varying from 28% to 89% [9 10 12]. Bozikov [17] observed that free flap failure was 4.6 times more likely to occur after a salvage free flap transfer with a success rate of 53%. Ross [18] in a series of 30 patients described a success rate of 73%, a percentage significantly lower in comparison with second free flaps performed for recurrences. On the contrary, our results, even if on a small group of patients, show a higher rate of success (100%) that mirrors the experiences of Wei of 94.1% [19], Alam and Khariwala of 100% [20] and Corbitt of 96.4% [14]. Such success rates suggest that free flaps can be still a safe option even after an initial failure.

Wei [19] reported the necessity to reach the contralateral neck for recipient vessels in 35% of cases, and the use of interpositional vein grafts in the 30% of cases. In our experience, in only one patient there was the necessity to reach the contralateral vessels, and venous or arterial grafts were not used in any case. Accordingly to Corbitt [14], in some cases we re-used vessels that had previously been used for the initial free flap, without complications. Moreover, the rich vascularity of the head and neck often allows finding adequate recipient vessels, even after prior resection, neck dissection and free flap reconstruction.

The choice of the donor site should be made based on prognosis, general conditions and functional needs. Ideally, a free flap lost should be replaced by the same option if the first selection of the donor site has been correctly done. When prognosis is poor, the patient has comorbidities and bony reconstruction is not mandatory to obtain adequate functional rehabilitation, a soft tissue free flap can be chosen instead of an osseous flap. It is, in fact, characterised by lower donor site morbidity and faster re-

habilitation time. Even if the overall complication rate in patients who undergo a subsequent free flap attempt is reported to be slightly higher than those who were primarily reconstructed, in our cases we did not observe any local or systemic complications. The relatively short times of hospitalisation after the second free flap (mean: 15.4 days; range: 11-20 days) show the possibility to obtain quick rehabilitation of patients even after a salvage procedure. Moreover, satisfactory results, both in terms of function and aesthetics, were observed. We acknowledge that the relatively small number of cases in this series, particularly of patients who underwent secondary pedicled flap reconstruction, does not permit meaningful comparison between free and regional flaps. However, more extensive studies have shown that free flap reconstruction usually results in superior functional outcomes [14 21 22]. Moreover, higher rates of local complications (fistulas, wound dehiscences, pedicle retraction, etc.) are reported in literature for pedicled flaps with respect to free flaps, both after primary and salvage harvesting.

These data confirm our opinion that a second subsequent free flap should be considered as the first option after the total loss of a free flap in most cases. It represents, in fact, the technique that allows the best functional and aesthetic results, together with low complication rates and acceptable hospitalisation times. However, we agree with Corbitt [14] in that good surgical and medical judgment, together with a careful primary selection of the patient and serious analysis of causes of loss, are crucial for the success of salvage free flaps.

Conclusions

The reconstruction of a head and neck defect after a free flap failure can be challenging for the surgeon. Even if pedicled flaps are classically considered the mandatory choice in salvage surgery after a free flap loss, accordingly with the most recent reports we consider the use of a subsequent second free flap the first option in salvage surgery. Despite major technical complexity and longer operative times, free flaps are reliable and safe procedures that bring the best aesthetic and functional results. The high success rates of the subsequent salvage free flaps and, on the contrary, the poor results and higher local complication rates of pedicled flaps, suggest that most patients would benefit from a reattempt at microvascular reconstruction.

References

1 Gusenoff JA, Vega SJ, Jiang S, et al. *Free tissue transfer: comparison of outcomes between university hospitals and community hospitals*. Plast Reconstr Surg 2006;118:671-5.

2 Almadori G, Rigante M, Bussu F, et al. *Impact of microvascular free flap reconstruction in oral cavity cancer: our experience in 130 cases*. Acta Otorhinolaryngol Ital 2015;35:386-93.

3 Tarsitano A, Ciocca L, Cipriani R, et al. *Mandibular reconstruction using fibula free flap harvested using a customised cutting guide: how we do it*. Acta Otorhinolaryngol Ital 2015;35:198-201.

4 Okazaki M, Asato H, Takushima A, et al. *Analysis of salvage treatments following the failure of free flap transfer caused by vascular thrombosis in reconstruction for head and neck cancer*. Plast Reconstr Surg 2007;119:1223-32.

5 Colletti G, Autelitano L, Tewfik K, et al. *Autonomized flaps in secondary head and neck reconstructions*. Acta Otorhinolaryngol Ital 2012;32:329-35.

6 Bianchi B, Copelli C, Ferrari S, et al. *Free flaps: outcomes and complications in head and neck reconstructions*. J Craniomaxillofac Surg 2009;37:438-42.

7 Herle P, Shukla L, Morrison WA, et al. *Preoperative radiation and free flap outcomes for head and neck reconstruction: a systematic review and meta-analysis*. ANZ J Surg 2015;85:121-7.

8 Cheng SW, Wu LL, Ting AC, et al. *Irradiation-induced extracranial carotid stenosis in patients with head and neck malignancies*. Am J Surg 1999;178:323-8.

9 Benatar MJ, Dassonville O, Chamorey E. *Impact of preoperative radiotherapy on head and neck free flap reconstruction: a report on 429 cases*. J. Plast. Reconstr Aesthet Surg 2013;66:478-82.

10 Yoshimoto S, Kawabata K, Mitani H. *Factors involved in free flap thrombosis after reconstructive surgery for head and neck cancer*. Auris Nasus Larynx 2010;37:212-6.

11 Nahabedian MY, Singh N, Deune EG, et al. *Recipient vessel analysis for microvascular reconstruction of the head and neck*. Ann Plast Surg 2004;52:148-55.

12 Ferrari S, Copelli C, Bianchi B, et al. *Free flaps in elderly patients: outcomes and complications in head and neck reconstruction after oncological resection*. J Craniomaxillofac Surg 2013;41:167-71.

13 Tarsitano A, Pizzigallo A, Sgarzani R, et al. *Head and neck cancer in elderly patients: is microsurgical free-tissue transfer a safe procedure?* Acta Otorhinolaryngol 2012;32:371-5.

14 Corbitt C, Skoracki RJ, Yu P, et al. *Free flap failure in head and neck reconstruction*. Head Neck 2014;36:1440-5.

15 Kadota H, Sakuraba M, Kimata Y, et al. *Analysis of thrombosis on postoperative day 5 or later after microvascular reconstruction for head and neck cancers*. Head Neck 2009;31:635-41.

16 Wax MK, Rosenthal E. *Etiology of late free flap failures occurring after hospital discharge*. Laryngoscope 2007;117:1961-3.

17 Bozikov K, Arnez ZM. *Factors predicting free flap complications in head and neck reconstruction*. J Plast Reconstr Aesthet Surg 2006;59:737-42.

18 Ross G, Yla-Kotola TM, Goldstein D, et al. *Second free flaps in head and neck reconstruction*. J Plast Reconstr Aesthet Surg 2012;65:1165-8.

19 Wei F-C, Demirkan F, Chen HC. *The outcome of failed free flaps in head and neck and extremity reconstruction: what is next in the reconstructive ladder?* Plast Reconstr Surg 2001;108:1154-60.

[20] Alam DS, Khariwala SS. *Technical considerations in patients requiring a second microvascular free flap in the head and neck*. Arch Otolaryngol Head Neck Surg 2009;135:268-73.

[21] Chepeha DB, Annich G, Pynnonen MA. *Pectoralis major myocutaneous flap vs revascularized free tissue transfer: complications, gastrostomy tube dependence, and hospitalization*. Arch Otolaryngol Head Neck Surg 2004;130:181-6.

[22] Tsue TT, Desyatnikova SS, Deleyiannis FW. *Comparison of cost and function in reconstruction of the posterior oral cavity and oropharynx. Free vs pedicled soft tissue transfer.* Arch Otolaryngol Head Neck Surg 1997;123:731-7.

Received: August 4, 2016- Accepted: March 11, 2017

Address for correspondence: Chiara Copelli, Maxillo-Facial Surgery, Head and Neck Department Hospital Casa Sollievo della Sofferenza, viale dei Cappuccini 1, 71013 San Giovanni Rotondo (FG), Italy. E-mail: copkids@tin.it

ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:393-400; doi: 10.14639/0392-100X-1709

Head and neck

Clinical analysis of Hashimoto thyroiditis coexistent with papillary thyroid cancer in 1392 patients

Analisi clinica dell'associazione fra tiroidite di Hashimoto e carcinoma papillare della tiroide in 1392 pazienti

J. LIANG[1], W. ZENG[1], F. FANG[1], T. YU[2], Y. ZHAO[1], X. FAN[1], N. GUO[1], X. GAO[1]

[1] Department of Head and Neck Surgery, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Liaoning Province, People's Republic of China; [2] Department of Radiology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Liaoning Province, People's Republic of China

SUMMARY

Papillary thyroid carcinoma (PTC) is the most common malignant tumour of the thyroid. The effect of the concurrent presence of Hashimoto's thyroiditis (HT) and PTC is still under debate. The aim of this study is to investigate the influence of coexistent HT on prognostic outcomes and the association of coexistent HT with clinicopathological features. The demographic and clinicopathological data of 1,392 patients who underwent surgery in our hospital from 2007 to 2016 was collected and analysed. Among 1,392 PTC patients, the rate of HT was 25.6%. There were significant differences in the mean levels of thyroid stimulating hormone (3.27 vs. 2.41 μIU/L, $p < 0.01$), thyroperoxidase antibodies (110.31 vs. 131.2 U/ml, $p < 0.01$) and thyroglobulin antibodies (131.90 vs. 113.53 ng/ml, $p < 0.01$) between the two groups. PTC patients with HT had the following characteristics compared to patients without HT: smaller tumour size ($p < 0.01$), female predominance ($p < 0.01$) and higher rate of multifocality ($p = 0.024$). In addition, patients with HT had a significantly lower rate of lymph node metastasis (LNM) and advanced TNM stage than patients without HT (all $p < 0.01$). Multivariate analysis found that both age and multifocality were significantly associated with central LNM in HT patients ($p < 0.01$, $p = 0.019$, respectively). Extrathyroidal invasion and TSH level were also significant independent factors for lateral LNM in HT patients ($p < 0.008$, $p = 0.04$, respectively). HT is associated with a significantly higher risk of PTC. The coexistence of HT in PTC patients is associated with favourable clinical outcomes compared to PTC without HT. Total thyroidectomy and prophylactic central compartment lymphadenectomy should be a choice for PTC patients with HT.

KEY WORDS: Hashimoto's thyroiditis • Papillary thyroid cancer • Clinicopathologic characteristics

RIASSUNTO

Il carcinoma papillare (PTC) è il più comune tumore maligno della ghiandola tiroide. L'effetto della concomitante presenza della tiroidite di Hashimoto (HT) e del PTC è ancora oggetto di studio. Scopo di questo studio è analizzare la coesistenza di una concomitante HT circa l'outcome prognostico e eventuali associazioni clinico-patologiche. Abbiamo raccolto ed analizzato i dati demografici e clinicopatologici di 1392 pazienti che sono stati sottoposti a chirurgia nel nostro ospedale dal 2007 al 2016. Fra i 1392 pazienti con PTC, la percentuale di coesistente HT era del 25,6%. Vi erano differenze significative tra i due gruppi nei livelli medi di ormone tireostimolante (3.27 vs. 2.41μIU/L, $p < 0.01$), anticorpi anti tireoperossidasi (110.31 vs. 131.2U/ml, $p < 0.01$) e anticorpi anti tireoglobulina (131.90 vs. 113.53 ng/ml, $p < 0.01$) I pazienti con PTC e HT avevano le seguenti caratteristiche se comparate con quelle dei pazienti senza HT: tumori di dimensioni più piccole ($p < 0.01$), predominanza del sesso femminile ($p < 0.01$) ed un piu' alto tasso di multifocalita'($p = 0.024$). Inoltre, i pazienti con HT avevano un tasso significativamente basso di metastasi linfonodali (LNM) ed uno stadio di TNM più elevato rispetto ai pazienti senza HT (tutti $p < 0.01$). L'analisi multivariata ha evidenziato come età e multifocalità erano significativamente associate con metastasi nel compartimento centrale nei pazienti con HT ($p < 0.01$, $p = 0.019$, rispettivamente). L'invasione extratiroidea ed i livelli di TSH erano fattori significativamente indipendenti per le metastasi linfonodali laterocervicali nei pazienti con HT ($p < 0.008$, $p = 0.04$, rispettivamente). HT era associata ad un maggior rischio di sviluppare PTC. La coesistenza di HT in pazienti con PTC favoriva un miglior outcome clinico rispetto a quei pazienti con PTC ma senza HT. La tiroidectomia totale associata allo svuotamento del compartimento centrale deve essere la prima scelta chirurgica nei pazienti con PTC e HT.

PAROLE CHIAVE: *Tiroidite di Hashimoto • Carcinoma papillare della tiroide • Caratteristiche clinicopatologiche*

Acta Otorhinolaryngol Ital 2017;37:393-400

Introduction

Thyroid cancer is the most common malignancy of the endocrine system, and its incidence rate is rapidly increasing by an average of 4.5% per year from 2007 to 2011 [1]. Approximately 70% to 80% of thyroid cancers are papillary thyroid carcinomas (PTCs), which exhibited a relatively benign clinical course [2,3]. Hashimoto's thyroiditis (HT), also called chronic lymphocytic or autoimmune thyroiditis, is the most common inflammatory thyroid disease. The incidence worldwide is estimated to be 0.3-1.5 cases per 1000 individuals [4]. This autoimmune disease is the most common cause of primary hypothyroidism and non-endemic goiter, and the incidence is estimated to be 10-15 times higher in women. In China, the rate is higher, with approximately 0.4%-1.5% of the population affected, which accounts for 20%-25% of all thyroid disease [5-7]. Since its first description by Dailey et al. in 1955 [8], many aetiological and epidemiological studies have investigated the relationship between PTC and HT. Some authors have demonstrated that PTC with HT is associated with pathologic factors that indicate decreased tumour aggressiveness, such as small tumour size and low stage. It has also been associated with lower rates of recurrence, better locoregional control and longer overall survival [8-11]. Other authors have shown no relationship between the presence of HT and tumour aggressiveness [12-15]. Nowadays, the correlation between the two diseases with regards to pathogenesis and prognostic outcomes is still unclear.

Given the relatively high incidence of both diseases and the ongoing debate, we undertook a retrospective study to investigate the potential relationship between PTC and HT, and the effect of coexistent HT on the presentation, management and clinical outcomes of PTC patients.

Patients and methods

Between January 2007 and April 2016, there were 7,354 patients who underwent thyroid surgery in Liaoning Cancer Hospital & Institute. In the pathological review of these patients, 5,844 had benign lesions and 1,510 had malignant tumours. There were 1,392 PTCs, 58 follicular thyroid cancers, 23 medullary thyroid cancers, 15 lymphomas, 10 squamous cell carcinomas and 12 undifferentiated carcinomas. Among all patients, 1,682 were diagnosed as having pathological changes consistent with HT, while 5,672 were identified without HT. Pathologically-demonstrated HT was defined as the presence of diffuse lymphoplasmacytic infiltration, germinal centres and enlarged epithelial cells with large nuclei and eosinophilic cytoplasm. Only peri-tumoural lymphocytic infiltration was not regarded as HT.

Thyroid lobectomy with isthmusectomy was performed in 520 patients, whereas total thyroidectomy was performed in 872 cases. During lymph node resection, the central compartment was delimited superiorly by the hyoid bone, inferiorly by the substernal notch, laterally by the median portion of the carotid sheath and dorsally by the prevertebral fascia. Central neck dissection without lateral compartment neck dissection was performed in 785 patients. Comprehensive neck dissections such as radical neck dissection and modified neck dissection were performed in 495 patients, and 143 of these underwent bilateral neck dissection.

The following variables were considered: age, gender, thyroid function tests, fine needle aspiration biopsy (FNAB), tumour size, multifocality, extrathyroidal invasion, extension of surgery, lymph node metastasis (LNM), TNM stage, recurrence and distant metastasis. Patients were staged according to the seventh edition of the UICC/AJCC TNM staging system [16]. This study was approved by ethical committees of our hospital, and informed consent was obtained from each patient. In addition, the AMES clinical staging system and the MACIS scoring system were used to evaluate the prognostic outcome. The AMES staging system divides patients into two groups: low risk (i) females < 51 years and males < 41 years without distant metastasis, and (ii) elderly patients with tumours < 5 cm with no extrathyroidal extension of the papillary carcinoma and high risk (i) patients with distant metastasis and (ii) females ≥ 51 years and males ≥ 41 years with tumours ≥ 5 cm or extrathyroidal extension if it is papillary carcinoma [17]. The MACIS staging system has established that high score is strongly correlated with poor prognosis. It is obtained by adding 3.1 if the patient is ≤ 39 years or 0.08 × age if the patient is > 40 years, +0.3 × tumour size in cm, +1 if the tumour is not completely resectable, +1 if it is locally invasive and +3 in the presence of distant metastasis. Patients are divided into four groups: group 1, < 6; group 2, 6-6.99; group 3, 7-7.99; and group 4, ≥ 8 [18].

Preoperative diagnostic evaluation

Diagnosis and preoperative evaluation of each patient were performed according to a strategy that was not changed during the study period. All patients underwent careful history and thorough physical examination in our department. All patients who qualified for surgical treatment were subjected to thyroid ultrasonography, determinations of free thyroid hormones (T3, T4) and thyroid stimulating hormone (TSH), as well as thyroperoxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb). FNAB and ultrasonography-guided FNAB were also used. A suspicious malignant nodule was diagnosed in the presence of at least one of the following ultrasound images: micro-calcification, infiltrative margin, increased nodular vascularity, taller that wide on transverse view and hypo-echoic. Metastases to the lung and lymph nodes were evaluated by preoperative imaging studies, such as CT.

Follow-up

Patient progress was followed by physical examination, ultrasonography and CT to identify recurrence. Furthermore, we also used FNAB on suspected masses or lymph nodes, and cytopathologic diagnosis was obtained. All patients were closely followed after surgery until August 2016. The median follow-up duration of patients was 38.4 months (range, 3.1-125.3).

Statistical analyses

All statistical analyses were performed using the SPSS 16.0 statistical package (SPSS, Inc., Chicago, IL, USA). Cancer-specific survival was analysed using Kaplan-Meier survival curves, and comparisons were made using the log-rank test. In univariate analysis, two-tailed χ^2 were used for statistical comparisons. In multivariate analysis, logistic regression analysis applied to identify the significant clinicopathologic factors correlated with LNM. For all analyses, only p values < 0.05 were considered significant.

Results

In total, 25.6% of patients with PTC (357/1,392) had coexisting HT. The proportion of female patients in the HT group was higher than that in the non-HT group (91.6% vs. 65.2%, p < 0.01). More PTC was found in patients with HT than in those without HT (21.2% vs. 18.2%, p = 0.007) (Table I). Of the 1,392 PTC patients, there were 278 males (20.0%) and 1,114 females (80.8%; ratio 1:4) with a mean age 45.04 ± 12.47 years (median 45 years; range 10-82 years). The mean tumour size was 1.85 ± 1.11 cm. The sensitivity of FNAB was 49.5%. In our study, 373 patients had multifocality, and extrathyroidal invasion was identified in 34.8% of the patients. Central lymph node involvement was identified in 295 patients, lateral lymph node involvement in 198 patients and central and lateral LNM in 182 patients. During lymphadenectomy, one to 34 lymph nodes were removed. The number of involved lymph nodes varied between 0 and 22. There were 896 patients with stage I disease (64.3%), 58 with stage II (4.2%), 242 with stage III (17.4%) and 196 with stage IV (14.1%).

Patients with PTC and HT appeared to be slightly younger than those without HT (mean age 44.14 ± 11.95 vs. 45.34 ± 12.63); this difference was not statistically significant (p = 0.197). A greater female preponderance was noted in the patients with HT compared with those without HT (p < 0.01). Compared with non-HT group, the patients with HT group had higher levels of preoperative TSH, TgAb and TPOAb (all p < 0.01). Mean tumour size in patients with HT was smaller than in those without HT (p < 0.01). Additionally, the rate of multifocality was significantly different between the two groups (31.4% *vs.* 25.2%, p = 0.024). There was no difference in extrathyroidal extension between the two groups (p = 0.085). In HT patients, central LNM had a lower frequency compared with non-HT patients (19.6% vs. 21.7%, p < 0.01). Patients with HT had a significantly lower frequency of advance-stage disease (p < 0.01). However, no significant differences were found in terms of recurrence (p = 0.787) and distant metastasis (p = 0.06) between the two groups. The clinicopathological characteristics of 1,392 patients are summarised in Table II.

A multivariate logistic regression analysis that included age, gender, tumour size, multifocality, extrathyroidal invasion and TSH level was performed to assess whether these clinicopathological factors were associated with LNM in PTC patients with HT. We found that age and multifocality were significantly associated with central LNM in HT patients (p < 0.01, p = 0.019) (Table III). Next, we investigated the risk factors associated with lateral LNM in PTC patients with HT. Extrathyroidal invasion and TSH level were significant independent factors for lateral LNM in HT patients, with odds ratio of 0.353 (95% CI, 0.164-0.757, p < 0.008), 2.223 (95% CI, 1.038-4.757, p = 0.04) (Table IV).

Two well-established prognosis classification systems of PTC patients were used. Using the AMES staging system, the rate of high risk group of PTC patients without HT was slightly higher than that of patients with HT (18.6% *vs.* 14.8%). However, no significant difference was found between the two groups (p = 0.113). According to the MACIS scoring system, the trend was more evident between the two groups (13.8% *vs.* 8.7%, p = 0.012). The PTC patients without HT had a higher mean score than those with HT (4.80 *vs.* 4.52, p < 0.01) (Table V).

During the follow-up period, 13 cases (3.6%) experienced recurrence in the HT group: 6 had thyroid recurrence and 7 had lymph node recurrence. In patients without HT, a total of 41 patients (4.0%) developed recurrence: 16 had thyroid recurrence and 25 had lymph node recurrence. All these patients underwent re-operation, and they all remain alive with no symptoms of further recurrence after second surgery. There were 2 patients who had lung metastasis in the HT group. In patients without HT, 20 had lung metastasis, while one had bone metastasis. Overall, one patient in the HT group and 10 patients in the non-HT group died, but only 3 of these deaths were due to PTC or related

Table I. Demographic information of 7,354 patients.

Variables	HT (n = 1,682)	Non-HT (n = 5,672)	P value
Age (years)	49.34 ± 11.33	49.98 ± 11.85	0.34
Gender			< 0.01
Male	141 (8.4%)	1,975 (34.8%)	
Female	1,541 (91.6%)	3,697 (65.2%)	
With PTC	357 (21.2%)	1,035 (18.2%)	0.007

Table II. Clinicopathologic characteristics of 1,392 patients with PTC stratified by the presence of HT.

Variables	PTC with HT (n = 357)	PTC without HT (n = 1,035)	P value
Age (years)	44.14 ± 11.95	45.34 ± 12.63	0.197
Gender (male:female)	1:9.5	1:3.2	< 0.01
TSH (μIU/L)	3.27 ± 5.46	2.41 ± 3.34	< 0.01
TgAb (ng/ml)	131.90 ± 348.92	113.53 ± 206.21	< 0.01
TPOAb (U/ml)	110.31 ± 171.83	131.2 ± 97.54	< 0.01
Tumour size (cm)	1.58 ± 0.97	1.94 ± 1.14	< 0.01
≤ 1	151 (42.3%)	280 (27.1%)	
> 1	206 (57.7%)	755 (72.9%)	
Multifocality	112 (31.4%)	261 (25.2%)	0.024
Extrathyroidal invasion	111 (31.1%)	374 (36.1%)	0.085
Lymph node metastasis			< 0.01
Central only	70 (19.6%)	225 (21.7%)	
Lateral only	34 (9.5%)	164 (15.8%)	
Central + lateral	45 (12.6%)	137 (13.2%)	
TNM staging			< 0.01
StageI	252 (70.6%)	644 (62.2%)	
Stage II	7 (2.0%)	51 (4.9%)	
Stage III	67 (18.8%)	175 (17.0%)	
StageIV	31 (8.6%)	165 (15.9%)	
Recurrence	13(3.6%)	41 (4.0%)	0.787
Distant metastasis	2 (0.6%)	21 (2.0%)	0.06

Table III. Univariate and multivariate analysis for central LNM with statistically significant variables.

Variables	Univariate analysis		Multivariate analysis		
	N	P value	OR	95% CI	P value
Age (year)		< 0.01	0.334	0.193-0.576	< 0.01
< 45	123 (44.2%)				
≥ 45	155 (55.8%)				
Gender		0.097			
Male	23 (8.3%)				
Female	255 (91.7%)				
Tumour size		0.154			
≤ 1	128 (46.0%)				
> 1	150 (54.0%)				
Multifocality	79 (28.4%)	0.021	2.002	1.118-3.583	0.019
Extrathyroidal invasion	81 (29.1%)	0.063			
TSH		0.293			
< 2.5	168 (60.4%)				
≥ 2.5	110 (39.6%)				

complications. The patients with HT tended to have better prognosis compared with that of patients without HT, and disease-free survival (DFS) in patients with HT was significantly higher than that without HT (p = 0.009, Fig. 1). However, the difference was not statistically significant when considering overall survival (OS) between the two groups (p = 0.706, Fig. 2).

Discussion

The thyroid gland is affected by autoimmune attacks more than any other organ, with HT being the most common thyroidal autoimmune disease. HT is regarded as a destructive tissue-specific autoimmune disease with detectable TPOAb and TgAb. It is characterised by widespread lymphocyte infiltration, fibrosis and parenchymal atrophy of thyroid tis-

Table IV. Univariate and multivariate analysis for lateral LNM with the statistically significant variables.

Variables	Univariate analysis		Multivariate analysis		
	N	P value	OR	95% CI	P value
Age (year)		0.053			
< 45	142 (45.6%)				
≥ 45	170 (54.4%)				
Gender		0.215			
Male	28 (9.0%)				
Female	284 (91%)				
Tumour size		0.130			
≤ 1	139 (44.6%)				
> 1	173 (55.4%)				
Multifocality	89 (28.5%)	0.904			
Extrathyroidal invasion	97 (31.1%)	0.033	0.353	0.164-0.757	0.008
TSH		0.032	2.223	1.038-4.757	0.04
< 2.5	182 (58.3%)				
≥ 2.5	130 (41.7%)				

Table V. AMES stage and MACIS score of 1,392 patients with PTC stratified by the presence of HT.

	PTC with HT (n = 357)	PTC alone (n = 1,035)	P value
AMES stage			0.113
Low risk	304 (85.2%)	843 (81.4%)	
High risk	53 (14.8%)	192 (18.6%)	
MACIS score			
Mean	4.52 ± 0.95	4.80±1.16	< 0.01
≤ 6	326 (91.3%)	892 (86.2%)	0.012
> 6	31 (8.7%)	143 (13.8%)	

sue. The disease usually leads to hypothyroidism, which is characterised by a deficit of T3 and T4 and elevated TSH levels. A visible increase in the incidence of co-existent PTC and HT has been found during the past 20 years, and the association between the two diseases has been a topic of discussion. According to abundant data from the literature and a meta-analysis performed by Singh et al., PTC coexisted with HT 2.8 more frequently and its prevalence in various studies ranged from 0.5% to 38.0% [7 19-21]. PTC was also found to occur almost twice as often as other types of thyroid cancer [22]. The observed variability in the rates could be explained by ethnic, geographic, patient characteristics and environmental factors. Moreover, the variability might also be attributed to differences in the pathologic definitions and histopathologic interpretation of HT used [20 23]. In this study, we found a similar rate (25.6%) as reported by others. Long-term HT frequently leads to hypothyroidism, which elevates TSH levels. Thus, when considering whether HT is a risk factor for PTC, it is necessary to investigate the levels of TSH. TSH is known to have a trophic effect on follicular-cell thyroid cancer and those of follicular-cell

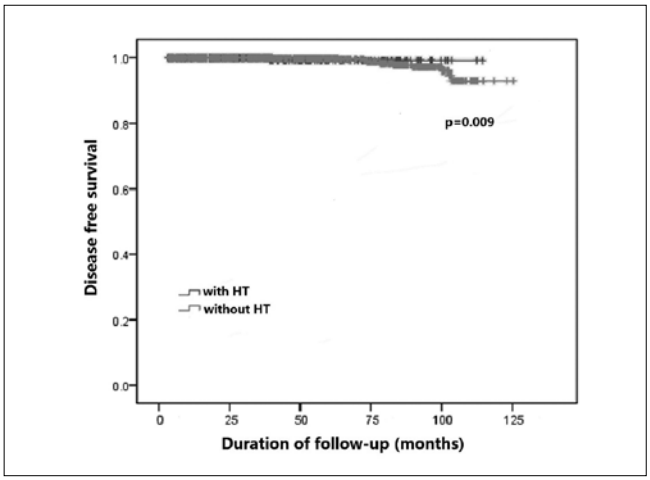


Fig. 1. Comparison of disease-free survival between groups.

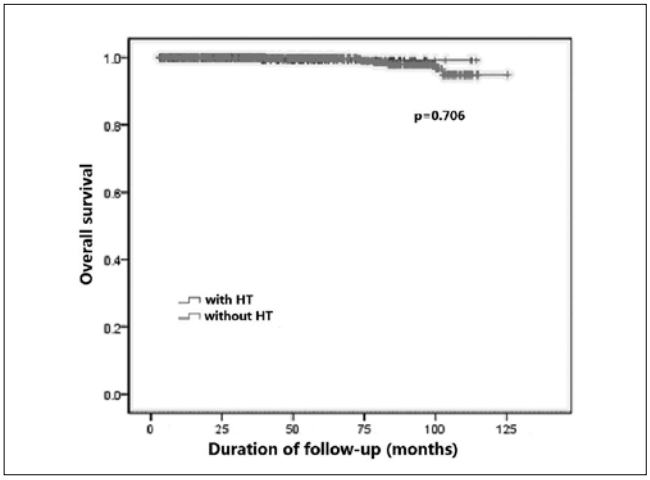


Fig. 2. Comparison of overall survival between groups.

origin [24]. Elevated TSH might potentially increase the risk of thyroid tumour because of TSH-induced proliferation of thyroid cells [25]. Some authors have proposed that the development of thyroid autonomy, reducing TSH levels, may slow cancer progression [26]. In our study, we found that the rate of PTC in patients with HT (21.2%) was much higher than in those without HT (18.2%), and TSH levels in HT patients were significantly higher compared to those without HT. Theses results indicate that HT might be a potential risk factor for PTC patients. We hypothesised that long-term HT causes elevated TSH, which probably is the main factor responsible for PTC. This hypothesis might also explain why some prospective studies had negative results in terms of the relationship between PTC and HT [10 19 22]. Thus, in clinical practice, patients with thyroid nodules and who are suspected of having HT need to be carefully monitored since the possibility of malignancy is increased.

There are conflicting results with regards to the biologic behaviour of PTC in the presence of HT. Some studies have reported that the presence of HT in PTC patients has been related to lower T stage, less extrathyroidal invasion and less nodal metastasis compared to patients without HT in previous studies [9-11]. Other studies have shown HT does not influence any prognostic factors such as size, extrathyroidal extension, or multifocality, thus showing no relationship between HT and PTC aggressiveness [7 15 20]. Our results revealed that PTC patients with HT were significantly more frequent in the population of females in a lower age range, presenting with small lesion and multifocal disease, but also with statistically less extrathyroidal extension. Moreover, PTC patients with HT had early-stage disease and less LNM at the time of surgery. Although no significant differences were found in terms of recurrence and distant metastasis, the rates of both were lower in HT patients.

In recent years, many researchers have tried to elucidate the relationship between PTC and HT from pathophysiological standpoint. The proto-oncogene RET, which is located on chromosome 10q11.2 and encodes a transmembrane receptor-tyrosine kinase, might play an important role between PTC and HT development by RET/PTC rearrangement [27]. This rearrangement has been described in the large majority of tissue with HT and without detectable PTC, which might exhibit progression to cancer from chronic thyroiditis [27 28]. Some authors proposed that the mitogen-activated protein kinase signalling pathway, which is activated by the RET/PTC rearrangement, is crucial in the relationship between both diseases. Mutations in the BRAF gene are also common in thyroid tumours [29]. Franco et al. reported that mice with thyroid-specific knockin of oncogenic BRAF present invasive thyroid cancer and have high TSH levels. However, when they were crossed with TSH-receptor knockout mice, the BRAF mutated gene was not able to induce cancer [30]. Currently, few studies have investigated the effect of HT and the $BRAF^{V600E}$ mutation on PTC patients. Additionally, Larson et al. found the PI3K/Akt signal pathway was highly activated in HT and thyroid cancer tissue, and they proposed that this is a molecular mechanism leading to carcinogenesis in HT [31]. Further investigations are needed to explain the relationship between HT and these genes in PTC patients.

Although recent studies have investigated the impact of HT on PTC tumour behaviour, only several studies have reported its association with LNM [32-34]. Jeong et al. found no difference in central LNM between PTC patients with and without HT, but they did not investigate additional factors associated with LNM [32]. Kim et al. suggested that HT associated with PTC may protect against central LNM, and there was no significant association between the coexistence of HT and central and lateral LNM [33]. We found that PTC patients with HT were associated with a low rate of central and lateral LNM (19.6% vs. 9.5%). It was suggested that the autoimmune response to thyroid specific antigens in patients HT might be involved in destruction of cancer cells expressing thyroid specific antigen in PTC, thus preventing recurrence and LNM. Additionally, we noticed that age and multifocality was significantly associated with central LNM in HT patients in multivariable analysis, and extrathyroidal invasion and TSH level were independent factors for lateral LNM. These results indicated a potential protective role of autoimmune thyroiditis in lymphatic tumour spread. However, the explanation for the difference in the rate of central and lateral LNM on the basis of whether HT is present is unknown.

Many studies have demonstrated that PTC patients with HT have better prognosis. Some authors revealed a positive correlation between HT in PTC patients and DFS and OS; hence, they concluded that these patients had a more favourable prognosis [7]. Kashima et al. reported a mortality and 10-year DFS of 0.7% and 95% in HT patients, compared to 5% and 85% non-HT patients, respectively [11]. In our cohort, PTC patients with HT tended to have a more indolent clinical course compared to those with PTC alone, including a lower rates of OS and DFS; however, the differences in overall survival did not reach statistical significance. Because prognosis of PTC is remarkably excellent, it is sometimes difficult to analyse survival differences between subgroups of PTC. At present, the AMES stage and MACIS scoring system are most commonly adopted for predicting survival and formulating selective treatment strategies for thyroid cancer patients. Thus, we also analysed prognostic outcomes separately for the low and high risk groups by AMES stage and MACIS scoring system. The results showed that the proportion of low risk patients with PTC and HT was higher, and these patients also had lower MACIS scores. Although some p-values did not reach statistical significance, our findings could possibly change with additional patients and a longer follow-up period.

HT by itself is not an indication for surgery, but concurrent malignancy or the presence of goiter should be treated by surgery as the preferred option. As for the extent of surgery in these patients, some authors are inclined to have total thyroidectomy to eliminate the possibility of a potential cancer [34-37]. Total thyroidectomy not only allowed for treating a disease already diagnosed based on FNAB, but also contributed to decreasing the rate of reoperation due to postoperative diagnosis of thyroid cancer. The various therapeutic strategies employed in HT patients have led the present surgeons to present their own opinion. PTC is the most common thyroid cancer with the predilection for lymphatic spread, and central lymph nodes are usually in the target area in differentiated thyroid cancer with LNM [38]. Thus, it is our belief that in view of the relatively high rate of PTC in HT, the strategy of surgical treatment of HT in these patients might include total thyroidectomy and prophylactic central compartment lymphadenectomy. Even if a second surgery is needed because of neck recurrence, a neck lymph node dissection will be sufficient without increasing the operational difficulty and risks of hoarseness and hypocalcaemia.

We acknowledge that there are several limitations in our study. First, it was retrospective and as such was limited by the content, accuracy and availability of the clinical records utilised. Further longitudinal prospective studies are required to assess the potential relationship between the two diseases, if any, and the pathogenetic mechanisms involved. Second, in some studies, HT and PTC may share a possible risk factor, namely excessive intake of iodine, and it has also been proposed that changes in iodine intake might be responsible for the increase of PTC with HT [39]. However, we were not able to perform more detailed assessment for lifestyle, such as dietary iodine intake, and this potential confounding parameter for the relationship between PTC and HT were not investigated fully. In a recent study, the $BRAF^{V600E}$ mutation was present in 72.1% of HT patients with PTC and the rate was significantly lower compared to 81.1% found in patients without HT [40]. Since it was not investigated in our study, it can be considered as another limitation. In addition, it is very difficult for us to assess the mean time of HT in patients with PTC. It is necessary that the studies on increased TSH causing PTC in HT patients should be investigated in the near future, which may provide more information for better comprehension of the relationship between PTC and HT.

In conclusion, we found a relatively common occurrence of HT in patients with PTC. Compared to patients with PTC alone, patients with HT were younger, predominantly female, had a smaller tumour size, multifocal and low stage disease at the time of surgery. Simultaneously, our results showed that HT may influence LNM in PTC patients. HT was associated with a reduced of central and lateral LNM, which indicated a potential protective effect. More studies on the immunoregulatory mechanism and molecular mechanisms, such as high iodine intake, mutations in proto-oncogenes, balance of cell proliferation and activation of kinase activity, are still needed to support or refute this association.

References

1 Siegel RL, Miller KD, Jemal A. *Cancer statistics, 2015*. CA Cancer J Clin 2015;65:5-29.

2 Jiwang L, Zhendong L, Shuchun L, et al. *Clinicopathologic characteristics of familial versus sporadic papillary thyroid carcinoma*. Acta Otorhinolaryngol Ital 2015;35:234-42.

3 Cho BY, Choi HS, Park YJ, et al. *Changes in the clinicopathological characteristics and outcomes of thyroid cancer in Korea over the past four decades*. Thyroid 2013;23:797-804.

4 Vanderpump MP, Tunbridge WM, French JM, et al. *The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey*. Clin Endocrinol (Oxf) 1995;43:55-68.

5 Jankovic B, Le KT, Hershman JM. *Clinical review: Hashimoto's thyroiditis and papillary thyroid carcinoma: is there a correlation?* J Clin Endocrinol Metab 2013;98:474-82.

6 Teng W, Shan Z, Teng X, et al. *Effect of iodine intake on thyroid disease in China. Effect of iodine intake on thyroid diseases in China.* N Engl J Med 2006;354:2783-93.

7 Singh B, Shaha AR, Trivedi H, et al. *Coexistent Hashimoto's thyroiditis with papillary thyroid carcinoma: impact on presentation, management, and outcome.* Surgery 1999;126:1070-106.

8 Dailey ME, Lindsay S, Skahen R. *Relation of thyroid neoplasms to Hashimoto disease of the thyroid gland.* AMA Arch Surg 1955;70:291-7.

9 Kim KW, Park YJ, Kim EH, et al. *Elevated risk of papillary thyroid cancer in Korean patients with Hashimoto's thyroiditis.* Head Neck 2011;33:691-5.

10 Repplinger D, Bargren A, Zhang YW, et al. *Is Hashimoto's thyroiditis a risk factor for papillary thyroid cancer?* J Surg Res 2008;150:49-52.

11 Kashima K, Yokoyama S, Noguchi S, et al. *Chronic thyroiditis as a favorable prognostic factor in papillary thyroid carcinoma.* Thyroid 1998;8:197-202.

12 Anil C, Goksel S, Gursoy A. *Hashimoto's thyroiditis is not associated with increased risk of thyroid cancer in patients with thyroid nodules: a single-center prospective study.* Thyroid 2010;20:601-6.

13 Haymart MR, Repplinger DJ, Leverson GE, et al. *Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage.* J Clin Endocrinol Metab 2008;93:809-14.

14 Holm LE, Blomgren H, Löwhagen T. *Cancer risks in patients with chronic lymphocytic thyroiditis.* N Engl J Med 1985;312:601-4.

15 Del Rio P, Cataldo S, Sommaruga L, et al. *The association between papillary carcinoma and chronic lymphocytic thyroiditis: does it modify the prognosis of cancer?* Minerva Endocrinol 2008;33:1-5.

[16] Edge SB, Byrd DR, Compton CC, et al. *AJCC cancer staging manual.* 7th ed. New York: Springer; 2010.

[17] Sanders LE, Cady B. *Differentiated thyroid cancer: reexamination of risk groups and outcome of treatment.* Arch Surg 1998;133:419-25.

[18] Hay ID, Bergstralh EJ, Goellner JR, et al. *Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989.* Surgery 1993;114:1050-7.

[19] Kim EY, Kim WG, Kim WB, et al. *Coexistence of chronic lymphocytic thyroiditis is associated with lower recurrence rates in patients with papillary thyroid carcinoma.* Clin Endocrinol (Oxf) 2009;71:581-6.

[20] Kebebew E, Treseler PA, Ituarte PH, et al. *Coexisting chronic lymphocytic thyroiditis and papillary thyroid cancer revisited.* World J Surg 2001;25:632-7.

[21] Okayasu I, Fujiwara M, Hara Y, et al. *Association of chronic lymphocytic thyroiditis and thyroid papillary carcinoma. A study of surgical cases among Japanese, and white and African Americans.* Cancer 1995;76:2312-8.

[22] Cipolla C, Sandonato L, Graceffa G, et al. *Hashimoto thyroiditis coexistent with papillary thyroid carcinoma.* Am Surg 2005;71:874-8.

[23] Loh KC, Greenspan FS, Dong F, et al. *Influence of lymphocytic thyroiditis on the prognostic outcome of patients with papillary thyroid carcinoma.* J Clin Endocrinol Metab 1999;84:458-63.

[24] Keshin M, Savas-Erdeve S, Aycan Z. *Co-existence of thyroid nodule and thyroid cancer in children and adolescents with Hashimoto thyroiditis: a single-center study.* Horm Res Paediatr 2016;85:181-7.

[25] Fiore E, Rago T, Latrofa F, et al. *Hashimoto's thyroiditis is associated with papillary thyroid carcinoma: role of TSH and of treatment with L-thyroxine.* Endocr Relat Cancer 2011;18:429-37.

[26] Fiore E, Rago T, Provenzale MA, et al. *Lower levels of TSH are associated with a lower risk of papillary thyroid cancer in patients with thyroid nodular disease: thyroid autonomy may play a protective role.* Endocr Relat Cancer 2009;16:1251-60.

[27] Wirtschafter A, Schmidt R, Rosen D, et al. *Expression of the RET/PTC fusion gene as a marker for papillary carcinoma in Hashimoto's thyroiditis.* Laryngoscope 1997;107:95-100.

[28] Arif S, Blanes A, Diaz-Cano SJ. *Hashimoto's thyroiditis shares features with early papillary thyroid carcinoma.* Histopathology 2002;41:357-62.

[29] Xing M. *BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications.* Endocr Rev 2007;28:742-62.

[30] Franco AT, Malaguarnera R, Refetoff S, et al. *Thyrotrophin receptor signaling dependence of Braf-induced thyroid tumor initiation in mice.* Proc Natl Acad Sci U S A 2011;108:1615-20.

[31] Larson SD, Jackson LN, Riall TS, et al. *Increased incidence of well-differentiated thyroid cancer associated with Hashimoto thyroiditis and the role of the PI3k/Akt pathway.* J Am Coll Surg 2007;204:764-73.

[32] Jeong JS, Kim HK, Lee CR, et al. *Coexistence of chronic lymphocytic thyroiditis with papillary thyroid carcinoma: clinical manifestation and prognostic outcome.* J Korean Med Sci 2012;27:883-9.

[33] Kim SS, Lee BJ, Lee JC, et al. *Coexistence of Hashimoto's thyroiditis with papillary thyroid carcinoma: the influence of lymph node metastasis.* Head Neck 2011;33:1272-7.

[34] Konturek A, Barczyński M, Wierzchowski W, et al. *Coexistence of papillary thyroid cancer with Hashimoto thyroiditis.* Langenbecks Arch Surg 2013;398:389-94.

[35] Serpell JW, Phan D. *Safety of total thyroidectomy*. ANZ J Surg 2007;77:15-9.

[36] Anand A, Singh KR, Kushwaha JK, et al. *Papillary thyroid cancer and Hashimoto's thyroiditis: an association less understood*. Indian J Surg Oncol 2014;3:199-204.

[37] Kurukahvecioglu O, Taneri F, Yüksel O, et al. *Total thyroidectomy for the treatment of Hashimoto's thyroiditis coexisting with papillary thyroid carcinoma.* Adv Ther 2007;24:510-6.

[38] Hall FT, Freeman JL, Asa SL, et al. *Intratumoral lymphatics and lymph node metastases in papillary thyroid carcinoma.* Arch Otolaryngol Head Neck Surg 2003;129:716-9.

[39] Oh CM, Park S, Lee JY, et al. *Increased prevalence of chronic lymphocytic thyroiditis in Korean patients with papillary thyroid cancer.* PLoS One 2014;9:e99054.

[40] Kwak HY, Chae BJ, Eom YH, et al. *Does papillary thyroid carcinoma have a better prognosis with or without Hashimoto thyroiditis?* Int J Clin Oncol 2015;20:463-73.

Received: June 27, 2017 - Accepted: July 7, 2017

Address for correspondence:Yuejiao Zhao, Department of Head and Neck Surgery, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, N0. 44 Xiaoheyan Road, Dadong District, Shenyang, 110042 Liaoning Province, People's Republic of China. Tel. 86 24 31916833. E-mail: 13352468831@qq.com

ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:401-405; doi: 10.14639/0392-100X-1237

LARYNOGOLOGY

There is no correlation between signs of reflux laryngitis and reflux oesophagitis in patients with gastro-oesophageal reflux disease symptoms

Non c'è nessuna correlazione tra segni di laringite da reflusso ed esofagite da reflusso nei pazienti con sintomi da malattia da reflusso gastroesofageo

K. ZELENIK[1 2], I.M. KAJZRLIKOVA[3], P. VITEK[2 3], O. URBAN[2 4], M. HANOUSEK[4], P. KOMINEK[1 2]

[1] Department of Otolaryngology, University Hospital Ostrava, Ostrava, Czech Republic; [2] Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic; [3] Beskydy Gastrocentre, Hospital Frýdek-Místek, Frýdek-Místek, Czech Republic; [4] Gastroenterology Department, Vitkovicka Hospital, Ostrava, Czech Republic

SUMMARY

The objective of the present study was to determine if there is correlation between signs of reflux laryngitis (RL) and reflux oesophagitis (RE) in patients with gastro-oesophageal reflux disease (GORD) symptoms. Laryngeal photography obtained from patients during oesophagogastroduodenoscopy were examined by two otolaryngologists experienced in the field of extra-oesophageal reflux regarding the presence and severity of RL. The presence of RE was evaluated by gastroenterologist. Smokers, heavy drinkers and patients with bronchial asthma were excluded from the statistical analysis. A total of 681 patients were analysed. RL was diagnosed in 367 (53.9%) cases, of whom 182 patients had mild, 118 moderate and 67 severe (Reflux Finding Score > 7) RL. RE was diagnosed in 103 (28.1%) patients with RL and in 80 (25.7%) patients without RL. Neither the difference between the overall group of patients with RL and those without (OR 1.141, 95% CI 0.811-1.605, p = 0.448), nor the differences between the respective subgroups of patients with mild, moderate and severe RL and those without RL were statistically significant. The OR and 95% CI for mild, moderate and severe RL were 1.042, 95% CI 0.712-1.526, p = 0.834, 1.182, 95% CI 0.764-1.831, p = 0.453 and 1.0, 95% CI 0.566-1.766, p = 0.999 respectively. It can be concluded that there is no correlation between RL and RE in patients with GORD symptoms.

KEY WORDS: Extra-oesophageal reflux • Laryngopharyngeal reflux • Reflux laryngitis • Reflux oesophagitis • Gastro-oesophageal reflux • Reflux Finding Score

RIASSUNTO

Lo scopo dello studio è stato determinare l'esistenza di una correlazione tra i segni di laringite da reflusso (RL) ed esofagite da reflusso (RE) in pazienti con sintomi da malattia da reflusso gastroesofageo (GORD). Durante l'esecuzione di esofagogastroduodenoscopie, sono state ottenute fotografie laringee, le quali sono state esaminate da otorinolaringoiatri esperti di reflusso extra-esofageo al fine di valutare la presenza e la gravità di RL. La presenza di RE, invece, è stata valutata dai gastroenterologi. Fumatori, alcolisti e pazienti con asma bronchiale sono stati esclusi dall'analisi statistica. Sono stati analizzati 681 pazienti. RL è stata diagnosticata in 367 (53,9%) pazienti, dei quali 182 avevano una forma lieve, 118 una forma moderata, e 67 una forma severa (Reflux Finding Score > 7). RE è stata diagnosticata in 103 (28,1%) pazienti con RL e in 80 (25,7%) pazienti senza RL. In merito alla presenza di RE, la differenza tra l'intero gruppo di pazienti con RL e quelli senza RL non è stata statisticamente significativa (OR 1.141, 95% CI 0.811-1.605, p = 0.448), e allo stesso modo non si sono rivelate statisticamente significative le differenze tra ciascuno dei sottogruppi di pazienti con RL lieve, moderata e severa, e quelli senza RL. L'OR e il 95% CI per RL lieve, moderata e severa sono stati rispettivamente i seguenti: 1.042, 95% CI 0.712-1.526, p = 0.834, 1.182, 95% CI 0.764-1.831, p = 0.453 and 1.0, 95% CI 0.566-1.766, p = 0.999. In conclusione, non è risultata nessuna correlazione tra RL e RE in pazienti con sintomi da malattia da reflusso gastroesofageo.

PAROLE CHIAVE: *Reflusso extra-esofageo • Reflusso faringolaringeo • Laringite da reflusso • Esofagite da reflusso • Reflusso gastroesofageo • Reflux Finding Score*

Acta Otorhinolaryngol Ital 2017;37:401-405

Introduction

It is broadly accepted that reflux oesophagitis (RE) is present in less than one-third of patients with laryngopharyngeal reflux (LPR), and oesophagogastroduodenoscopy (EGD) is not routinely recommended for these patients by otolaryngologists [1]. On the other hand, some studies have shown that extra-oesophageal symptoms may be the first sign of severe RE, as well as of adenocarcinoma [2]. If a patient suffers from frequent typical symptoms of gastro-oesophageal reflux disease (GORD), such as heartburn and regurgitation, or experiences some of the "alarm symptoms" such

as dysphagia, odynophagia, weight loss, anaemia etc., EGD should be done to understand the severity of the pathological changes within the oesophagus [1]. However, most patients with extra-oesophageal symptoms do not suffer from such symptoms [1 3]. As a result of the above mentioned contradiction, otolaryngologists often struggle with a dilemma: should a patient with extra-oesophageal symptoms and signs of reflux disease be referred for EGD or not?

The objective of the present study was to determine if there is correlation between signs of reflux laryngitis (RL) and reflux oesophagitis (RE) in patients with GORD symptoms. If this were true, the presence of reflux laryngitis (RL), which is considered the most characteristic endoscopic sign of LPR, would mean that reflux changes within the oesophagus (erosive oesophagitis) could be expected frequently in patients with GORD symptoms and patient should be referred for EGD. From this point of view, laryngoscopy done by an otolaryngologist as a routine examination would bring additional information in decision-making process whether patient with GORD symptoms should be referred to upper gastrointestinal endoscopy. To our knowledge, this is the largest study to examine the association between RL and RE in patients with GORD symptoms, and the first study to use Reflux Finding Score (RFS) to quantify laryngeal changes for this reason.

Materials and methods

The prospective study was performed in accordance with the 1983 Declaration of Helsinki, the requirements of good clinical practice and all applicable regulatory requirements, and was approved by the Institutional Review Board. Written informed consent was obtained from all participants before initiating any procedure.

Patients undergoing EGD due to GORD symptoms (heartburn, regurgitation) and/or upper gastrointestinal discomfort/dyspepsia lasting for at least two months within the study period of January 2014 to December 2014 were included. Epidemiologic data (age, sex, BMI, bronchial asthma, smoking history, alcohol abuse) were obtained via questionnaire. The presence of RE was established and classified by a gastroenterologist according to the Los Angeles classification (grades A-D). The high-definition endoscope Olympus GIF H180 was used for all examinations. As part of the EGD, laryngeal photography of high-definition quality was obtained from all patients (Fig. 1).

The presence of RL was determined from photographs by two otolaryngologists (KZ, PK) experienced in the field of LPR and blinded for the result of EGD. RFS proposed by Belafsky et al. was not used for the initial evaluation of laryngeal changes because it is not widely used as first-line by otolaryngologists. To make the results of our study widely usable, a much easier system of evaluation of the laryngeal changes was used. Three degrees (mild, moderate, severe) of RL were distinguished. Patients with changes limited to the posterior commissure or arytenoids (hypertrophy, oedema, erythema) were included in group I (mild changes). Patients with changes in both the posterior commissure and arytenoids (hypertrophy, oedema, erythema) were included in group II (moderate changes). Patients with more severe changes affecting at least three areas of the larynx (e.g. erythema of the arytenoids, oedema of the vocal cords, pseudosulcus vocalis, hypertrophy of the false vocal cords, ventricular obliteration, granuloma etc.) were included in group III (severe changes) (Fig. 1). After this initial selection, group III was re-evaluated using RFS. All patients in group III had RFS higher than seven, which is the diagnostic threshold for LPR for this tool.

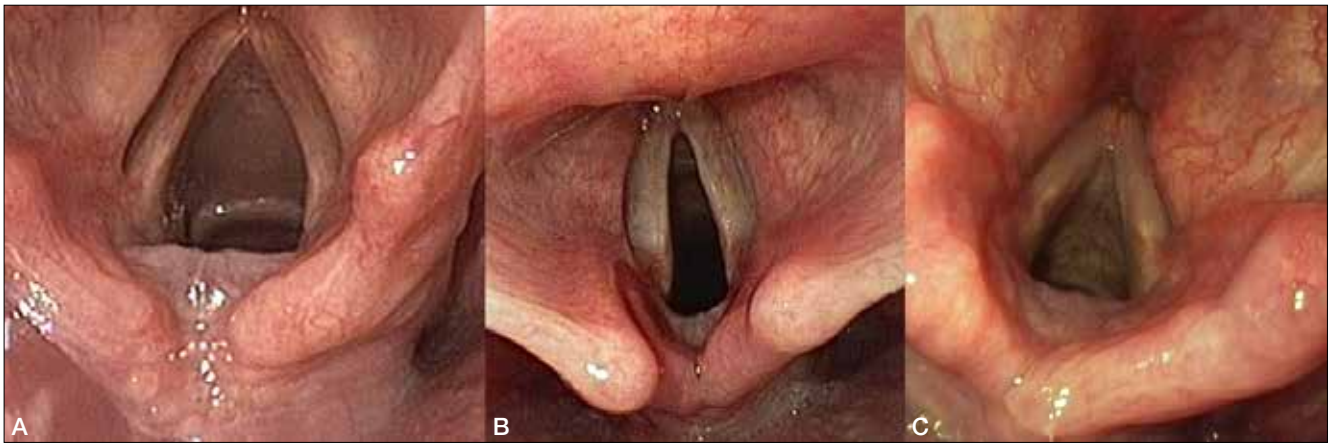


Fig. 1. High definition pictures obtained during routine oesophagogastroduodenoscopy. Three grades of reflux laryngitis were determined in all patients:
a – mild (hypertrophy, oedema or erythema limited only on the posterior commissure or arytenoids)
b – moderate (hypertrophy, oedema or erythema present on both the posterior commissure and arytenoids)
c – severe (pathological changes affecting at least three areas of the larynx (e.g. erythema of the arytenoids, oedema of the vocal cords, pseudosulcus vocalis, hypertrophy of the false vocal cords, ventricular obliteration, granuloma etc.).

Smokers, heavy drinkers and patients with bronchial asthma were excluded from the statistical analysis, because inflammatory changes of the larynx are very common within these groups of patients and the results of the study could be biased.

The presence of RE in the groups of patients with RL and without RL as well as in all three subgroups (mild, moderate, severe) of RL was statistically analysed. Univariate logistic regression analysis was used to assess the relationship between RL and RE – by odds ratios (OR) and their 95% confidence interval (CI 95%). The dependent variable was the presence of RE. Statistical analysis was performed using SPSS statistical package (version 19.0).

Results

A total of 1224 patients were recruited for the study, 35 of whom were excluded because of the low quality of their laryngeal photographs. An additional 508 patients (smokers, heavy drinkers, patients with bronchial asthma) were excluded, and thus 681 patients (303 male, 378 female, mean age 57, SD ± 16) were analysed.

RL was diagnosed in 367 (53.9%) patients, of whom 182 patients had mild, 118 moderate and 67 severe (RFS > 7) RL. RE was diagnosed in 103 (28.1%) out of 367 patients with RL and in 80 (25.7%) out of 314 patients without RL. We ascertained that RE was not statistically more frequent in the overall group of patients with RL (OR 1.141, 95% CI 0.811-1.605, p = 0.448), nor in the subgroups of patients with mild, moderate and severe (RFS > 7) RL than in patients without RL. The OR and 95% CI for mild, moderate and severe reflux laryngitis were 1.042, 95% CI 0.712-1.526, p = 0.834, 1.182, 95% CI 0.764-1.831, p = 0.453 and 1.0, 95% CI 0.566-1.766, p = 0.999 respectively.

Discussion

LPR and its relationship to GORD and RE continues to be a controversial issue because there is a lack of diagnostic criteria and inconsistency in response to therapy. Nevertheless, it is a very real problem and affects hundreds of thousands of patients annually [4 5]. It is estimated that up to 10-15% of all visits to otolaryngology offices are prompted by manifestations of LPR [1 6-8]. One of the daily dilemmas otolaryngologists struggle with concerns whether or not a patient with GORD symptoms who do not fall within the "alarm symptoms" group and with concurrent signs suggesting LPR should be referred for EGD to determine the extent of pathological changes in the oesophagus.

While our understanding of LPR continues to evolve, one fact is already clear. LPR is considered to be a distinct disorder from GORD, with a different pathophysiology [3 4]. When compared to the oesophageal mucosa, the laryngeal mucosa is more susceptible to injury, which may be caused by much lower levels of acid and pepsin exposure than those capable of damaging the oesophageal epithelium [4]. Moreover, the negative role of biliary laryngopharyngeal reflux in the pathogenesis of chronic laryngeal changes has been revealed recently [9]. This condition, as an acid one, seems to represent an important dangerous, endogenous risk factor involved in the pathogenesis of inflammatory, precancerous and neoplastic laryngeal lesions [9]. As a result, many patients diagnosed with LPR do not suffer from the classic symptoms of GORD (heartburn, regurgitation) and oerosive esophagitis. Therefore, EGD is not routinely recommended for patients with isolated LPR by otolaryngologists [1 10]. For example, an international survey conducted by Book et al. demonstrated that only 5 (4.4%) of 120 otolaryngologists reported ordering EGD as a first-line adjunctive test for patients with suspected LPR [10].

On the other hand, some case control studies have shown an association between RE and RL [5 8 11-14]. Also, it has been estimated that up to 50% of patients with laryngeal and voice disorders have reflux [1], prompting some authors to recommend endoscopic evaluation of the upper gastrointestinal tract in all patients with LPR [4 15]. The reasoning is that some symptoms of more severe conditions within the oesophagus may be masked by empiric therapy. A peculiar subgroup of patients requiring EGD are those with chronic cough. Reawis et al. demonstrated that these individuals are more likely to have metaplastic changes of the oesophagus than those with classic symptoms of GORD [2].

In our study, we set out to understand whether RL, which is the most common and easy to access independent sign of LPR, is of diagnostic importance for prediction of RE in patients with GORD symptoms. We decided not to evaluate potential symptoms of LPR (voice problems, throat cleaning, globus pharyngeus, cough, etc.) and not to fill out questionnaire reflux symptom index in our study. The main reason is that symptoms of LPR and Reflux symptom index are even less specific than laryngeal signs of LPR, very prone to transitory changes and patient dependent with very high risk of subjective bias.

On the other hand, RL is considered to be one of the most characteristic signs of LPR. An international survey of 120 otolaryngologists conducted by Book et al. showed that arytenoid oedema and erythema and posterior commissure hypertrophy were considered the most typical signs of LPR by most [10]. Similarly, a survey of more than 700 otolaryngologists revealed that the two signs most likely to be used to diagnose laryngitis associated with reflux were erythema and oedema of the larynx [16].

Nevertheless, it is very important to keep in mind that the signs of LPR are not very specific and can be the result of injury by non-GORD mechanisms (tobacco, alcohol, allergies, infection, postnasal discharge, vocal trauma etc.). This often leads to over-diagnosis of this condition and makes the study of the relationship between LPR and GORD (with or without RE) complicated and challeng-

ing. For example, Hicks et al. revealed at least one finding considered to be associated with reflux in 86% of 105 healthy volunteers without any throat symptoms [17]. Additionally, abnormal laryngeal signs are more likely to be suspected when flexible rather than rigid laryngoscopes are used, suggesting that flexible laryngoscopy is more sensitive but less specific in identifying laryngeal tissue irritation [18]. Besides the non-specificity of the signs currently employed in diagnosing LPR, an additional problem is the inter- and intra-observer variability of laryngoscopic exams. To improve reliability of the laryngoscopic evaluation, RFS was proposed by Belafsky et al. [19]. Initial studies found good inter- and intra-observer reproducibility of this tool. However, RFS is seldom used in clinical practice as it is not user friendly, as well as being difficult to remember and time consuming. The reliability of this score has been questioned as well [20].

In the present study, three degrees (mild, moderate, severe) of RL were identified (Fig. 1) and patients divided into three groups accordingly. The groups "mild" and "moderate" included patients with laryngeal changes limited to the posterior commissure and/or arytenoids, for these changes are often construed by otolaryngologists as characteristic signs of reflux. The group "severe" included patients with many laryngeal signs of LPR, and all of these patients had RFS higher than seven. We did not find that RE was statistically more frequent in the overall group of patients with RL in comparison to the group of patients without RL. Moreover, RE was not statistically more frequent in subgroups of patients with mild, moderate and severe (RFS higher than seven) RL than in the group without RL. Thus our result is consistent with the result of a study evaluating the prevalence of laryngeal signs in GORD versus non-GORD patients (based on EGD) conducted by Vavricka et al. [20]. The authors found that there was no difference between the groups, suggesting the lack of diagnostic specificity of laryngeal signs for GORD [21]. Also, another smaller study conducted by Tauber et al. did not find statistically significant differences in the above mentioned laryngeal changes between GORD and non-GORD groups [8].

Moreover, Cammarota et al. referred that 52 of 83 patients with laryngitis (63%) had no erosion of the oesophageal mucosa. The authors concluded that inflammation of the laryngeal epithelium (when defense mechanisms are absent) is more frequent than erosive oesophagitis in patients with chronic reflux symptoms [22 23]. They recommend future studies in this area to better delineate these associations.

Going beyond the results of formerly mentioned studies, we selected a group of patients with severe laryngeal changes, which corresponded to RFS over seven. Even in this group of patients, RE was not found to be statistically more frequent. To our knowledge, this result is novel and has not been published in the literature to date.

As a result of our study, it can be concluded that laryngeal signs (reflux laryngitis) in patients with GORD symptoms are not of diagnostic specificity for RE. This supports the claim that LPR and GORD are two distinct diseases and that otolaryngologists cannot predict the presence of RE from the laryngeal examination. The other possible interpretation of our result is that signs of LPR are so non-specific and widely present in the population that the relationship with RE cannot be reliably established. Of course, in some cases these two entities can coexist and this can be the reason for the broad range of association reported in the literature. RE confirmed by EGD was reported in 26% (Paterson 1997), 43% (Deveney 1993 and Tauber 2002) and 62% (Koufman 1991) of patients with LPR [6 8 12 13]. Likewise, RE was confirmed in 28% of patients with RL in the present study.

Conclusions

There is no correlation between reflux laryngitis and reflux oesophagitis in patients with GORD symptoms.

Acknowledgements

The authors would like to thank MSc. Hana Tomášková, Ph. D. from the Institute of Epidemiology and Public Health, Medical Faculty of the Ostrava University, Czech Republic, for help with statistical analysis.

References

1 Sataloff RT et al. *Reflux laryngitis and related disorders.* First Edition. San Diego: Plural Publishing; 2006

2 Reavis KM, Morris CD, Gopal DV, et al. *Laryngopharyngeal reflux symptoms better predict the presence of esophageal adenocarcinoma than typical gastroesophageal reflux symptoms.* Ann Surg 2004;239:849-56.

3 Koufman JA. *Laryngopharyngeal reflux is different from classic gastroesophageal reflux disease*. Ear Nose Throat J 2002;81:7-9.

4 Weinberger PM, Postma GN. *Laryngopharyngeal reflux from the otolaryngologist's perspective.* In: Vaezi MF, editor. *Extraesophageal reflux*. San Diego: Plural Publishing; 2009. p. 49-66.

5 Galli J, Scarano E, Agostino S, et al. *Pharyngolaryngeal reflux in outpatient clinical practice: personal experience.* Acta Otorhinolaryngol Ital 2003;23:38-42.

6 Koufman JA. *The otolaryngologic manifestations of gastroesophageal reflux disease: a clinical investigation of 225 patients using ambulatory 24-h ph monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury.* Laryngoscope 1991;101:1-78.

7 Richter JE. *Extraesophageal presentations of gastroesophageal reflux disease: an overwiew.* Am J Gastroenterol 2000;95:S1-S3.

8 Tauber S, Gross M, Issing WJ. *Association of laryngopharyngeal symptoms with gastroesophageal reflux disease.* Laryngoscope 2002;112:879-86.

9 Galli J, Cammarota G, De Corso E, et al. *Biliary laryngopharyngeal reflux: a new pathological entity.* Current Op Otolaryngol Head Neck Surg 2006;14:128-32.

[10] Book DT, Rhee JS, Toohill RJ, et al. *Perspectives in laryngopharyngeal reflux: an international survey.* Laryngoscope 2002;112:1399-1406.

[11] El-Serag HB, Sonnenberg A. *Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans.* Gastroenterology 1997;113:755-60.

[12] Paterson WG. *Extraesophageal complications of gastroesophageal reflux disease.* Can J Gastroenterol 1997;11:45B-50B.

[13] Deveney CW, Benner K, Cohen J. *Gastroesophageal reflux and laryngeal disease.* Arch Surg 1993;128:1021-7.

[14] Koufman JA, Amin MR, Panetti M. *Prevalence of reflux in 113 consecutive patients with laryngeal and voice disorders.* Otolaryngol Head Neck Surg 2000;123:385-8.

[15] Bove MJ, Rosen C. *Diagnosis and management of laryngopharyngeal reflux disease.* Curr Opin Otolaryngol Head Neck Surg 2006;14:116-23.

[16] Ahmed TF, Khandwala F, Abelson TI, et al. *Chronic laryngitis associated with gastroesophageal reflux: prospective assessment of differences in practice patterns between gastroenterologists and ENT physicians.* Am J Gastroenterol 2006;101:470-8.

[17] Hicks DM, Ours TM, Abelson TI, et al. *The prevalence of hypopharynx findings associated with gastroesophageal reflux in normal volunteers.* J Voice 2002;16:564-7.

[18] Milstein CF, Charbel S, Hicks DM, et al. *Prevalence of laryngeal irritation signs associated with reflux in asymptomatic volunteers: impact of endoscopic technique (rigid vs. flexible laryngoscope).* Laryngoscope 2005;115:2256-61.

[19] Belafsky CP, Postma GN, Koufman JM. *The validity and reliability of the Reflux Finding Score.* Laryngoscope 2001;111:1313-7.

[20] Branski RC, Bhattacharyya N, Shaprio J. *The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease.* Laryngoscope 2002;112:1019-24.

[21] Vavricka SR, Storck CA, Wildi SM, et al. *Limited diagnostic value of laryngopharyngeal lesions in patients with gastroesophageal reflux during routine upper gastrointestinal endoscopy.* Am J Gastroenterol 2007;102:716-22.

[22] Cammarota G, Galli J, Agostino S, et al. *Accuracy of laryngeal examination during upper gastrointestinal endoscopy for premalignancy screening: prospective study in patients with or without reflux symptoms.* Endoscopy 2006;38:376-381.

[23] Cammarota G, Agostino S, Rigante M, et al. *Preliminary laryngeal examination during magnifying upper gastrointestinal videoendoscopy in two patients with reflux symptoms.* Endoscopy 2006;38:287.

Received: May 9, 2016 - Accepted: January 15, 2017

Address for correspondence: Karol Zeleník, Department of Otolaryngology and Head and Neck Surgery, University Hospital Ostrava, 17. listopadu 1790, 708 52 Ostrava-Poruba, Czech Republic. Tel. +42 0608946759. E-mail: karol.zelenik@fno.cz

ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:406-409; doi: 10.14639/0392-100X-1321

OSAHS

Palatal surgery in a transoral robotic setting (TORS): preliminary results of a retrospective comparison between uvulopalatopharyngoplasty (UPPP), expansion sphincter pharyngoplasty (ESP) and barbed repositioning pharyngoplasty (BRP)

La chirurgia palatale all'interno di un setting robotico transorale (TORS): risultati preliminari di uno studio retrospettivo comparativo tra UPPP, ESP e BRP

G. CAMMAROTO[1], F. MONTEVECCHI[2], G. D'AGOSTINO[2], E. ZECCARDO[2], C. BELLINI[2], G. MECCARIELLO[2], C. VICINI[2]

[1] Department of Otolaryngology, University of Messina, Italy; [2] Department of Special Surgery, ENT and Oral Surgery Unit, Ospedale Morgagni Pierantoni, Forlì, Italy

SUMMARY

It has become increasingly clear in the past decade that surgical management of obstructive sleep apnoea hypopnoea syndrome (OSAHS) is most successfully managed with multilevel surgery. We evaluated the outcomes of multilevel interventions comparing three different palatal techniques added to TORS: uvulopalatopharyngoplasty (UPPP), a modified expansion sphincter pharyngoplasty (ESP), inspired by the Pang expansion sphincter pharyngoplasty technique and the latest barbed repositioning pharyngoplasty (BRP). Thirty patients were retrospectively evaluated. Ten patients underwent UPPP by Fairbanks, 10 BRP and 10 a modified ESP already described. All patients underwent TORS, tonsillectomy and septo-turbinoplasty. For all cases, the following data were retrieved and revaluated: preoperative and postoperative apnoea-hypopnoea index (AHI), preoperative and postoperative Epworth Sleepiness Scale (ESS), pain visual analogue scale (VAS; 0–10) for the first 5 days postoperatively, palatal operative time for each surgical technique, discharge date and complication types and rate. Both BRP and ESP resulted in better postoperative AHI values and higher surgical success rates in comparison with UPPP. On the other hand, BRP was not more effective than ESP. ESP surgery time was significantly higher than UPPP, while BRP was the quickest procedure. In summary, ESP and BRP seem to be more effective than UPPP in a multilevel surgical robotic setting. However, being quicker, easy to learn and with a low rate of complications, BRP is a safe, effective and promising option for treatment of OSAHS patients.

KEY WORDS: TORS • OSAHS • Palatal surgery

RIASSUNTO

Negli ultimi anni si è diffusa l'opinione che la chirurgia multilivello nel trattamento della sindrome delle apnee ostruttive garantisca risultati pià soddisfacenti. L'obiettivo del nostro lavoro è quello di confrontare tre tecniche palatali associate alla TORS: l'uvulopalatofaringoplastica (UPPP), l'expansion sphincter pharyngoplasy (ESP) e la barbed repositioning pharingoplasty (BRP). Trenta pazienti, trattati con TORS, tonsillectomia e settoturbinoplastica e chirurgia palatale sono stati retrospettivamente studiati. I seguenti valori pre e post-operatori sono stati presi in considerazione: AHI, ESS, VAS per la valutazione del dolore, tempi operatori palatali, data di dimissione e complicanze (tipi ed incidenza). Sia la BRP che l'ESP hanno garantito dei valori postoperatorio di AHI inferiori rispetto all'UPPP con un maggior tasso di successo chirurgico. Dall'altra parte non è stato possibile dimostrare una superiorità della BRP sull'ESP. I tempi operatori più lunghi sono stati registrati nel gruppo ESP mentre i più brevi sono stati riscontrati nel gruppo BRP. Riassumendo, ESP e BRP sono risultate più efficaci dell'UPPP in un setting robotico multilivello. Inoltre, essendo una tecnica rapida, di facile apprendimento e dal basso tasso di complicanze, la BRP si presenta come una valida opzione chirurgica nel trattamento dell'OSAS.

PAROLE CHIAVE: *TORS • OSAHS • Chirurgia palatale*

Acta Otorhinolaryngol Ital 2017;37:406-409

Introduction

Today, transoral robotic surgery (TORS) for obstructive sleep apnoea-hypopnea syndrome (OSAHS) is a widely recognised effective therapeutic option.

It has become increasingly clear in the past decade that surgical management of OSAHS is most successfully managed with multilevel surgery [1-8].

In particular, drug-induced sleep endoscopy (DISE) has shown that the hypopharynx and base of tongue are im-

portant anatomic components of obstruction in OSAHS and therefore must be treated [9].

During the last decades, several variations in palatal surgery have been proposed. We evaluated the outcomes of multilevel interventions comparing three different palatal techniques added to TORS: uvulopalatopharyngoplasty (UPPP), a modified expansion sphincter pharyngoplasty (ESP), inspired by the Pang expansion sphincter pharyngoplasty technique and the latest barbed repositioning pharyngoplasty (BRP) [10-13].

Materials and methods

Thirty patients were retrospectively evaluated. The patients were randomly selected from the dataset including OSAHS patients treated surgically from May 2008 to December 2015 at the ENT unit of the Hospital Morgagni-Pierantoni, Forlì, Italy. Incomplete or very recent cases, with a postoperative polysomnographic evaluation shorter than 6 months, were excluded. Patients met inclusion criteria if they were 18 years of age or older, had failed continuous positive airway pressure as a nonsurgical treatment alternative and had an apnoea-hypopnoea index (AHI) of 20 or above. Patients who had had prior airway surgery, such as UPPP or tonsillectomy, were not eligible. Preoperative workup also included DISE. Only patients who were found to have significant collapse contemporarily at the retropalatal, retrolingual and hypopharyngeal levels were included. Three groups, each with 10 patients, were compared. Ten patients underwent UPPP by Fairbanks [11], 10 BRP [12] and 10 a modified ESP already described [10]. All 30 patients were treated with a robotic tongue base reduction with supraglottoplasty (SGP) by Vicini [4] with temporary tracheostomy, tonsillectomy and septo-turbinoplasty. For all cases, the following data were retrieved and revaluated:

1. age;
2. sex;
3. preoperative BMI;
4. preoperative and postoperative AHI (all sleep studies were carried out in an unattended fashion by means of a Polymesam 8-channel; reviewed and scored by the same expert in sleep medicine according to the American Academy of Sleep Medicine Guidelines 2007 [14];
5. preoperative and postoperative Epworth Sleepiness Scale (ESS), using the Italian version of the Epworth test that was adapted and tested for the Italian-speaking population [15];
6. pain visual analogue scale (VAS; 0–10) for the first 5 days postoperatively;
7. palatal operative time for each surgical technique (excluding tonsillectomy), as measured by our operating theatre electronic system;
8. discharge date;
9. complication types and rate.

The 3 groups were reasonably matched for sex, age, BMI and preoperative AHI. The definition of surgical response and success were a reduction from the preoperative AHI of at least 50% (response) and less than 20 events per hour (success). All clinical records were reviewed to examine all the differential features between the 3 groups potentially related to the different palate procedures applied.

The study met the approval of the Local Board of Ethics (Institutional Review Board of the Hospital Morgagni–Pierantoni, Forlì). Statistical evaluation of pre-postoperative changes between groups was performed by means of Mann-Whitney, Kruskal Wallis and Wilcoxon tests, with the latter used to evaluate pre-postoperative changes in each group.

Results

The 3 groups showed no significant difference in F/M ratio (1/9 in all groups), age, BMI and preoperative AHI (Table I). The AHI decreased significantly after surgery in all groups except UPPP. ESS values, however, decreased significantly postoperatively in all groups (Table II). No significant differences in post-operative pain, deltaAHI (preAHI-postAHI) and hospital stay were recorded (Table III).

Surgical success rate was 90% in the ESP and BRP groups, and 50% in the UPPP group. ESP and BRP post-operative AHI values were significantly lower than UPPP. On the other hand, ESP and BRP did not show any differences in this measure. Both ESP and BRP post-operative ESS values were significantly lower than the UPPP figure, while no differences were seen between the first two groups. ESP surgery time was significantly higher than UPPP while BRP was seen to be the quickest procedure (Table IV).

No complications were recorded in any group.

Table I. Pre-operative intergroup analysis.

		N	Mean	Std. deviation	P
Age	UPPP	10	58.40	9.90	0.170
	ESP	10	52.80	11.39	
	BRP	10	48.20	11.39	
	Total	30	53.13	11.36	
BMI	UPPP	10	26.79	3.72	0.181
	ESP	10	27.03	2.12	
	BRP	10	28.77	2.56	
	Total	30	27.53	2.92	
preAHI	UPPP	10	34.04	14.03	0.953
	ESP	10	35.59	13.87	
	BRP	10	37.84	21.60	
	Total	30	35.82	16.37	

Table II. Intragroup analysis: pre-postoperative variations.

	Group	Mean	Std. Deviation	P
preAHI	BRP	34.04	14.03	0.005
postAHI		13.53	7.76	
preESS		10.40	2.50	0.008
postESS		3.90	3.57	
preAHI	ESP	35.59	13.87	0.005
postAHI		9.63	9.25	
preESS		13.00	4.49	0.005
postESS		4.90	3.87	
preAHI	UPPP	37.84	21.60	0.059
postAHI		22.92	13.30	
preESS		12.30	4.24	0.021
postESS		8.50	5.42	

Table III. Post-operative intergroup analysis (not significant).

		N	Mean	Std. Deviation	P
Pain	UPPP	10	1.69	0.62	0.416
	ESP	10	1.79	0.90	
	BRP	10	2.79	2.02	
	Total	30	2.09	1.37	
Hospital stay	UPPP	10	6.70	1.25	0.811
	ESP	10	7.10	1.52	
	BRP	10	7.10	3.24	
	Total	30	6.96	2.12	
deltaAHI	UPPP	10	20.51	12.45	0.313
	ESP	10	25.96	13.95	
	BRP	10	14.92	26.83	
	Total	30	20.46	18.78	

Table IV. Post-operative intergroup analysis.

	Group	Mean	Std. Deviation	P
palatalTIME	BRP	15.70	2.16	0,00
	UPPP	28.20	2.29	
postESS	BRP	3.90	3.57	0,019
	UPPP	8.50	5.42	
postAHI	BRP	13.53	7.76	0,043
	UPPP	22.92	13.30	
PalatalTIME	BRP	15.70	2.16	0,00
	ESP	37.60	4.59	
postESS	BRP	3.90	3.57	0,62
	ESP	4.90	3.87	
postAHI	BRP	13.53	7.76	0,29
	ESP	9.63	9.25	
palatalTIME	ESP	37.60	4.59	0,00
	UPPP	28.20	2.29	
postESS	ESP	4.90	3.87	0,013
	UPPP	8.50	5.42	
postAHI	ESP	9.63	9.25	0,019
	UPPP	22.92	13.30	

Discussion

In our sleep disorder breathing surgical practice, it is routine to perform multilevel surgery at the same surgical session.

In our philosophy, TORS is just a step devised to address tongue base and supraglottic collapse, and is routinely carried out together with nose and palate surgery if required, according to DISE findings.

In the last years, many palatal techniques have been proposed. The introduction of the Pang ESP technique and, more recently, BRP have changed our OSAHS multilevel surgical setting [10 12 13]. These two techniques soon became our first option with the robot-assisted multilevel procedure.

Recently, the effectiveness of ESP was demonstrated in a meta-analysis by Pang [16]. Moreover, our group reported on the superiority of ESP in a multilevel setting when compared to UPPP [8].

However, in a 2015 study by our group it was shown that the BRP technique is feasible, safe and effective in the management of OSAHS patients [12]. The use of a barbed suture allows to perform a quick procedure and to respect mucosal and muscular structures (Figs. 1, 2).

The purpose of the present study was to show the superiority of ESP and BRP compared to traditional UPPP in a multilevel setting, highlighting the advantages of BRP.

Taking into account the retrospective nature of our study and the limited size of the three groups, our preliminary results may be interpreted as follows. Both BRP and ESP resulted in better postoperative AHI values and higher surgical success rate in comparison with UPPP. On the other hand, BRP was not more effective than ESP.

ESP surgery time was significantly higher than UPPP while BRP was seen to be the quickest procedure. Furthermore, in our series no complications were recorded, likely due to the small size of our sample. However, we assume that the probability of bleeding is significantly lower in BRP patients, as the soft palate and the pharyngopalatine muscle are respected when performing this technique.

No difference in postoperative pain was recorded between groups, probably because all patients underwent tonsillectomy contemporarily.

The higher effectiveness of BRP and ESP may be interpreted considering their more focused action on the lateral wall area. Moreover, the authors feel that circular scarring and tension produce a significantly delayed reduction of oropharyngeal section in UPPP cases. In ESP, the same scar retraction would probably tend to straighten the angle between the plane of tonsillar fossa and the intrapalatal muscular flap, producing a progressive enlarging vector for the lateral wall and palate.

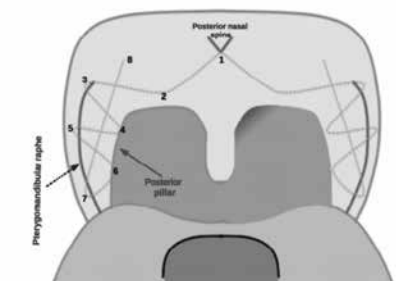


Fig. 1 Descriptive scheme of all BRP steps highlighting the anchoring points for the barbed suture.

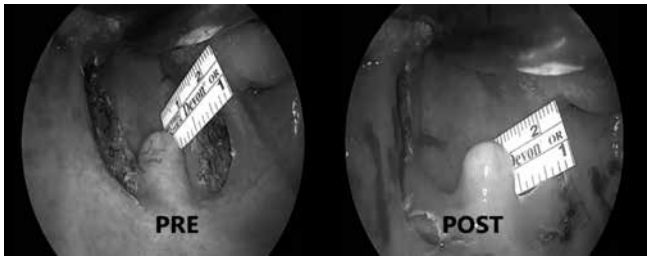


Fig. 2 Pre-operative and post-operative images of a patient treated with a BRP technique: the improvement of the anterior-posterior diameter is shown.

BRP, instead, allows to displace the posterior pillar (palatopharyngeal muscle) in a more lateral and anterior position to enlarge the oropharyngeal inlet as well as the retropalatal space. In a previous study published by our group, it was shown how this technique is easy to learn even for non-experienced surgeons, less time consuming and with no significant complications [12].

Conclusions

ESP and BRP seem to be more effective than UPPP in a multilevel surgical robotic setting. Being quicker, easy to learn and with a low rate of complications, BRP appears to be a safe, effective and promising option for the treatment of OSAHS patients.

References

1 Vicini C, Montevecchi F, Campanini A, et al. *(2014) Clinical outcomes and complications associated with TORS for OSAHS: a benchmark for evaluating an emerging surgical technology in a targeted application for benign disease*. ORL J Otorhinolaryngol Relat Spec 2014;76:63-9.

2 Hoff PT, D'Agostino MA, Thaler ER. *Transoral robotic surgery in benign diseases including obstructive sleep apnea: safety and feasibility*. Laryngoscope 2015;125:1249-53.

3 Lee J, Weinstein G, O'Malley B, et al. *Transoral robot-assisted lingual tonsillectomy and uvulopalatopharyngoplasty for obstructive sleep apnea*. Ann Otol Rhinol Laryngol 2012;121:635-9.

4 Vicini C, Dallan I, Canzi P, et al. *Transoral robotic tongue base resection in obstructive sleep apnoeahypopnoea syndrome: a preliminary report*. ORL J Otorhinolaryngol Relat Spec 2010;72:22-7.

5 Vicini C, Dallan I, Canzi P, et al. *Transoral robotic surgery of the tongue base in obstructive sleep Apnea-Hypopnea syndrome: anatomic considerations and clinical experience*. Head Neck 2012;34:15-22.

6 Friedman M, Hamilton C, Samuelson CG, et al. *Transoral robotic glossectomy for the treatment of obstructive sleep apnea-hypopnea syndrome*. Otolaryngol Head Neck Surg 2012;146:854-62.

7 Meccariello G, Cammaroto G, Montevecchi F, et al. *Transoral robotic surgery for the management of obstructive sleep apnea: a systematic review and meta-analysis*. Eur Arch Otorhinolaryngol 2017;274:647-53.

8 Vicini C, Montevecchi F, Pang K, et al. *Combined transoral robotic tongue base surgery and palate surgery in obstructive sleep apnea-hypopnea syndrome: expansion sphincter pharyngoplasty versus uvulopalatopharyngoplasty*. Head Neck 2014;36:77-83.

9 De Vito A, Carrasco Llatas M, Vanni A, et al. *European position paper on drug-induced sedation endoscopy (DISE)*. Sleep Breath 2014;18:453-65.

10 Pang KP, Woodson BT. *Expansion sphincter pharyngoplasty: a new technique for the treatment of obstructive sleep apnea*. Otolaryngol Head Neck Surg 2007;137:110-4.

11 Fairbanks DN. *Operative techniques of uvulopalatopharyngoplasty*. Ear Nose Throat J 1999;78:846-50.

12 Vicini C, Hendawy E, Campanini A, et al. *Barbed reposition pharyngoplasty (BRP) for OSAHS: a feasibility, safety, efficacy and teachability pilot study*. *"We are on the giant's shoulders"*. Eur Arch Otorhinolaryngol 2015;272:3065-70.

13 Mantovani M, Minetti A, Torretta S, et al. *The velo-uvulopharyngeal lift or "roman blinds" technique for treatment of snoring: a preliminary report*. Acta Otorhinolaryngol Ital 2012;32:48-53.

14 Morgenthaler T, Alessi C, Friedman L, et al. *Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007*. Sleep 2007;30:519-29.

15 Vignatelli L, Plazzi G, Barbato A, et al. *Italian version of the Epworth sleepiness scale: external validity*. Neurol Sci 2003;23:295-300.

16 Pang KP, Pang EB, Win MT, et al. *Expansion sphincter pharyngoplasty for the treatment of OSA: a systemic review and meta-analysis*. Eur Arch Otorhinolaryngol 2016;273:2329-33.

Received: June 25, 2016 - Accepted: October 18, 2016

Address for correspondence: Giovanni Cammaroto, Department of Otorhinolaryngology, University of Messina, Messina, Italy. Tel. +39 090 2212251. E-mail: giovanni.cammaroto@hotmail.com

ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:410-415; doi: 10.14639/0392-100X-1385

Rhinology

Mathematical model for preoperative identification of obstructed nasal subsites

Modello matematico per l'identificazione preoperatoria dei sotto-siti nasali sede di ostruzione

M. GAMERRA[1*], E. CANTONE[2*], G. SORRENTINO[1], R. DE LUCA[3], M.B. RUSSO[4], E. DE CORSO[5], F. BOSSA[6], A. DE VIVO[6], M. IENGO[2]

[1] ENT Unit, "S. Leonardo" Hospital, Castellammare di Stabia, Italy; [2] Department of Neuroscience, ENT Unit, University of Naples "Federico II", Naples, Italy; [3] Department of Physic "E. R. Caianiello", University of Salerno, Salerno, Italy; [4] Department of Engineering Second University of Naples, Italy; [5] Catholic University of the Sacred Heart, A Gemelli Hospital, Department of Head and Neck Surgery, Rome, Italy; [6] Neuro Diagnostic Center "Bossa", Torre del Greco, Italy

* These authors equally contributed to the study and should be considered first authors

SUMMARY

The planning of experimental studies for evaluation of nasal airflow is particularly challenging given the difficulty in obtaining objective measurements in vivo. Although standard rhinomanometry and acoustic rhinometry are the most widely used diagnostic tools for evaluation of nasal airflow, they provide only a global measurement of nasal dynamics, without temporal or spatial details. Furthermore, the numerical simulation of nasal airflow as computational fluid dynamics technology is not validated. Unfortunately, to date, there are no available diagnostic tools to objectively evaluate the geometry of the nasal cavities and to measure nasal resistance and the degree of nasal obstruction, which is of utmost importance for surgical planning. To overcame these limitations, we developed a mathematical model based on Bernoulli's equation, which allows clinicians to obtain, with the use of a particular direct digital manometry, pressure measurements over time to identify which nasal subsite is obstructed. To the best of our knowledge, this is the first study to identify two limiting curves, one below and one above an average representative curve, describing the time dependence of the gauge pressure inside a single nostril. These upper and lower curves enclosed an area into which the airflow pattern of healthy individuals falls. In our opinion, this model may be useful to study each nasal subsite and to objectively evaluate the geometry and resistances of the nasal cavities, particularly in preoperative planning and follow-up.

KEY WORDS: Nose • Manometry • Fluid dynamics • Airflow • Rhinomanometry

RIASSUNTO

La realizzazione di studi sperimentali per la valutazione dei flussi aerei nasali è particolarmente indaginosa, data la difficoltà di ottenere in vivo un'accurata misurazione degli stessi. Inoltre, sebbene la rinomanometria standard e la rinometria acustica rappresentino i metodi più utilizzati nella pratica clinica, esse forniscono solo una misura globale ed approssimativa dei flussi aerei nasali, senza definirne i particolari temporali o spaziali. Allo stesso modo gli studi sulla fluidodinamica computazionale rappresentano solo una simulazione numerica, ben lontana da quelle che sono le variabili anatomiche e fisiologiche delle cavità nasali. Pertanto, ad oggi, non esistono ancora strumenti diagnostici in grado di misurare oggettivamente la geometria delle cavità nasali, le resistenze ed il grado di ostruzione nei diversi sotto-siti nasali, elemento quest'ultimo fondamentale per una corretta programmazione chirurgica. Allo scopo di superare i limiti della diagnostica standard abbiamo elaborato un modello matematico basato sull'equazione di Bernoulli applicata alle cavità nasali di soggetti sani per lo studio dei gradienti pressori di vari sotto-siti nasali, che sono stati misurati grazie ad un particolare manometro digitale. Il nostro studio, unico in letteratura, ha identificato due curve limite che racchiudono un'area rappresentativa entro cui cadono i livelli "normali" di flusso in corrispondenza del vestibolo nasale. Il modello descritto potrebbe essere utile per studiare tutti i sotto-siti nasali sede di ostruzione ai fini di una corretta programmazione chirurgica e di un valido follow-up postoperatorio.

PAROLE CHIAVE: *Naso • Manometria • Fluidodinamica • Flusso aereo • Rinomanometria*

Acta Otorhinolaryngol Ital 2017;37:410-415

Introduction

Nasal obstruction is the most common symptom observed in rhinological practice, afflicting millions of people and accounting annually for over $5.8 billion in healthcare costs in the USA alone [1].

Deviated nasal septum is one of the most common causes of nasal obstruction and septoplasty is the third most common surgery performed by otorhinolaryngologists [2]. However, septal deviation may not always be the only cause of nasal obstruction. Indeed, there are many asymptomatic individuals with nasal deviation and many others suffering from nasal obstruction without septal deviation. Thus, despite successful surgical correction, many patients are not satisfied with the outcomes after septoplasty or nasal surgery in general, which might lead to medico-legal issues. Moreover, some investigators have criticised the high number of unnecessary nasal surgical procedures performed each year [2].

This happens because very often there are other causes responsible for nasal obstruction, such as nasal valve collapse or lateral wall insufficiency, which may alter the physiological dynamics of the nasal airflow.

For instance, in humans the physiological functions of nasal breathing (conditioning, warming and humidifying of inhaled air, smelling, etc.) are closely related to the mechanical properties of fluids [3]. In healthy adults, most of the airflow occurs in the middle meatus, the nasal respiratory rate at rest is about 16 breaths/min and the airflow volume in a single inspiration is about 500 ml. The airflow velocity (V) depends on the strength of breath and on the width of a given nasal subsite, so that during a steady inspiration in standard conditions V is about 2-3 m/sec at the nostril level and 12-18 m/sec at the nasal valve area level [4].

Since the nasal valve and vestibular airflow accounts for 52.6%-78.3% of total nasal airway resistance, these sections are considered the main nasal airflow limiting structures [4]. Thus, this anatomical and physiological narrowing at the "entrance" of the functional segment of the nose causes a significant increase in the velocity of the airflow [5 6] and represents the accelerator of the inspired air. Therefore, any obstruction at this level results in a significant reduction in nasal airflow.

To summarise, effective nasal breathing requires certain airflow volumes, a pressure drop, temperature variations and the right proportions between laminar flow and turbulent flow regions, in addition to the ability to provide sufficient air to the lungs [7].

Hence, from a purely anatomical point of view, changes in the architecture of nasal cavities [8] for pathological disorders, trauma or surgery may alter the nasal resistances and functions and, consequently, the mechanical properties of nasal airflow, which are strongly affected by the geometry of the airflow passage.

Unfortunately, to date, there are no diagnostic tools to objectively evaluate the geometry and mechanical properties of the nasal cavities and to measure nasal resistance and degree of nasal obstruction. Indeed, despite recent advances in the research of nasal diagnostic strategies, the currently available diagnostic tools for the study of nasal airflow and resistance have some limitations and the individual subjective sensations of the patients do not always match objective measurements [9].

For instance, the most widely used methods to evaluate the nasal airflow, standard rhinomanometry (RNM) and acoustic rhinometry (AR), can evaluate changes in overall nasal airflow and resistance, and measure cross-sectional areas in nasal cavity. However, due to the structural and physiological complexity of human nose, these techniques are not able to show sufficient details of dynamic airflow through the nasal cavity to fully evaluate many intranasal conditions and anatomical variations, whereas 4-phase rhinomanometry (4PR) might provide supplementary information; nonetheless, all open technical and mathematical inconsistencies conjoint with this technique have been clarified [9 10].

Furthermore, the numerical simulation of nasal airflow [10 11] as computational fluid dynamics (CFD) technology, whose data are not yet validated, requires such a burden of time and resources that it cannot be routinely used [12].

For all these reasons, the treatment of nasal obstruction in daily clinical practice of otolaryngologists represents a challenge for researchers in constantly searching for reliable objective tests to quantify nasal obstruction.

To overcome these limitations and to objectively measure nasal resistances, the degree and, primarily, the subsite of nasal obstruction, we developed a mathematical model based on Bernoulli's equation applied to clinical practice with the help of the digital DDM-MG1 manometer Endoflower (Gamerra patented, 2007) [6].

Materials and methods

The study was performed in accordance with the principles of the 1983 Declaration of Helsinki and was approved by the local board of medical ethics. Written informed consent was obtained from all participants prior to the inclusion in the study. Forty Caucasian subjects, non-smokers suffering from cephalea and without lung disease or nasal obstruction, underwent nasal endoscopy and computed tomography (CT) scan, previously planned for the cephalea, to exclude anatomic variants or sinonasal diseases. The sample was homogeneous for age, sex and body weight (20 M 20 F; mean age 42.64 ± 13.1; BMI 22.9 ± 2.1 kg/m^2).

To carry out pressure measurements, we used a DDM-MG1 manometer (Gamerra patented, 2007) [6]. Technical characteristics of the digital manometer were as follows: "Auto Zero" adjustable with respect of the atmospheric

pressure; range of measurement = 0 +/- 100 mbar; overrange pressure: max 300 mbar, resolution: 0.1 mbar (between 0 and 70 mbar), 0,2 mbar (between 70 and 100 mbar); accuracy at 23°C: +/- 0.5% mbar (between 0 and 70 mbar); +/- 1% mbar (between 70 and 100 mbar); temperature range: 0° to + 40°C; not condensing humidity: 10 to 90% relative humidity.

Under endoscopic guidance we placed the probe of the manometer in the nasal vestibulum corresponding to the CT imaging of the same subsite. Furthermore, to confirm the exact correspondence between the nasal point and the CT scan we chose a point easily detectable corresponding to the dome, part of the vestibulum.

Subjects were asked to slowly and deeply breathe through the nose for 4 seconds, while the nasal section was checked by video-endoscopy for the entire duration of the examination. The manometer was connected to a computer with software for visualisation and recording of pressure values. Images were acquired with an 8-slice CT scanner (LightSpeed, GE Medical Systems, Milwaukee). The volume datasets were processed by a workstation equipped with OsiriX MD software (release 7.0.3, Pixmeo sarl, Bernex, Switzerland) and axial images were reconstructed in coronal and sagittal planes using the MPR (Multi Planar Reconstruction) protocol integrated in the software. The perimeter of air sections was outlined with "pencil" function to obtain the geometric area measurement in cm^2.

To estimate the airflow rate through a defined nasal section, we developed software depending on the mathematical model, based on an integral equation, concerning the minimum and maximum value of the area delimited by the two curves in Figure 1, carrying out the volume of the nasal inhaled air for each inhalation.

Assuming the validity of Bernoulli's equation, we can calculate the gauge pressure in the vestibulum by considering one central point N within this duct. In this expression, we denote the pressure in N as p_N. By considering a second point O at the entrance of the nasal valve and by taking the pressure in O equal to the atmospheric pressure p_a, we can write:

$$p_N + \frac{1}{2}\rho V_N^2 = p_a \quad (1)$$

where r is the density of air and V_N is the flow velocity in the central part of one section of the nostril, assumed to have circular shape with area S_N for simplicity. By taking a parabolic profile as the one shown in Figure 2, we can write:

$$V(r,t) = V_N(t)\left[1 - \left(\frac{r}{R}\right)^2\right] \quad (2)$$

where r is radial distance from point N, t is the time measured from the beginning of inhalation, and R is the radius of the circular section of area S_N (Fig. 2).

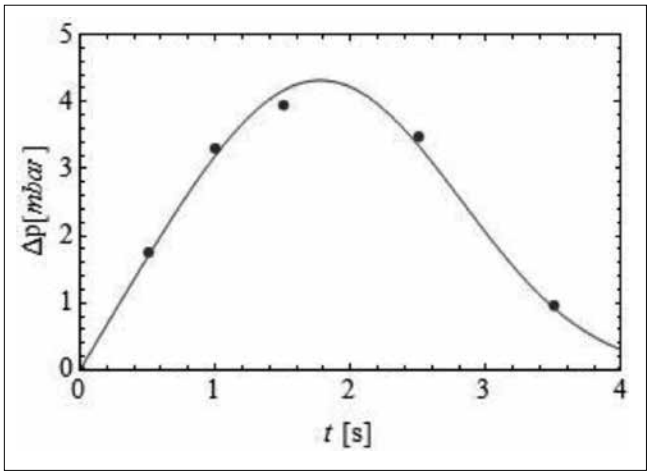


Fig. 1. Minimum and maximum value of the area delimited by the two curves into which the air respiration patterns of healthy people fall.

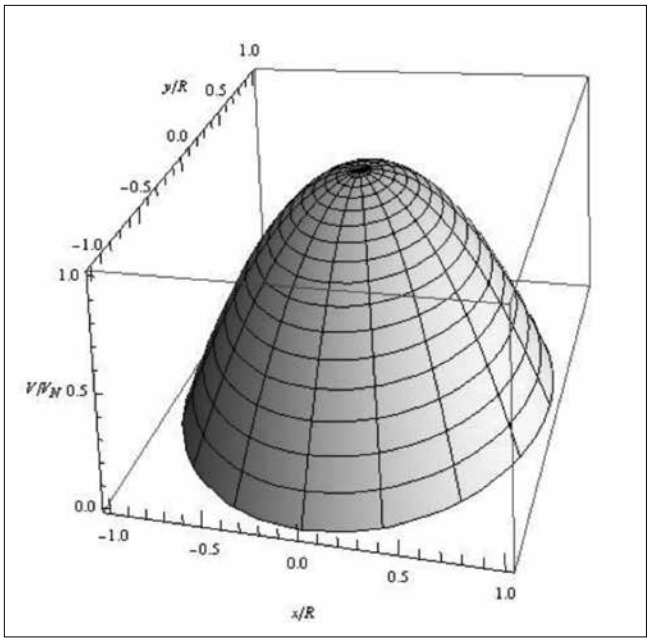


Fig. 2. Parabolic velocity profile of air flowing within a circular duct of radius R.

Notice that in Eq. (1) the velocity profile $V(r,t)$ is taken to depend on time through the time dependence of the velocity V_N. Let us now calculate the flow rate through S_N, so that we write:

$$q(t) = \int_{S_N} V(r,t)\,dS \quad (3)$$

where $dS = 2\pi r\,dr$ is the area of an elementary ring of radius r and thickness within S_N. By performing the integral, we found:

$$q(t) = \frac{S_N}{2} V_N(t) \quad (4)$$

The $K_1 = \int_0^T q(t)\,dt = \frac{S_N}{2}\int_0^T V_N(t)\,dt$ equation is based on the fluid dynamic criterion that the nasal airflow is concentrated in the centre of a hypothetical circumference, because most of the energy pushing the air through the nasal cavity is dissipated for effect of the laminar boundary layer flow (LBLF) against the nasal wall for which it is ineffective (Fig. 2).

Results

No complications were found during nasal manometry. In Table I we report the values of nasal sections expressed in mm^2, pressure in mbar and time in sec. We gathered experimental data for a deep breath of a standard-group subject. Observed data were pressure versus (/) time.
The data showed that the effective velocity regarding the

Table I. Values of nasal sections.

Patient no.	Sect mm^2	mb/t0 = 0s	mb/t1 = 0.5	mb/t2 = 1s	mb/t3 = 1.5	mb/t4 = 2.5	mb/t5 = 3.5	mb/t6 = 4s
1	51	0	1.5	3	3.7	3	0.9	0
2	51	0	1.6	3.3	4	2.8	0.8	0
3	51	0	1.76	3.3	3.96	3.08	0.88	0
4	52	0	1.7	3.5	3.9	3	0.9	0
5	53	0	1.9	3.1	4.2	3.2	0.6	0
6	53	0	1.7	3.5	4.2	3.1	0.7	0
7	53	0	1.8	3.4	4.3	3	0.8	0
8	54	0	1.9	3.5	4.3	2.9	0.8	0
9	54	0	1.9	3.5	4	3.3	0.7	0
10	56	0	2	3.7	4	3.1	0.9	0
11	56	0	1.7	3.9	4.1	3.2	1	0
12	56	0	1.8	4	4	3.1	1.1	0
13	57	0	1.8	3.8	4.5	3.5	1.1	0
14	57	0	1.7	3.8	4.5	3.5	1.1	0
15	57	0	1.8	3.8	4.4	3.2	1.1	0
16	58	0	1.8	3.9	4.5	3.2	1.1	0
17	58	0	1.8	3.9	4.5	3.2	1.1	0
18	58	0	1.8	3.8	4.6	3.2	1.1	0
19	59	0	2.04	3.7	4.5	3.4	1	0
20	59	0	2.1	3.9	4.7	3.3	1	0
21	60	0	2.07	3.89	4.67	3.63	1.03	0
22	60	0	2.06	3.8	4.7	3.53	1	0
23	61	0	2	3.7	4.8	3.4	0.9	0
24	61	0	1.8	3.7	4.9	3.8	0.8	0
25	61	0	2.2	3.7	4.5	3.8	0.8	0
26	62	0	1.9	4.2	4.6	3.5	1	0
27	62	0	1.9	4.1	4.9	3.5	1	0
28	63	0	2	4.7	4.9	3.7	0.9	0
29	63	0	2	4.6	4.8	3.8	0.89	0
30	63	0	2	4.5	4.8	3.8	0.9	0
31	64	0	2.1	4	4.7	3.9	1.1	0
32	64	0	2.1	4.1	4.8	3.9	1.1	0
33	64	0	2.1	4.1	4.8	3.8	1.1	0
34	66	0	2.2	4.2	4.95	3.82	1.1	0
35	66	0	2.3	4.2	4.98	3.8	1.1	0
36	66	0	2	4	5.3	4.1	1	0
37	66	0	1.9	4.3	5.1	3.9	1.1	0
38	67	0	2.3	4.4	5.3	4	1.1	0
39	68	0	2.32	4.3	5.4	4	1	0
40	69	0	2.34	4.2	5.38	4	1	0

Pat = patient; sect. = section of the nose, mm^2; mbar. = millibar; t/s.= time/second.

calculation of airflow rate is one half the time dependent maximum velocity.
In figure 3 we show the average of the standard group measurements as full circles.
By integrating this curve as a function of time we found that the volume of inhaled air in one nostril (K_1) was 221 ml and the total volume (K_2) was 442 ml.
We compared the volume of inhaled air by the standard-group subject with an average reference value (250 ml) for each nostril, as reported in the literature [7].
The standard deviations (SD) for each set of data at a fixed time were then calculated:

$[(t_1)=0.20, s(t_2)=0.34, s(t_3)=0.43, s(t_4)=0.36, s(t_5)=0.14]$.

These statistical parameters suggested the presence of two limiting curves, one below and one above the average representative curve depicted in Figure 1, enclosing an area into which the respiratory pattern of healthy people falls. Therefore, two limiting values of the volume of inhaled air per nostril exist: K_{inf}=191 ml and K_{sup}=267 ml.

Discussion

Nasal surgery aims at improving nasal breathing, yet decisions pertaining to the need for surgical treatment implies a significant degree of subjective judgement by the surgeon [13]. So far, NMR and AR are the most widely used tools to evaluate the nasal airflow, but they provide only a global airflow measurement, without temporal or spatial details. Furthermore, these methods do not suffice to reliably guide the surgeon in the choice of the best therapeutic strategy [14]. In addition, they do not provide information about local details of nasal airflow, often of utmost importance from a clinical standpoint. Although AR [10] produces a more detailed evaluation of the geometry of the nasal cavities, it does not evaluate the flow field, but only the geometric boundaries. Indeed, previous studies [15] showed the validity of AR in the evaluation of functional outcomes following endoscopic surgery in correlation with volumetric CT, but it did not provide any information on the physiology of nasal pressures [16].
Unlike NMR or AR, CFD showing the airflow characteristics in 3D can make accurate predictions about the variables of fluids in a computer model [17]. For instance, many authors made airflow calculations by reconstructing the nasal geometry from CT sequences of healthy subjects, whose nose was assumed to be normal in terms of flow and symmetry [18]. However, they pointed out some challenging aspects related to the geometric complexity of nasal airways: the non-uniqueness of standard measurement of engineering type procedures applied to humans, the presence of physical phenomena implicated (viscosity, flow conditions, Reynolds number, wall roughness, heat transfer, humidity, fluid tissue interaction, turbulence) and, most important, the fact that CFD studies are only

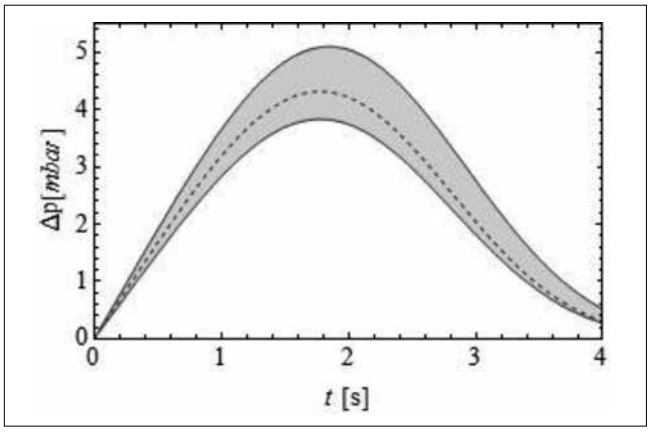


Fig. 3. Fitting experimental data of gauge pressure in the nasal valve by means of the continuous function Δp(t) = A t exp(- B t3) with A = 3.3914 and B = 0.05951, we depicted an area into which the air respiration patterns of healthy people fall.

simulations and the predicted results derived from complex calculations of the Navier-Stokes equation, which may not represent real-life conditions [10 18].
In our study, we evaluated the nasal airflow by means of a mathematical model based on the validity of Bernoulli's equation in the central part of the nostril. To take account of nasal airflow viscosity, we applied a quadratic velocity profile in the nostril, whose section was assumed to be circular for simplicity. Under these assumptions experimental data, reporting the gauge pressure Δp_N inside the nostril as a function of time, were gathered by DDM-MG_1 Endoflower that allowed to study the pressure inside the nose, pointing the probe in the specific nasal subsite we wanted to investigate [19 20].
The inner nasal structures were assimilated to a sequence of tubes under stationary conditions in which single particles close to the centre of the flow described laminar trajectories without energy loss [21]. Although this model represents a valid approximation for airflow away from the ducts, a viscous effect could be considered in the proximity of the walls of the nasal cavity. Therefore, in our model we assumed the validity of Bernoulli's equation in the central part of the duct, where the gradient of the velocity profile could be considered to be negligible. To achieve mathematical computed values of the volume of air during a single inhalation act, obtained pressure values were processed with data from the corresponding CT scan slide.
We found that the average inhaled air volume in a single nostril in a standard-group subject during a deep breath was 221 ml, with an overall volume of 442 ml. Conversely, the literature reports values of 250 ml and 500 ml, respectively [18].
Our study, for the first time, identified two limiting curves, one below and one above an average representative curve, describing the time dependence of the gauge pressure inside a single nostril. These upper and lower curves enclosed an area into which the airflow pattern of healthy people falls. Two limiting values of the volume of inhaled

air per nostril, K_{inf}=191 ml and K_{sup}=267 ml, were found. It can be argued that in order to measure nasal airflow a CT scan is needed and this would limit the clinical usefulness of the model. However, CT is not strictly necessary as the probe is placed under endoscopic guidance, which allows the perfect positioning of the probe at the chosen subsite. It is also to be considered that CT is often performed in any case as a diagnostic and preoperative tool for surgical planning.

Conclusions

In conclusion, despite recent advances in nasal diagnostics, there are still open questions on the management of nasal obstruction and on the opportunity to perform nasal surgery [22 23]. Furthermore, given the lack of reliable tools to objectively measure nasal resistances and to identify the right subsite of nasal obstruction, the goal of this study was to allow clinicians to obtain pressure measurements over time at various subsites of nasal airway to identify which ones are obstructed. In the present study, a mathematical model has been applied to healthy subjects to assess the normal range of resistances, with the aim to compare, in future studies, these data with those from subjects with nasal obstruction at different subsites [18].

Acknowledgments

We are also deeply indebted to Anna Marino, MD, for her cooperation.

References

1 Zhao K, Blacker K, Luo Y, et al. *Perceiving nasal patency through mucosal cooling rather than air temperature or nasal resistance*. PLoS ONE 2011;6: e24618.

2 Hong SD, Lee NJ, Cho HJ, et al. *Predictive factors of subjective outcomes after septoplasty with and without turbinoplasty: can individual perceptual differences of the air passage be a main factor?* Int Forum Allergy Rhinol 2015;5:616-21.

3 Zojaji R, Keshavarzmanesh M, Bakhshaee M, et al. *The effects of inferior turbinoplasty on nasal airflow during cosmetic rhinoplasty.* Acta Otorhinolaryngol Ital 2016;36:97-100.

4 Yu S, Liu Y, Sun X, et al. *Influence of nasal structure on the distribution of airflow in nasal cavity.* Rhinology 2008;46:137-43.

5 Eichhorn KW, Schneider B, Bley TA, et al. *CT rhinometry: a correlation of rhinomanometry and multiplanar computer tomography of the nasal cavity*. HNO 2012;60:1067-74.

6 Gamerra M, De Luca R, Pagano G, et al. *The nose and sinus manometry: a bio-physical model applied to functional endoscopic sinus surgery.* J Biol Regul Homeost Agents 2013;27:1021-7.

7 Huizing EH, De Groot Johan AM. *Functional Reconstructive Nasal Surgery.* Stuttgard: Thieme; 2003.

8 Cantone E, Castagna G, Ferranti I, et al. *Concha bullosa related headache disability*. Eur Rev Med Pharmacol Sci 2015;19:2327-30.

9 Clement PA, Halewyck S, Gordts F, et al. *Critical evaluation of different objective techniques of nasal airway assessment: a clinical review*. Eur Arch Otorhinolaryngol 2014;271:2617-25.

10 Wang de Y, Lee HP, Gordon BR. *Impacts of fluid dynamics simulation in study of nasal airflow physiology and pathophysiology in realistic human three-dimensional nose models*. Clin Exp Otorhinolaryngol 2012;5:181-87.

11 Sung Kyun K. *Yang N, Jee-In K, et al. Patient specific CFD models of nasal airflow: overview of methods and challenges*. J Biomech 2013;46:299-306.

12 Tan J, Han D, Wang J, et al. *Numerical simulation of normal nasal cavity airflow in Chinese adult: a computational flow dynamics model.* Eur Arch Otorhinolaryngol 2012;269:881-9.

13 Cantone E, Castagna G, Sicignano S, et al. *Impact of intranasal sodium hyaluronate on the short-term quality of life of patients undergoing functional endoscopic sinus surgery for chronic rhinosinusitis*. Int Forum Allergy Rhinol 2014;4:484-7.

14 Ting L, Demin H, Jie W, et al. *Effects of septal deviation on the airflow characteristics: using computational fluid dynamics models*. Acta Oto-Laryngologica 2012;132:290-8.

15 Yang N, Kang Soo C, Seung-Kyu C, et al. *Effects of single-sided inferior turbinectomy on nasal function and airflow characteristics*. Respir Physiol Neurobiol 2012;180:289-97.

16 Kass ES, Salman S, Montgomery WW. *Manometric study of complete ostial occlusion in chronic maxillary atelectasis.* Laryngoscope 1996;106:1255-8.

17 Wide K, Sipila J, Suonpaa J. *The value of computerised rhinomanometry and a simple manometry with saline in predicting the outcome of patients with acute trephined frontal sinusitis.* Rhinology 1996;34:151-5.

18 Anthony TR, Anderson KR. *Computational fluid dynamics investigation of human aspiration in low-velocity air: orientation effects on mouth-breathing simulations.* Ann Occup Hyg 2013;57:740-57.

19 Gamerra M, Bruno R, Pagano G, et al. *The nose function and aesthetic.* Ann Otorhinolaringology Iber-Amer 2004;31:307-23.

20 Bertrand B, Collet S, Betsch C, et al. *Diagnostic techniques in chronic sinusitis: endoscopy, sinusomanometry.* Acta Otorhinolaryngol Belg 1997;51:259-69.

21 De Luca R, Gamerra M, Sorrentino G, et al. *Nose and sinus air flow model*. Natural Science 2014; 6:685-90.

22 De Corso E, Bastanza G, Di Donfrancesco V, et al. *Radiofrequency volumetric inferior turbinate reduction: long-term clinical results*. Acta Otorhinolaryngol Ital 2016;36:199-205.

23 Zojaji R, Keshavarzmanesh M, Bakhshaee M, et al. *The effects of inferior turbinoplasty on nasal airflow during cosmetic rhinoplasty*. Acta Otorhinolaryngol Ital 2016;36:97-100.

Received: August 10, 2016 - Accepted: October 23, 2016

Address for correspondence: Elena Cantone, Department of Neuroscience, ENT Unit, University of Naples "Federico II", via Pansini, 5 80100 Naples, Italy. Tel. +39 081 7463598. Fax +39 081 7463592. E-mail: elena.cantone@unina.it

ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:416-422; doi: 10.14639/0392-100X-1493

Audiology

Cochlear implant in prelingually deafened oralist adults: speech perception outcomes, subjective benefits and quality of life improvement

Impianto cocleare in adulti con ipoacusia prelinguale e riabilitazione di tipo oralista: percezione del linguaggio, benefici soggettivi e miglioramento della qualità della vita

F. FORLI[1], G. TURCHETTI[2], G. GIUNTINI[1], S. BELLELLI[2], S. FORTUNATO[1], L. BRUSCHINI[1], M.R. BARILLARI[3], S. BERRETTINI[1, 4]

[1] ENT, Audiology and Phoniatric Unit, University of Pisa, Italy; [2] Istituto di Management, Scuola Superiore Sant'Anna, Pisa, Italy; [3] Dipartimento di Salute Mentale e Fisica e Medicina Preventiva, Divisione di Audiologia e Foniatria, II Università di Napoli, Italy; [4] Department of Clinical Science, Intervention and Technology, Karolinska Institutet, 17177, Stockholm, Sweden

SUMMARY

The aim of this study is to report our results in a group of prelingually deafened adults, who followed an oralist rehabilitation programme, and submitted to cochlear implant at our institution. We evaluated 30 prelingually deafened adult patients, 18 males and 12 females, median age 35 years, of a group of 36 prelingually deafened adult patients consecutively submitted to unilateral cochlear implantation at the ENT Unit of the University of Pisa. After implantation, patients achieved significant benefits in terms of speech perception skills, including the ability to have telephone conversations in some cases, quality of life and their own perception of disability. According to literature data, the results herein reported are quite variable but generally satisfactory. Procedures other than traditional speech perception measures should be used to evaluate the benefits of cochlear implant in such patients, to compressively evaluate the global benefits, not only in terms of speech perception, but also in terms of quality of life and daily life.

KEY WORDS: Prelingual deafness • Cochlear implant • Quality of life

RIASSUNTO

Lo scopo di questo studio è riportare i risultati ottenuti in un gruppo di pazienti adulti con ipoacusia prelinguale, che hanno seguito un programma di riabilitazione di tipo oralista, sottoposti ad impianto cocleare nella nostra clinica. Sono stati analizzati 30 pazienti adulti, 18 maschi e 12 femmine, con un'età media di 35 anni, selezionati da un gruppo di 36 adulti con sordità prelinguale sottoposti ad impianto cocleare unilaterale nella U.O. Otorinolaringoiatria, Foniatria ed Audiologia Universitaria di Pisa. Dopo la procedura di impianto cocleare i pazienti hanno raggiunto significativi benefici in termini di percezione del linguaggio, inclusa la capacità di avere una conversazione telefonica in qualche caso; benefici sono stati raggiunti anche riguardo la qualità della vita e la percezione della propria disabilità. In accordo con i dati riportati in letteratura i risultati da noi presentati sono variabili ma generalmente soddisfacenti. Per valutare i benefici dell'impianto cocleare nei pazienti riportati in questo studio devono essere considerate altre procedure oltre a quelle tradizionali di valutazione della percezione verbale, così da poter apprezzare complessivamente i benefici, non solo in termini di percezione verbale ma anche di miglioramento della qualità della vita quotidiana.

PAROLE CHIAVE: *Sordità prelinguale • Impianto cocleare • Qualità della vita*

Acta Otorhinolaryngol Ital 2017;37:416-422

Introduction

Cochlear implantation is the treatment of choice for patients affected with severe to profound sensorineural hearing loss [1-5]. Until the mid 1990s, these patients were considered poor CI candidates, because improvement in speech perception was limited. However, several recent studies have suggested that the latest implant technology results in open-set speech perception abilities, although variability among individuals was great and performance lagged behind that of post-lingually deafened adults [6-10]. These conclusions are mainly based on results obtained in small and heterogeneous samples [7 8 11 12].

It is useful to underscore that in Italy since the sixties oralism has been the main rehabilitative choice for patients suffering with preverbal deafness. As a consequence, in Italy the vast majority of adult patients with preverbal

deafness seeking a CI consistently using hearing aids, have been following an oralist rehabilitation mode and developed oral language, even if at variable degrees of performance.

The aim of this study was to report our results in a group of 30 prelingually deafened adults, who followed an oralist rehabilitation program, and submitted to CI in our institution. Gains in speech perception abilities and subjective benefits are reported, as well as benefits in the quality of life. A correlation with individual factors is provided in order to define the impact of the different variables on outcomes.

Materials and methods

The sample was composed of 30 prelingually deafened adult patients, 18 males and 12 females, median age 35 years (IQR (interquartile range): 28-42, range: 16-54) of a group of 36 prelingually deafened adult patients (83%) consecutively submitted to unilateral cochlear implantation at the ENT Unit of the University of Pisa (Italy), during the period from July 1999-July 2011. All prelingually deafened adult patients implanted in our institution were oral language users and consistently used hearing aids before implantation. The 30 patients enrolled in the study are those who gave their consent to participate to the study. Among the 6 implanted patients not included in the study sample, one is a not user, one has not come for follow-up at our centre for many years and the others do not come frequently for follow-up visits, as they live far from the centre.

Pre-operatively, all patients were submitted to comprehensive audiological evaluation, including a speech perception test [13] without lip-reading with hearing aids, neuroradiological evaluation by petrous bone high resolution computed tomography (CT) and brain and inner ear magnetic resonance (MR). Aetiology of hearing loss was also investigated by molecular analysis of the connexin 26 and 30 genes, and mitochondrial DNA A1555G mutation analysis in all cases, and PDS gene mutation analysis in patients with a large vestibular aqueduct. The most salient features of patients are summarised in Table I.

Post-operatively, during follow-up visits, all patients were assessed by pure tone audiometry in a free field with the CI in use and to a speech perception test [13] without lip-reading with the CI in use.

Pure-tone audiometry was conducted with an Interacoustics Clinical Audiometer AC40. When measuring the hearing threshold, both without HA and with HA, we assigned a value of 125 dB to any frequency threshold over the maximum output limit of the audiometer (105 dB for 0.25 KHz and 125 dB for 0.5 and 1 KHz, 120 dB for 2 KHz). Any vibrotactile sensation was excluded.

Speech perception was assessed using a speech perception test in Italian language [13] both before (with hearing aids) and after implantation (with CI) in free field, by the same speech therapist in all the patients to avoid bias, with live voice, and without lip-reading. We evaluated the disyllabic words recognition score using lists of 20 disyllabic Italian words at a level of 65 dB.

In order to obtain information about personal factors and subjective benefits from CI, at the moment of the study setup we administered a questionnaire "University of Pisa Questionnaire" (UPQ) to all enrolled patients. This questionnaire was specifically developed by our research team and is a 40 question survey, divided into 3 sections. In the first section, pre-operative information, such as type of hearing aid, ability to have telephone conversations, perception of music and rehabilitation are collected; in the second section, the same aspects after implantation are investigated; in the third section, information about social life, education level and working life are recorded.

Patients were also submitted to the APHAB questionnaire to assess improvement in the patients' own perception of the disability and in quality of life derived from CI procedure.

Table I. Summary of salient patient features.

	All patients
Patients, n (%)	30 (100%)
Males, n (%)	18 (60%)
Use of hearing aids before implantation, n (%)	30 (100%)
Oral language users, n (%)	30 (100%)
Presence of additional disabilities associated to deafness, n (%)	0 (0%)
Age at diagnosis (years), median (IQR)	2.5 (1-3)
Age at diagnosis (years), range (min-max)	0.5-6
Progression of hearing loss, progressive, n (%)	19 (63%)
Progression of hearing loss, stable, n (%)	11 (37%)
Presence of anomalies of the cochlea	0 (0%)
Aetiology of hearing loss:	
Genetic (Connexin 26 mutation), n (%)	2 (7%)
Large vestibular aqueduct syndrome, n (%)	3 (10%)
Prenatal infection, n (%)	4 (13%)*
Postnatal infection, n (%)	1 (3%)**
Unknown, n (%)	20 (67%)
Cochlear Implant	
Freedom Contour Advance, n (%)	11 (37%)
Nucleus CI24M, n (%)	4 (13%)
Nucleus 24 Contour, n (%)	3 (10%)
Nucleus 24 Contour Advance, n (%)	10 (33%)
CI512, n (%)	2 (7%)
Speech Processing Strategy	
ACE, n (%)	27 (90%)
SPEAK, n (%)	3 (10%)

*Note: *4 patients (3 fetopathy rubella, 1 toxoplasmosis); **1 patient (mumps at 2 years) IQR, interquartile range*

Table II. Summary of subjective benefits after implantation, collected using the UPQ.

Questions	Before implantation		After implantation	
	Yes	No	Yes	No
Have telephone conversations, n (%)	2 (7%)*	28 (93%)	18 (60%)**	12 (40%)
Understand television without reading subtitles***, n(%)	1 (3%)	28 (93%)	9 (30%)	20 (67%)
Listen to music††, n(%)	16 (54%)	10 (33%)	23(77%)	7(23%)
With CI the human voice seems to be‡	It doesn't change 3% More natural 77% Metallic 11% Shrilly 8%			

*Note: *1 patient can have free conversations with unfamiliar people; **5 patients can have free conversations with unfamiliar people; *** 3% missing data pre- and post-operatively; ††13% missing pre-operative data, ‡1% missing data*

The questionnaire was administered both before and after implantation at the moment the study was initiated. Quality of life (QoL) was measured in all the patients after implantation and at the moment of study initiation by using the Italian version of the Short Form-36 Health Survey, version 1 (SF36 v1). Authorisation from the company was obtained. The SF36 is a generic QoL questionnaires that, through a 36-item short form survey, assesses eight health scale scores in relation to physical functioning, role-physical, physical pain, general health, vitality, social functioning, role-emotional, mental health) [14]. The SF36 scores estimated from the studied sample were compared to that reported in the Italian literature for normal hearing subjects and to that reported for hearing impaired subjects [15].

Finally, we studied the relationship between the results, in terms of speech perception with CI, and age at the first hearing aid fitting, progression of hearing loss, pre-operative PTA without hearing aids and pre-operative PTA with hearing aids in order to find any possible associations.

The mean follow-up duration after surgery was 6.2 years, ranging from 1 to 13 years.

Statistical analysis

Statistical analysis was performed with the aim to investigate differences between the pre-operative and the post-operative speech perception abilities and health conditions of patients. The distribution of numeric variables was assessed by the Shapiro-Wilk W test for normality. Comparisons between pre- and post-CI intervention patients data were conducted using the Wilcoxon matched-pairs signed-ranks test for non-parametric distribution of continuous variables and the McNemar's chi-squared test for categorical variables. The difference between paired data was considered statistically significant with a $p < 0.05$. Using the quantile regression model, we examined the relationship between the post implantation open-set speech recognition score and selected patient characteristics (covariates) such as as age at first hearing aid fitting, pre-operative PTA with hearing aids and progression of hearing loss, as well as the APHAB scales and SF36 scales for the 50th percentile. Compared with the traditional linear model, quantile regression is robust for departures from normality and heteroscedasticity assumptions in the response variable [16].

Statistical analyses have been performed using the statistical software Stata 12.1 (Stata Corp, College Station, Texas USA).

Results

The mean pre-operative hearing threshold in the implanted ear (pure tone audiometry - PTA between 0.5-1-2 KHz) was 111.08 dB (range 93 dB-125 dB). The mean pre-operative PTA in free field with hearing aids was 54.6 dB (range 31.6 dB-125 dB).

The mean pre-operative speech perception score was 15.7% (range 0-50). Before implantation, 7% of the patients were able to have telephone conversations.

After implantation, the mean pure tone audiometry (PTA between 0.5-1-2 KHz) in free field with the speech processor on was 34.7 dB (range 25-51.6 dB).

With regards to speech perception skills, the mean post-operative open-set words recognition score was 60% (range 0-100%) Two of 30 patients scored 0%. The improvement in terms of speech perception was statistically significant ($p = 0.000$).

After implantation, 60% of patients are able to have telephone conversations. The difference between the proportion of patients able to have telephone conversations before and after implantation was significant ($p = 0.000$).

The most significant data, regarding subjective benefits after implantation, collected at the UPQ questionnaire are shown in Table II.

Results of APHAB scales are reported in Table III.

The norm-based scores of the SF36 eight scales measured in prelingual deafened patients revealed a significant improvement after CI intervention compared to the before situation in terms of general health, social functioning and mental health as reported in Table IV.

In the post-intervention framework, a significant as-

Table III. Results of APHAB scales before and after the cochlear implant intervention.

	Pre CI	Post CI	p*
EC scale median (IQR)	54.2 (41.7-74.7)	37.5 (16.5-46.2)	<0.005
BN scalemedian (IQR)	64.3 (41.8-87.0)	47.8 (33.7-56.2)	<0.005
RV scale median (IQR)	70.7 (54.2-82.7)	54.2 (33.7-66.3)	<0.005
AV scale median (IQR)	8.3 (1-26.8)	31.7 (8.3-49.8)	<0.005

*Note: *Wilcoxon signed-rank test, CI, Cochlear implant. IQR, interquartile range (25° percentile-75° percentile), EC, ease of communication; BN, background noise; RV, reverberation; AV, aversiveness*

sociation was found between disyllabic word recognition scores and the Ease of Communication scale of the APHAB questionnaire ($p = 0.030$). Considering the other scales of the APHAB questionnaire and the eight scales of the SF36 questionnaires, we found no significant associations between each scale and disyllabic word recognition scores after CI intervention.

From the univariate quantile regression model, there are no evidence of statistically significant associations between post-implantation open-set speech recognition score and age at first hearing aid fitting, pre-operative PTA without hearing aids and pre-operative PTA with hearing aids ($p > 0.05$). Nevertheless, we found a significant association between post-implantation open-set speech recognition score and progression of hearing loss ($p < 0.05$).

Discussion

In the present paper, we report the results achieved in a group of 30 oralist prelingually deafened adults, submitted to CI.

Cochlear implantation in prelingual adult patients is still a true challenge since it requires a difficult decision making process for both clinicians and patients due to the uncertainty of the outcome and the risk of obtaining poor or no improvement in speech perception and stopping to use the implant; nevertheless, an increasing number of recent studies attest the efficacy of CI even in these cases, albeit with variable results [6-9 17-19].

In a recent systematic review of the literature on effectiveness and cost-efficacy of CI in children and adults, we reported that cochlear implantation is both clinically- and cost-effective even in adults with prelingual deafness [1 2].

In the sample herein, the results in terms of speech perception skills are quite satisfactory. After implantation, we recorded a significant improvement in *open-set* speech recognition scores: before implantation the mean *open-set* speech recognition score was 15.7% and after implantation it increased to 63.6%. Moreover, before surgery 7% of the patients were able to have telephone conversations, while after implantation 60% of patients were able, even if at various degrees of ability.

Most of the studies reporting post-implantation results in prelingual deafness have focused on speech perception results and only a few have dealt with patient satisfaction, subjective benefits and impact of CI on the quality of life. Studies investigating the impact of cochlear implantation on the quality of life in prelingually deaf adults found that, even when the results are poor in terms of speech perception abilities, participants reported satisfaction with the CI procedure. These observations suggest that measures other than speech perception test should be used to evaluate the benefit of a CI in this population, and therefore benefit and performance should be viewed as two separate outcomes [3-5 8 9 20].

In the present study, at the UPQ questionnaire we recorded an improvement in the ability to carry out some daily life activities such as the use of the telephone and the abil-

Table IV. Comparison between the norm-based scores of the 8 SF36 domains in the sample of prelingually deafened patients before and after the cochlear implant intervention.

	Pre CI		Post CI		p*
	Median	IQR	Median	IQR	
Physical Functioning (PF)	57.2	55.1-57.2	57.2	55.1-57.2	0.516
Role-Physical). (RP)	56.2	49.2-56.2	56.2	49.2-56.2	0.415
Body Pain (BP)	62.8	47.3-62.8	62.8	51.6-62.8	0.271
General Health (GH)	57.9	50.9-61.7	60.3	54.6-61.7	0.003
Vitality (VT)	53.8	46.7-60.9	56.2	51.4-63.3	0.107
Social Functioning (SF)	46.3	35.4-57.2	49.0	40.9-57.1	0.026
Role-Emotional (RE)	55.3	44.8-55.3	55.3	55.3-55.3	0.138
Mental Health (MH)	45.9	39.1-55.0	52.7	45.9-55.0	0.004

IQR, Interquartile Range (25° percentile-75° percentile)

* *Wilcoxon signed-rank test*

ity to listen to television and music. After implantation, 60% of the patients (n = 18) were able to have telephone conversations and 28% of these (n = 5) were able to have free telephone conversations even with unknown persons. In addition, 30% of patients were able to listen to television without reading subtitles, compared to only 3% before implantation. Furthermore, 77% of patients reported that after implantation the perception of music improved and 70% of patients indicated that with CI the perception of voice was more natural than with hearing aids (see Table I).

Concerning the results of the APHAB questionnaire, we recorded significant improvement after surgery in terms of median frequency of troubles while hearing in each of the four situations investigated by the questionnaire, such as ease of communication, background noise, reverberation and aversiveness *($p < 0.05$).* Substantial improvements due to CI interventions were observed for ease of communications and background noise: median benefit 24.8 (IQR: 0-49.5, *$p = 0.003$*) and 16.2 (IQR: *3.7-40.5, $p = 0.000$*).

With regards to the SF 36 questionnaire, our patients reported very high scores after CI intervention. The patient's own quality of life perception after CI intervention was very similar to that of the normative sample of healthy Italian subjects, and even better for some aspects. Patients scored as well as the normative healthy sample for physical health, in terms of Physical Activity, Role and Physical Health and Physic Pain, and for mental health in terms of Role and Emotional Status. Implanted prelingually deafened patients did not experience limitations or pain due to their health condition in work or domestic activities nor problems resulting from emotional status. The general health and the mental health subjective perception was better in the sample of patients with CI than that of healthy patients. Implanted patients experienced lower scores for Vitality and Social Activities as compared to healthy subjects (median score: 70 (IQR: 60-85) versus 75 (IQR: 65-85) and 81.3 (IQR: 63-100) versus 87.5 (IQR: 75-100).

When comparing the scores recorded at SF 36 in our sample to the normative sample of Italian hearing impaired patients, our sample scored better than the normative sample in every aspect except for Role and Emotional State, where they achieved the same score (see Fig. 1).

The SF36 scores obtained in our sample of prelingually deafened patients have to be interpreted with much caution, as they are related to subjective evaluations on their own perception of quality of life. Moreover, the sample is small and in some subscales we recorded a high variability in answers. The comparison between our sample and the Italian normative one has some limitations due to the self-reported conditions identifying the Italian healthy group (mean age 34.8 years, age > 65 years 3.7%, female gender 46.8%) and the Italian hearing impaired group (mean age 63 years, age > 65 years 50.7%, female gender 45%).

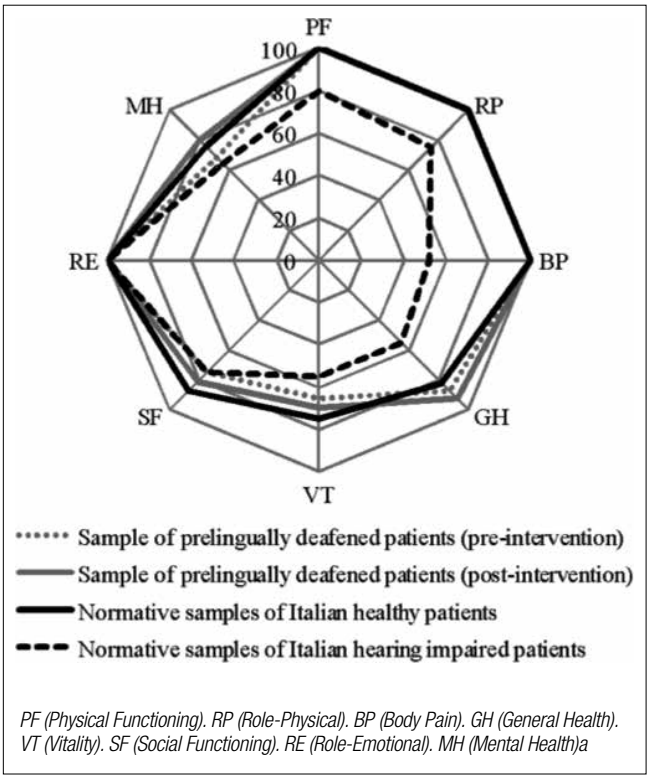


Fig. 1. Radar chart showing SF36 domains in the sample of prelingually deafened patients (pre-intervention and post-intervention) and in normative samples of Italian hearing impaired patients and healthy patients.

According to literature data, even in the reported group, patients who did not achieve improvements in terms of open set speech recognition abilities reported substantial benefits in daily life activities and in the QoL.

It is well known that the outcome after CI in prelingually deafened adults is quite variable and is best shown in the work by Klop et al (2007) [8]. This is likely to be related to the wide variability of the characteristics of patients. Post-implantation benefits both in adults and children is related to several individual factors, and this is mostly true in the case of pre-lingually deafened adults. Pre-operative factors that seem to make a significant contribution to post-operative hearing performance are age at onset of hearing loss and at first hearing aid fitting, speech perception performance with hearing aids [6 7 11 12 21], residual hearing [21], communication mode [21], type of rehabilitation, educational environment [21], motivation and psychological aspects [21 6 7 11 12].

Moreover, Dijkhuizen et al. in 2011 reported that speech intelligibility is predictive of post-implantation hearing results in a group of prelingually deafened adults, using a specifically developed test battery [22] and in a recently published paper has confirmed this [23].

With regards to predictive factors in prelingually deafened adult patients, it has to be undescored that prelingually deafened adults have some peculiar aspects, as they have never experienced normal hearing in life and

thus their neural system lacks the spatial and structural organisation for auditory processing. The literature ì suggests that the colonisation of the auditory cortex by other sensory modalities is the main limiting factor in post-implantation performance, and not the pathological degenerative changes of the auditory nerve, cochlear nucleus, or auditory midbrain [11 12]. Consequently the educational programs that stress oral communication as the preferred educational modality could potentially reduce the cortical colonisation of the central speech and language processing centres, and consequently the use of oral communication should be an important candidacy criterion in cochlear implantation of patients with long-term prelingual deafness. Moreover, some recent studies have explored the role of early auditory input on CI performance in prelingually deafened adults, and it was concluded that the availability of effective auditory input in early life may be the fundamental factor underlying the potential for speech perception with a CI in later life [11 12 7].

Considering the sample herein reported, a relatively high percentage of the patients (63%) experienced a progression of hearing loss. These patients presumably had a better auditory input early in life. We believe that this factor, associated with oralism as an exclusive mode of rehabilitation, played an important role in achieving satisfactory results reported, also in terms of *open-set* speech recognition abilities and consequently in the ability to have telephone conversations. In this regard, we recorded a statistically significant correlation between post-operative dysillabic word recognition score and progression of hearing loss ($p < 0.05$) in our sample; nevertheless, we did not find a significant correlation between post-operative results and pre-implant hearing threshold either with or without hearing aids and age of first hearing aid fitting.

Conclusions

In conclusion, our results demonstrate that cochlear implantation is an effective option for prelingually deafened adult patients.

In accordance with the literature data, the results reported herein are quite variable but generally satisfactory, both in terms of improvement of speech perception abilities and in terms of improvement of the quality of life and patients' perception of their disability.

Indeed, some individual factors significantly affect the results, and among these effective auditory input in early life and oralist rehabilitation mode seem to be the fundamental factors underlying the potential for speech perception with a CI later in life [6 7 11 12 21]. In this regard, we found a significant correlation between the progression of hearing loss and post-operative results. Such patients had experienced a relatively good and effective auditory input early in life, and this allowed their auditory cortex to develop properly, which in turn allowed them to gain satisfactory results in terms of speech perception after implantation.

Therefore, the indications to CI and prognostic factors must be discussed on a case by case basis, taking into account mainly the progression of hearing loss, hearing aid use and results before implantation, rehabilitation mode, motivations and psychological aspects, and it is important to perform accurate counselling to provide patients with realistic expectations.

References

1. Turchetti G, Bellelli S, Palla I, et al. *Systematic review of the scientific literature on the economic evaluation of cochlear implants in adult patients*. Acta Otorhinolaryngol Ital 2011;31:319-27.
2. Berrettini S, Baggiani A, Bruschini L, et al. *Systematic review of the literature on the clinical effectiveness of the cochlear implant procedure in paediatric patients*. Acta Otorhinolaryngol Ital 2011;31:281-98.
3. Peasgood A, Brooks N, Graham J. *Performance and benefit as outcome measures following cochlear implantation in non-traditional adult candidates: a pilot study*. Cochlear Implants Int 2003;4:171-90.
4. Schramm D, Fitzpatrick E, Séguin C. *Cchlear implantation for adolescents and adults with prelinguistic deafness*. Otol Neurotol 2002;23:698-703.
5. Zwolan TA, Kileny PR, Telian SA. *Self-report of cochlear implant use and satisfaction by prelingually deafened adults*. Ear Hear 1996;17:198-210.
6. Kaplan DM, Shipp DB, Chen JM, et al. *Early-deafened adult cochlear implant users: assessment of outcomes*. J Otolaryngol 2003;32:245-9.
7. Santarelli R, De Filippi R, Genovese E, et al. *Cochlear implan-tation outcome in prelingually deafened young adults*. A speech percep-tion study. Audiol Neuro-otol 2008;13:257-65.
8. Klop WMC, Briaire JJ, Stiggelbout AM, et al. *Cochlear implant outcomes and quality of life in adults with prelingual deafness*. Laryngoscope 2007;117:1982-7.
9. Chee GH, Goldring JE, Shipp DB, et al. *Benefits of cochlear implantation in early-deafened adults: the Toronto experience*. J Otolaryngol 2004;33:26-31.
10. Bosco E, Nicastri M, Ballantyne D, et al. *Long term results in late implanted adolescent and adult CI recipients*. Eur Arch Otorhinolaryngol 2013;270:2611-20.
11. Teoh SW, Pisoni DB, Miyamoto RT. *Cochlear implantation in adults with prelingual deafness. Part I: Clinical results.* Laryngoscope 2004;114:1536-40.
12. Teoh SW, Pisoni DB, Miyamoto RT. *Cochlear implantation in adults with prelingual deafness. Part II. Underlying constraints that affect audiological outcomes.* Laryngoscope 2004;114:1714-9.
13. Burdo S. *Protocollo comune di valutazione dei risultati in audiologia riabilitativa*. I Care 1997.
14. Ware JE, Sherbourne CD. *The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection*. Med Care 1992;30:473-83.
15. Apolone G, Moscone P, Ware JE. *Questionario sullo stato di*

salute SF-36, Manuale d'uso e guida all'interpretazione dei risultati. Milano: Guerini e Associati; 1997.

[16] Koenker R, Hallock KF. *Quantile regression: an introduction*. The Journal of Economic Perspectives 2001;15:143-56.

[17] Arisi E, Forti S, Pagani D, et al. *Cochlear implantation in adolescents with prelinguistic deafness*. Otolaryngol Head Neck Surg 2010;142:804-8.

[18] Waltzman SB, Roland J, Thomas Jr, et al. *Delayed implantation in congenitally deaf children and adults*. Otol Neurotol 2002;23:333-40.

[19] Shpak T, Koren L, Tzach N, et al. *Perception of speech by prelingual pre-adolescent and adolescent cochlear implant users*. Int J Audiol 2009;48:775-83.

[20] Most T, Shrem H, Duvdevani I. *Cochlear implantation in late-implanted adults with prelingual deafness*. Am J Otolaryngol 2010;31:418-23.

[21] Yang WS, Moon IS, Kim HN, et al. *Delayed cochlear implantation in adults with prelingual severe-to-profound hearing loss*. Otol Neurotol 2011;32:223-8.

[22] Van Dijkhuizen JN, Beers M, Boermans PP, et al. *Speech intelligibility as a predictor of cochlear implant outcome in prelingually deafened adults*. Ear Hear 2011;32:445-58.

[23] Van Dijkhuizen JN, Boermans PP, Briaire JJ, et al. *Intelligibility of the patient's speech predicts the likelihood of cochlear implant success in prelingually deaf adults*. Ear Hear 2016;37:e302-10.

Received: November 8, 2016 - Accepted: March 11, 2017

Address for correspondence: Francesca Forli, Audiology and Phoniatrics Unit University of Pisa, via Paradisa 2, 56126 Pisa, Italy. Tel. +39 050 997500. E-mail: francesca.forli@gmail.com

ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:423-429; doi: 10.14639/0392-100X-1402

Otology

Endolymphatic sac tumour in von Hippel-Lindau disease: management strategies

Carcinoma del sacco endolinfatico nella sindrome di von Hippel-Lindau: strategie di trattamento

E. ZANOLETTI[1], L. GIRASOLI[1], D. BORSETTO[1], G. OPOCHER[2], A. MAZZONI[1], A. MARTINI[1]

[1] UOC Otorinolaringoiatria, Dipartimento di Neuroscienze DNS, Università di Padova, Italy; [2] Dipartimento SSD Tumori Ereditari e Endocrinologia Oncologica, Istituto Oncologico Veneto, Padova, Italy

SUMMARY

Endolymphatic sac tumour (ELST) is infrequent, as emerges from small series reported in the literature. It is a slow-growing malignancy with local aggressiveness and a low risk of distant metastases. It is often misdiagnosed because of the late onset of symptoms and difficulty in obtaining a biopsy. Its frequency is higher in von Hippel-Lindau (VHL) disease (a genetic systemic syndrome involving multiple tumours), with a prevalence of around 25%. The diagnosis is based on radiology, with specific patterns on contrast-enhanced MRI and typical petrous bone erosion on bone CT scan. Our experience of ELST in the years between 2012-2015 concerns 7 cases, one of which was bilateral, in patients with VHL disease. Four of the 7 patients underwent 5 surgical procedures at our institution. Each case is described in detail, including clinical symptoms, and the intervals between symptom onset, diagnosis and therapy. Postoperative morbidity was low after early surgery on small tumours, whereas extensive surgery for large tumours was associated with loss of cranial nerve function (especially VII, IX, X). The critical sites coinciding with loss of neurological function were the fallopian canal, jugular foramen, petrous apex and intradural extension into the posterior cranial fossa. Early surgery on small ELST is advocated for patients with VHL disease, in whom screening enables a prompt diagnosis and consequently good prognosis.

KEY WORDS: Endolymphatic sac tumour (ELST) • Cerebellopontine angle (CPA) tumour • Temporal bone tumour • Von Hippel-Lindau disease (VHL) • Low-grade adenocarcinoma

RIASSUNTO

Il carcinoma del sacco endolinfatico è un tumore molto raro come evidente dai dati presenti in letteratura ove anche centri di esperienza riferiscono tuttavia casistiche limitate. E' un tumore maligno a lenta crescita, con tendenza all'invasione locale e scarsa tendenza alla disseminazione metastatica. L'insorgenza spesso tardiva dei sintomi e la difficoltà ad eseguire indagini bioptiche a livello della sede di origine, parete posteriore della rocca, ha reso la diagnosi di questo tumore spesso difficile, nonostante si riconoscano attualmente dati radiologici patognomonici della neoplasia. Patterns tipici di presentazione sono evidenziabili alla RM con mezzo di contrasto e alla TC per osso a strato sottile, rendendo nella maggior parte dei casi possibile la diagnosi radiologica. L'incidenza del tumore del sacco endolinfatico è maggiore nei pazienti affetti da sindrome di von Hippel Lindau (VHL), con una frequenza del 25% che fa parte del quadro sindromico. Negli anni dal 2012 al 2015 abbiamo osservato 7 casi, uno di essi con manifestazione della patologia bilaterale, tutti affetti da VHL. Quattro tra questi sono stati sottoposti a chirurgia presso il nostro centro per un totale di 5 procedure chirurgiche. Ogni caso è stato descritto dettagliatamente analizzando sintomi, intervallo tra comparsa dei sintomi, diagnosi e terapia. Non vi è stata morbidità post-operatoria aggiuntiva nei pazienti in cui la diagnosi e la terapia sono state precoci, mentre la gestione di tumori localmente avanzati è stata associata a deficit neurologici postoperatori, in particolare del VII, IX e X nervo cranico. I siti anatomici critici di coinvolgimento della malattia che hanno coinciso con un pianificato rischio di danno neuronale sono risultati essere il canale di Falloppio, il forame giugulare, l'apice della rocca petrosa. L'estensione intradurale nella fossa cranica posteriore è stato un altro elemento caratterizzante i tumori in stadio avanzato. I tumori del sacco endolinfatico che lo screening permette di evidenziare precocemente nei pazienti VHL, hanno buona prognosi quando affrontati precocemente, compatibilmente con le esigenze terapeutiche della malattia di base.

PAROLE CHIAVE: *Tumore del sacco endolinfatico • Tumore dell'angolo ponto-cerebellare • Tumore dell'osso temporale • Sindrome di von Hippel-Lindau • Adenocarcinoma a basso grado*

Acta Otorhinolaryngol Ital 2017;37:423-429

Introduction

Endolymphatic sac tumour (ELST) is a rare malignancy originating from the endolymphatic system [1-4]. Embryologically, the sac derives from the neuroectoderm and is located on the posteromedial surface of the temporal bone. ELST was historically classified as primary adenomatous tumour of the temporal bone, and was not clearly defined until the end of the 1980s when Gaffey et al. distinguished

it from adenomatous temporal bone tumours, which have a benign behaviour. The biological pattern and aggressive growth of ELST was found to resemble a papillary histology [5]. Benecke et al. subsequently described middle ear tumours with a papillary growth pattern that were more aggressive and associated with significant bone and dural involvement [6]. With the aid of histological, ultrastructural and immunohistochemical studies, Heffner established in 1989 that papillary tumours of the temporal bone originated from the endolymphatic sac epithelium, and not from the middle ear mucosa as previously believed [7]. Aggressive papillary tumours of the temporal bone were reclassified as ELST by Li et al. in 1993 [8] and the World Health Organization tumour classification has now recognised ELST is synonymous with Heffner tumour and aggressive papillary adenoma. Recent studies have confirmed that these tumours arise specifically from the endolymphatic sac/duct tissue [9].

Sporadic cases are relatively rare [10 11], the largest series being accumulated over a period of 30 years [12]. ELST is syndromic in von Hippel-Lindau (VHL) disease, with a prevalence of up to 24% [9]. Patients with VHL syndrome are also more likely to have bilateral ELST, seen in up to one in three cases [11].

VHL disease is a genetic disorder inherited as an autosomal dominant trait with a variable expression. It is caused by inactivation of the VHL tumour suppressor gene. This mutation predisposes patients to multiple haemangioblastomas of the central nervous system, and tumours and cysts in various organs, such as clear cell renal carcinoma, pheochromocytoma and pancreatic serous cystadenoma [13-15]. A gene responsible for VHL disease has been mapped on the short arm of chromosome 3[10]. In sporadic cases, tumourigenesis is associated with somatic alterations of both alleles of the tumour suppressor gene [15].

No cases of distant metastases have been reported, whereas local aggressiveness has been well documented.

Late-onset symptoms relating to tumour growth include neurological disability with severe vestibulocochlear and facial cranial nerve impairments. Typical early symptoms caused by ELST are tinnitus (~ 92%), vertigo and disequilibrium (~ 62%), and sensorineural hearing loss (~ 95%). These may be caused by intralabyrinthine haemorrhage or endolymphatic hydrops irrespective of tumour size [16].

Its location in the posteromedial wall of the petrous bone allows the tumour to spread posteromedially into the cerebellopontine angle, superiorly into the medial cranial fossa, laterally to the middle ear and anteromedially towards the cavernous and sphenoid sinuses.

Slow growth is the main reason why ELST is classified as a minimally malignant tumour [17] and also explains why it is difficult to diagnose at an early stage. ELST remains relatively asymptomatic until significant surrounding tissue destruction has occurred; the severity of the related functional impairment depends on the sites and subsites affected by tumour extension [10].

A review of the literature showed an increase in the number of cases reported in the last decade, even though the disease remains rare; this could be attributed to improvements in imaging methods and to screening of VHL patients [18]. While sporadic tumours are usually diagnosed as a result of symptoms prompting specific petrous bone imaging (contrast-enhanced MRI and bone CT scan), screening in VHL disease enables early detection of the tumour.

When part of the VHL syndrome, the tumour has a relentless and more aggressive growth, and its onset is at a younger age than in sporadic cases [16]. When early diagnosis is followed by early surgery, hearing loss is the price to pay in terms of surgical morbidity (though there are some reports in the literature of cases in which hearing was preserved) [19]. The origin of the tumour being well-established, if left untreated its growth can involve critical sites such as the fallopian canal, jugular foramen and cerebellopontine angle, and subsequent surgical morbidity is severe [20].

Our experience of ELST in VHL in the years between 2012-2015 is described herein, together with a discussion of the main diagnostic and therapeutic controversies of this infrequent disease.

Materials and methods

This was a retrospective analysis on all cases of ELST managed at the Department of Otolaryngology of Padua University Hospital between January 2012 and September 2015.

We reviewed the clinical, audiological, radiological, surgical and pathological records of 7 consecutive ELST patients. Four patients underwent resection with 5 surgical procedures (one patient had a bilateral procedure performed elsewhere, then came to our attention with bilateral residual disease and was treated with further surgery, and is awaiting a cochlear implant). The other 3 cases were not surgically treated and, up to now, managed differently.

This study included only adult patients with a clinical or genetic diagnosis of VHL syndrome. All patients were assessed at the Department for Hereditary Tumours and Oncological Endocrinology of the Istituto Oncologico Veneto. VHL mutations were ascertained from peripheral blood samples using Southern blotting, fluorescence in situ hybridization and complete gene sequencing.

Common clinical manifestations included hearing loss, tinnitus, vertigo, dizziness, aural fullness, balance disturbances, ear pain and facial nerve palsy. Large tumours growing posteromedially caused symptoms secondary to cerebellopontine angle invasion, or lower cranial nerve palsy due to jugular foramen invasion.

Audiological examination was conducted with pure tone audiometry (air and bone conduction thresholds) and vo-

cal audiometry (speech reception thresholds and discrimination loss); the four-frequency pure-tone average based on air conduction thresholds at 0.5, 1, 2 and 4 kHz was used to judge the degree of hearing loss.

Facial nerve function was measured according to the House-Brackman scale, and was tested by electromyography of the cranial district. Subjects were assessed on unenhanced high-resolution computed tomography (CT) scans and contrast-enhanced high-resolution magnetic resonance imaging (MRI) of the temporal bone; diagnostic magnetic resonance sequences analysed were T1-weighted (with and without contrast), T2-weighted, and fluid attenuated inversion recovery (FLAIR) (with and without contrast).

Radiological findings typically included: retrolabyrinthine involvement with focal erosion of the posterior wall of the petrous bone, intratumoural calcification with calcified spicules on CT scan, hyperintense focal signals on T1-weighted (unenhanced) MRI and heterogeneous signals on T2-weighted MRI.

Surgical specimens of resected tumours were routinely stained with haematoxylin and eosin for immunohistochemical analysis.

Surgery was performed by the same team of ENT surgeons. During the follow-up, patients underwent clinical/audiological examination every 6 months and MRI annually. All patients gave their verbal consent to participation in the study.

Results

Our series consisted of 7 patients, 5 females and 2 males, aged 35-62 years (mean 42.7). Table I lists the clinical and audiological examinations carried out on all patients, and Table II the surgical and postoperative details for patients who underwent skull-base surgery. Four of the 7 patients underwent surgery with radical intent, while 3 have yet to be treated surgically. The 3 cases who were not yet operated on, are detailed herein. In VHL syndrome, the presence of concomitant cerebral, cerebellar or brainstem tumours with impending risk or neurologic sequelae involved the necessity to postpone surgical treatment of ELST in favour of other more urgent conditions.

One 36-year-old woman (patient 6) had a bilateral neurosurgical procedure elsewhere and presented with bilateral residual disease involving the petrous bone and bilateral deafness. Transpetrous revision surgery and cochlear implant was scheduled at our institution, but at the time of writing the latter had been postponed due to the concomitant need to operate on a cerebellar haemangioblastoma.

One patient who was totally deaf on the affected side (patient 5) had undergone surgery via a neurosurgical approach 10 years earlier, at the age of 30, followed by postoperative radiotherapy (60 Gy multifractioned), and had residual disease in the petrous bone, which had since been growing. A period of at least 10 years was judged necessary before any new surgical treatment could be performed on an irradiated petrous bone to prevent infectious sequelae, such as osteonecrosis or osteomyelitis. The patient will be a candidate for revision surgery with translabyrinthine approach after 10 years have elapsed.

Patient 7 presented with a tumour involving the petrous bone, the jugular foramen area and the cerebellopontine angle, having recently been treated for a cerebellar haemangioblastoma on the same side, via a neurosurgical approach. ELST was not properly identified at radiology,

Table I. Clinical and audiological examinations in ELST patients.

Patient	Age (years)	Gender	Side	Audiometry	FN impairment	HB	Other symptoms	Other VHL manifestations
1 – C.G.	62	F	L	Moderate SN hearing loss	No	I	Ear pain	CNS Hbs, ret. Hbs, RCC, renal cysts, pancreatic cysts
2 – C.A.	35	F	R	Total deafness	No	I	None	CNS Hbs, ret. Hbs, renal cysts, pancreatic cysts
3 – M.S.	42	F	R	Severe SN hearing loss	Moderate neuropathy at EMG	I	Vertigo, tinnitus	Ret. Hbs, renal cysts, Pheo, pancreatic cysts
4 – M.P.	38	F	R	Severe SN hearing loss	Severe neuropathy at EMG	I	Tinnitus, imbalance, facial paresthesias	CNS Hbs, Pheo
5 – C.I.R.	36	F	L	Severe SN hearing loss	No	I	None	CNS Hbs, RCC bilat., renal cysts, pancreatic cysts
6 – C.L.	37	M	Bilateral	Left severe SN hearing loss; right deafness	No	I	None	CNS Hbs, ret. Hbs, RCC, renal cysts, pancreatic cysts
7 – V.F.	49	M	R	Total deafness	No	I	Imbalance	CNS Hbs, ret. Hbs, RCC, renal cysts, pancreatic cysts

Abbreviations: SN, sensorineural; FN, facial nerve; HB, House-Brackmann; Hbs, haemangioblastoma; ret., retinal; RCC, renal clear cell carcinoma; Pheo, pheochromocytoma

Table II. Surgical and postoperative details of treated patients.

Patient	Surgical approach	FN function post-op (HB)	Diagnostic delay (months)	Therapeutic delay (months)	Follow-up (months)
1 – C.G.	Translabyrinthine	I	41	5	50
2 – C.A.	(Retrosigmoid - 11 years before) Translabyrinthine	I	(36) 2	(12) 7	43
3 – M.S.	Translabyrinthine	I	64	20	37
4 – M.P.	1^: Petrooccipital transsigmoid + translabyrinthine 2^: Subtotal petrosectomy	1^: III 2^: V	24	100	36

and was initially considered an extension of the haemangioblastoma, but intraoperative findings confirmed the diagnostic suspicion of concomitant, aggressive ELST originating from the petrous bone. The patient experienced postoperative IX to XII nerve palsy, which was given time to compensate before planning another procedure on the jugular foramen that would involve a definitive paralysis of the nerves.

On retrospective review of our ELST patients, delays emerged between symptom onset and diagnosis, and between diagnosis and treatment. The mean delay between diagnosis and surgery was 33 months (range: 5 months to 8 years).

In patients 1 (Fig. 1) and 2, the sites of tumour involvement were the endolymphatic sac, labyrinth and dura of the posterior fossa; in patients 3 and 4 (Fig. 2), who had the greatest diagnostic and therapeutic delays, the tumour extended to and infiltrated the jugular bulb and infra-labyrinthine area.

No perioperative or postoperative complications were recorded. Postoperatively, the facial nerve was intact in 3 of the 4 surgically-treated cases; the fourth (patient 4) received a graft after intraoperative sacrifice of the facial nerve due to tumour infiltration. All surgical patients are alive and disease-free at mean follow-up of 41.5 months (range 36-50). No adjuvant therapy was administered.

Discussion

ELST is a locally aggressive tumour originating in the endolymphatic sac on the posterior border of the petrous ridge. Its slow but relentless growth into the petrous bone and then into the cerebellopontine angle and middle cranial fossa can involve the surrounding neurovascular structures, such as the carotid artery and the cranial nerves from VII to XII. The VI cranial nerve involves the tumour's extension into the petrous apex, which is infrequent but possible [21].

Before being reclassified, ELST was underestimated and for years it was often misinterpreted as paraganglioma, metastatic renal cell carcinoma, choroid plexus papilloma, ceruminous gland adenocarcinoma, or aggressive papillary tumour [8]. Its diagnosis is radiological, and it has quite a specific pattern of presentation: a retrolabyrinthine location with focal erosion of the posterior wall of the petrous bone, intratumoural calcification with calcified spicules on CT scan, hyperintense focal signals on T1-weighted (unenhanced) MRI scan, markedly heterogeneous enhancement after gadolinium and heterogeneous signal on T2-weighted sequences [22–24].

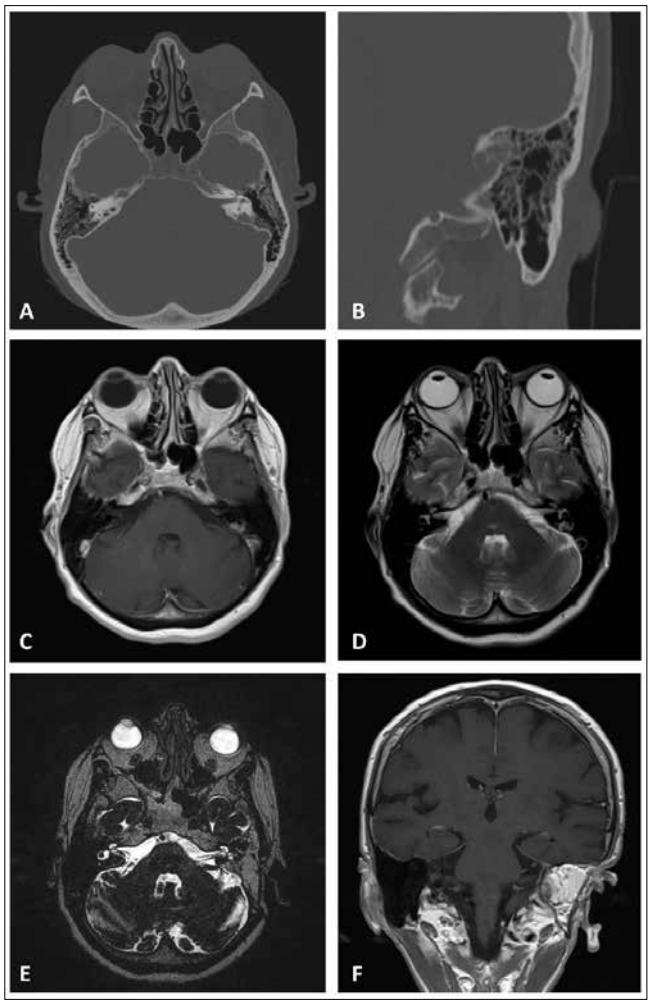


Fig. 1. Small left endolymphatic tumour. A: axial bone CT scan with erosion in posterior ridge of petrous bone. B: bone erosion and tumour seen in retrolabyrinthine area in a coronal plane. C: axial contrast-enhanced T1 MRI showing tumour in petrous bone, in the presigmoid-extradural area. D: axial T2 MRI showing hyperintense signal in tumour foci. E, F: no residual disease evident on T2 high-resolution and contrast-enhanced T1 MRI.

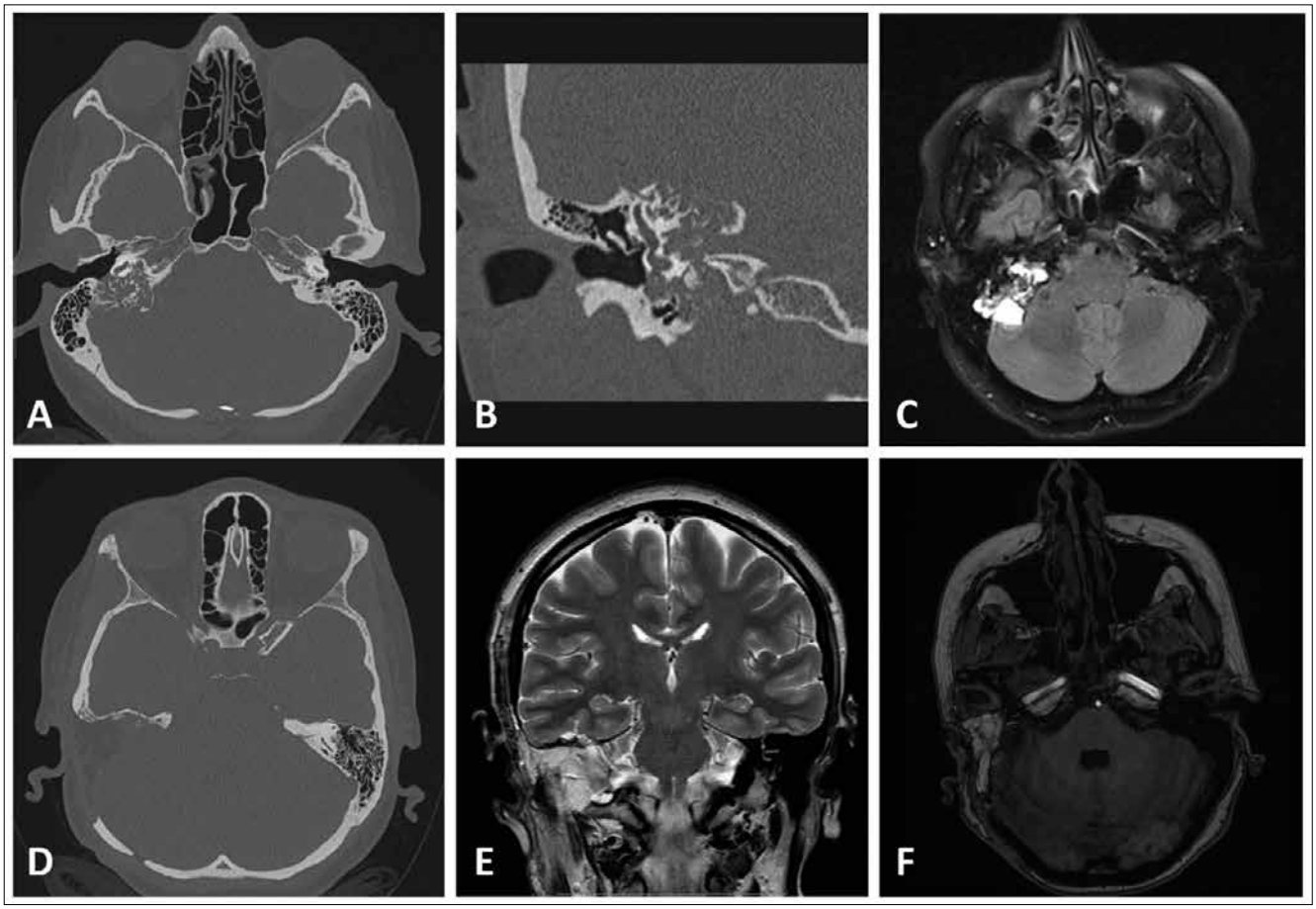


Fig. 2. Extended right endolymphatic tumour. A: axial bone CT scan with extended erosion in petrous bone. B: bone erosion and tumour seen in retrolabyrinthine area in a coronal plane. C: axial T2 MRI with flair, showing tumour in the petrous bone and posterior cranial fossa. D: axial bone CT scan after the first surgical step, showing the area of drilled bone of a lateral petrosectomy and the retrosigmoid craniotomy. E: coronal T2 MRI after the first surgical step. F: no residual disease visible on contrast-enhanced T1 MRI after the second surgical step.

It is easier to diagnose in small lesions, when the tumour's origin is still pathognomonic. On the other hand, when the disease involves the jugular foramen or the intradural compartment, extensive bony destruction prevents the typical origin of the tumour from being established [25 26].

Further investigations might be useful to rule out intracranial vessel involvement in order to plan safe surgery. Arteriography may give information about carotid artery infiltration, or when part of the approach or in case of disruption or planned sacrifice: in such cases, a balloon occlusion test may be added. In our series, it was never necessary.

It is essential to consider the differential diagnosis, although in VHL patients ELTS may be a presenting sign of the syndrome.

Treatment of ELTS demands extensive surgery with adequate bone removal around the area of macroscopically evident tumour. Lateral skull base approaches each have their intrinsic morbidity [27] but, in principle, morbidity is directly proportional to the extension of the tumour. Microsurgical approaches through the temporal bone are directed to the site of origin of ELST along the petrous ridge and the surrounding subsites of tumour involvement, and may be combined if required.

A transmastoid-retrolabyrinthine approach is for a small endolymphatic tumour, with no extension in the surrounding subsites. The translabyrinthine approach is for larger tumours, with poor hearing and extending through the labyrinth and/or intradurally in the posterior fossa. The involvement of the middle ear is better managed through a petrosectomy, lateral or subtotal [27]. When ELST extends to the jugular foramen, POTS [28] allows good and safe exposure of the infralabyrinthine and jugular foramen area. Similarly, involvement of the petrous apex or the middle cranial fossa, is managed by combining a transmastoid-transpetrous approach with a subtemporal/middle cranial fossa approach. The pure retrosigmoid approach, directed to the intradural extension of the tumour in the posterior fossa, may be not large enough to allow extensive drilling of the petrous bone around the site of origin of ELST.

Small tumours, as seen when ELTS is diagnosed early and treated promptly, entail hearing loss but no further morbidity. When hearing is already impaired, there can be no doubt about the advisability of surgery for early le-

sions. When hearing is unaffected (an infrequent situation that may be encountered on screening or in the case of incidentally-found tumours), it is nonetheless at risk. As a rule, it is difficult to ensure the removal of even a very small tumour within the endolymphatic sac and vestibular aqueduct without hearing loss or impairment, although some experiences of hearing preservation after the resection of very small tumours have been described [12 19 29]. Hearing preservation after early surgery for very small tumours seems a distinctly sporadic event, and should not (in our opinion) be presented as a likely outcome when proposing surgery to patients. Any disruption of the endolymphatic sac and vestibular aqueduct can be a cause of hearing loss, per se, even in patients with very small tumours.

If the tumour is left untreated and reaches surrounding subsites like the fallopian canal with the facial nerve, jugular foramen area, petrous apex and intradural compartment of the cerebello-pontine angle and middle cranial fossa, the related surgical morbidity is a completely different story. Bambakidis [21] proposed a classification of ELST based on size and sites of extension, but does not reflect the problems of the related surgical morbidity, since this is already evident for stage I tumours.

Early diagnosis and prompt therapy are key to avoid unavoidable foreseeable tumour extension into critical sites. When aggressive and extensive surgery is required, the prognosis is unfavourably affected because of the related surgical morbidity, and radicality is rarely achievable even with very extensive surgery.

The effectiveness of radiotherapy (stereotactic or fractionated) is still unclear, without any evident benefit in long-term prognosis for patients [10]. Postoperative radiotherapy in subtotal resection may give some beneficial results, but with a risk of relapse > 50% [9].

Since ELST can be a facet of VHL disease, accurate screening should be considered to detect the tumour early and thus offer patients early surgery with a good prognosis, good long-term disease-free survival rates and limited treatment-related morbidity [30]. Delaying treatment is not uncommon in patients with the syndromic form of ELST, due to the complexity of VHL disease, with multiple tumour localisations in other body districts that often require prompt surgery [16]. In principle, awareness that early surgery for small tumours is associated with a low impact in terms of morbidity and a prompt recovery after the procedure should enable the treatment of ELTS to be scheduled appropriately in the frame of VHL.

Clinical-radiological screening in VHL populations at risk of ELST may favourably affect prognosis, providing that early diagnosis is followed by prompt therapy.

When the tumour is bilateral – a situation seen in 30% of syndromic patients [3] and, to the best of our knowledge, never reported in sporadic cases – there is the problem of bilateral deafness as the natural outcome of the evolution of the disease. The mechanisms behind it are direct invasion of the inner ear, endolymphatic hydrops that mimic Meniere's disease [31], and intralabyrinthine haemorrhage (even in small tumours), which is responsible for sudden sensorineural hearing loss [32].

Early rehabilitation with a cochlear implant may be the solution, but the tumour has to be resected before it reaches and destroys the cochlea as well as the posterior labyrinth. Though not involved directly, damage to the posterior labyrinth (vestibule or/and semicircular canals) and surgical trauma associated with tumour removal may cause ossification in the cochlea and prevent its proper functioning, or even the insertion of the cochlear implant [33].

There seem to be sporadic cases of hearing preservation after early surgery for very small tumours, but it would be wrong (in our opinion) to consider sparing natural hearing as one of the goals of any proactive surgery. Disruption of the endolymphatic sac and vestibular aqueduct suffices in itself to cause hearing loss, even in patients with very small tumours.

Conclusions

ELTS is infrequent and usually misdiagnosed, but screening for this cancer can be routinely performed in VHL patients. The most appropriate timing of its treatment should be established for the purpose of achieving a low morbidity by performing early surgery on a small tumour.

Hearing is always at risk when surgery is performed for ELST, but preserved normal hearing in a patient with detectable ELST is unusual; hearing loss is generally identified already at diagnosis, even in the case of small tumours. There have been some sporadic reports of hearing being preserved after surgery for ELTS [19 29].

A 'wait-and-see' strategy can only be a temporary solution for ELTS in VHL disease to enable the treatment of multiple tumours to be planned. The slow, but relentless growth of ELTS – especially in syndromic cases – leads to unfavourable outcomes once critical structures have been affected, because they cannot be spared, meaning that postoperative morbidity is significant and long-term disease control rates are low.

Screening VHL patients for the early detection of ELST is very important in order to ensure the most favourable timing of radical surgery and the least possible morbidity.

Acknowledgements

We thank Frances Coburn for English editing.

Refereces

1 Hamazaki S, Yoshida M, Yao M, et al. *Mutation of von Hippel-Lindau tumor suppressor gene in a sporadic endolymphatic sac tumor*. Hum Pathol 2001;32:1272-6.

2 Lonser RR, Baggenstos M, Kim HJ, et al. *The vestibular aq-*

ueduct: site of origin of endolymphatic sac tumors. J Neurosurg 2008;108:751-6.

3 Manski TJ, Heffner DK, Glenn GM, et al. *Endolymphatic sac tumors. A source of morbid hearing loss in von Hippel-Lindau disease.* JAMA 1997;277:1461-6.

4 Barnes L, Eveson JW, Reichart P, et al. *Pathology and genetics of head and neck tumours*. WHO Classif Tumour 2005;9:163-75.

5 Gaffey MJ, Mills SE, Fechner RE, et al. *Aggressive papillary middle-ear tumor. A clinicopathologic entity distinct from middle-ear adenoma*. Am J Surg Pathol 1988;12:790-7.

6 Benecke JE, Noel FL, Carberry JN, et al. *Adenomatous tumors of the middle ear and mastoid*. Am J Otol 1990;11:20-6.

7 Heffner DK. *Low-grade adenocarcinoma of probable endolymphatic sac origin. A clinicopathologic study of 20 cases*. Cancer 1989;64:2292-302.

8 Li JC, Brackmann DE, Lo WW, et al. *Reclassification of aggressive adenomatous mastoid neoplasms as endolymphatic sac tumors*. Laryngoscope 1993;103:1342-8.

9 Diaz RC, Amjad EH, Sargent EW, et al. *Tumors and pseudotumors of the endolymphatic sac*. Skull Base 2007;17:379-93.

10 Poletti AM, Dubey SP, Barbò R, et al. *Sporadic endolymphatic sac tumor: its clinical, radiological, and histological features, management, and follow-up*. Head Neck 2013;35:1043-7.

11 Husseini ST, Piccirillo E, Taibah A, et al. *The Gruppo Otologico experience of endolymphatic sac tumor*. Auris Nasus Larynx 2013;40:25-31.

12 Hansen MR, Luxford WM. *Surgical outcomes in patients with endolymphatic sac tumors*. Laryngoscope 2004;114:1470-4.

13 Linehan WM, Lerman MI, Zbar B. *Identification of the von Hippel-Lindau (VHL) gene. Its role in renal cancer.* JAMA 1995;273:564-70.

14 Libutti SK, Choyke PL, Alexander HR, et al. *Clinical and genetic analysis of patients with pancreatic neuroendocrine tumors associated with von Hippel-Lindau disease*. Surgery 2000;128:1022-7.

15 Lonser RR, Glenn GM, Walther M, et al. *von Hippel-Lindau disease*. Lancet 2003;361:2059-67.

16 Bausch B, Wellner U, Peyre M, et al. *Characterization of endolymphatic sac tumors and von Hippel-Lindau disease in the International Endolymphatic Sac Tumor Registry*. Head Neck 2016;38(Suppl 1):E673-9.

17 Hou Z, Huang D, Han D, et al. *Surgical treatment of endolymphatic sac tumor*. Acta Otolaryngol 2012;132:329-36.

18 Kim HJ, Hagan M, Butman JA, et al. *Surgical resection of endolymphatic sac tumors in von Hippel-Lindau disease: findings, results, and indications*. Laryngoscope 2013;123:477-83.

19 Megerian CA, Haynes DS, Poe DS, et al. *Hearing preservation surgery for small endolymphatic sac tumors in patients with von Hippel-Lindau syndrome*. Otol Neurotol 2002;23:378-87.

20 Roche PH, Dufour H, Figarella-Branger D, Pellet W. *Endolymphatic sac tumors: report of three cases*. Neurosurgery 1998;42:927-32.

21 Bambakidis NC, Megerian CA, Ratcheson RA. *Differential grading of endolymphatic sac tumor extension by virtue of von Hippel-Lindau disease status*. Otol Neurotol 2004;25:773-81.

22 Mukherji SK, Albernaz VS, Lo WW, et al. *Papillary endolymphatic sac tumors: CT, MR imaging, and angiographic findings in 20 patients*. Radiology 1997;202:801-8.

23 Lo WW, Applegate LJ, Carberry JN, et al. *Endolymphatic sac tumors: radiologic appearance*. Radiology 1993;189:199-204.

24 Patel NP, Wiggins RH, Shelton C. *The radiologic diagnosis of endolymphatic sac tumors*. Laryngoscope 2006;116:40-6.

25 Bell D, Gidley P, Levine N, Fuller GN. *Endolymphatic sac tumor (aggressive papillary tumor of middle ear and temporal bone): sine qua non radiology-pathology and the University of Texas MD Anderson Cancer Center experience*. Ann Diagn Pathol 2011;15:117-23.

26 Yang X, Liu X-S, Fang Y, et al. *Endolymphatic sac tumor with von Hippel-Lindau disease: report of a case with atypical pathology of endolymphatic sac tumor*. Int J Clin Exp Pathol 2014;7:2609-14.

27 Zanoletti E, Martini A, Emanuelli E, Mazzoni A. *Lateral approaches to the skull base*. Acta Otorhinolaryngol Ital 2012;32:281-7.

28 Mazzoni A. *the petro-occipital trans-sigmoid approach for lesions of the jugular foramen*. Skull Base 2009;19:048-56.

29 Rodrigues S, Fagan P, Turner J. *Endolymphatic sac tumors: a review of the St. Vincent's hospital experience.* Otol Neurotol 2004;25:599-603.

30 Choo D, Shotland L, Mastroianni M, et al. *Endolymphatic sac tumors in von Hippel-Lindau disease*. J Neurosurg 2004;100:480-7.

31 Kitahara T, Maekawa C, Kizawa K, et al. *Endolymphatic sac tumor with overexpression of V2 receptor mRNA and inner ear hydrops*. Acta Otolaryngol 2011;131:951-7.

32 Butman JA, Kim HJ, Baggenstos M, et al. *Mechanisms of morbid hearing loss associated with tumors of the endolymphatic sac in von Hippel-Lindau disease*. JAMA. 2007;298:41-8.

33 Jagannathan J, Lonser RR, Stanger RA, et al. *Cochlear implantation for hearing loss associated with bilateral endolymphatic sac tumors in von Hippel-Lindau disease*. Otol Neurotol 2007;28:927-30.

Received: August 20, 2016 - Accepted: March 11, 2017

Address for correspondence: Laura Girasoli, UOC Otorinolaringoiatria, Dipartimento di Neuroscienze DNS, Az. Ospedaliera ed Università di Padova, via Giustiniani 2, 35128 Padova, Italy. E-mail: laura.girasoli@alice.it

ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:430-435; doi: 10.14639/0392-100X-1243

VESTIBOLOGY

Utricular hypofunction in patients with type 2 diabetes mellitus

Ipofunzione utricolare in pazienti con diabete mellito di tipo 2

K. JÁUREGUI-RENAUD[1], C. ARANDA-MORENO[1, 2], A. HERRERA-RANGEL[1]

[1] Unidad de Investigación Médica en Otoneurología; [2] Hospital General Regional no.72, Instituto Mexicano del Seguro Social, México

SUMMARY

The aim of this study was to assess the function of the utricle and horizontal semicircular canals in patients with type 2 diabetes mellitus receiving primary health care, with/without a history of falls. 101 patients with type 2 diabetes mellitus, 34 to 84 years old (26 with and 75 without a history of falls) and 51 healthy volunteers (40-83 years old) accepted to participate. They denied having a history of dizziness, vertigo, unsteadiness, hearing loss, or neurological disorders. None of them were seeking care due to sensory or balance decline. After a clinical evaluation and report of symptoms related to balance using a standardised questionnaire, lateral canal function was assessed by sinusoidal rotation at 0.16 Hz and 1.28 Hz (60°/sec peak velocity), otolith function was assessed by static visual vertical (average of 10 trials) and dynamic visual vertical during unilateral centrifugation (300°/sec at 3.5 cm) and static posturography was performed on hard/soft surface with eyes open/closed. Compared to healthy volunteers, patients showed decreased responses to unilateral centrifugation, but similar responses to horizontal canal stimuli (independently of age, peripheral neuropathy or a history of falls) (ANCoVA $p < 0.05$) and a larger sway area with a lengthier sway path. Compared to patients with no falls, patients with falls had a higher female/male ratio and a higher frequency of score ≥ 4 on the questionnaire of symptoms related to balance, but similar age, body mass index and frequency of peripheral neuropathy. In patients with type 2 diabetes mellitus, receiving primary healthcare who are not seeking care due to sensory or balance decline, utricular function may be impaired even in the absence of horizontal canal dysfunction or a history of falls.

KEY WORDS: Diabetes mellitus • Vestibular function • Falls

RIASSUNTO

L'obiettivo di questo studio è stato quello di valutare la funzione utricolare e la funzione dei canali semicircolari laterali in pazienti con diabete mellito di tipo 2, con o senza cadute, afferenti all'assistenza sanitaria di base. Sono stati arruolati 101 pazienti con diabete mellito di tipo 2 (26 con storia di cadute, 75 senza), di età compresa tra 34 e 84 anni, e 51 volontari sani di età compresa tra 40 e 83 anni, i quali hanno negato vertigini, capogiri, instabilità, ipoacusia o disordini neurologici. Nessuno di loro era in cerca di cure per deficit sensoriali o dell'equilibrio. Dopo aver effettuato una valutazione clinica e dopo aver indagato i sintomi relativi alla sfera dell'equilibrio con l'ausilio di un questionario standardizzato, la funzione dei canali semicircolari laterali è stata studiata con il test sinusoidale alle velocità di 0,16 Hz e 1,28 Hz (il picco della velocità è stato fissato a 60°/s); la funzione otolitica, invece, è stata studiata con la verticale visiva soggettiva, determinata sia tramite test statico sia tramite test dinamico, durante centrifugazione unilaterale (300°/s a 3.5 cm); è stata eseguita inoltre la posturografia statica, su pedana soffice e dura, ad occhi aperti e chiusi. Confrontando i risultati ottenuti nei pazienti diabetici e in quelli sani, i pazienti diabetici hanno mostrato risposte inferiori alla centrifugazione unilaterale, ma risposte simili alla stimolazione dei canali semicircolari laterali, indipendentemente da età, neuropatie periferiche o storia di cadute (ANCoVA $p < 0.05$). I pazienti con storia di cadute, rispetto a quelli senza storia di cadute, erano per lo più donne e hanno raggiunto più facilmente un punteggio maggiore o pari a 4 al questionario sui sintomi relativi al senso dell'equilibrio; tuttavia i due gruppi hanno mostrato simili età, indice di massa corporea e neuropatia periferica. Nei pazienti con diabete di tipo 2, afferenti all'assistenza sanitaria di base e non in cerca di cure per deficit sensoriali o dell'equilibrio, la funzione utricolare potrebbe essere alterata, anche in assenza di disfunzione dei canali semicircolari laterali o di storia di cadute.

PAROLE CHIAVE: *Diabete mellito • Funzione vestibolare • Cadute*

Acta Otorhinolaryngol Ital 2017;37:430-435

Introduction

To maintain balance, any perturbation of stance must be opposed by coordinated motor responses, requiring sensory information from multiple sources, including somatosensory, vestibular and visual inputs. Evidence has shown that individuals with somatosensory or vestibular deficit are limited in their ability to re-weight postural sensory inputs [1 2], with the risk of falling.

Falls occur as a result of complex interactions between intrinsic (demographic and biological factors) and extrinsic

factors (environmental and behavioural factors) [3]. Diabetes mellitus is an independent risk factor for falling, particularly in the elderly [4 5]. Patients with diabetes mellitus may have sensory deficits as well as unrecognised postural instability [6-9]. In this group of patients, the frequency of symptoms related to balance has been associated with both the time elapsed since the diabetes was diagnosed and the history of peripheral neuropathy and retinopathy [9]. Studies in murine models of acquired diabetes have shown deterioration of utricular function, with increased latency and decreased amplitude of the short latency vestibular evoked potentials in response to linear acceleration [10], as well as a high incidence of osmophilic inclusion bodies in the saccular and utricular nerves, with disrupted myelin-sheath lamellae [11]. Accordingly, in patients with type 2 diabetes mellitus vestibular dysfunction on clinical tests has been observed [12-14]. However, studies evaluating the otolith function of patients with type 2 diabetes mellitus are scarce, even more so in patients receiving primary health care. In a recent study, otoconial organ impairment by cervical and ocular vestibular-evoked myogenic potentials was recognised in 50% of adult patients with type 2 diabetes mellitus (saccular, utricular or both organs) [14].

The aim of this study was to assess the function of the urticular macula and the horizontal semicircular canals, as well as postural stability of patients with type 2 diabetes mellitus receiving primary health care, who were not seeking medical care due to sensory or balance decline, with/without a history of falls, compared to age-matched controls.

Materials and methods

After approval of the research protocol by the Research and Ethics Committees of the Institution, informed consent was obtained from all participants and the study was performed according to the Declaration of Helsinki and amendments. A total of 101 consecutive patients with type 2 diabetes mellitus, who met selection criteria (age range 34 to 84 years, mean 60.3 ± 9.8; 27 men; BMI 29.1 ± 4.5) and 51 age-matched healthy volunteers (age range 40 to 83 years, 56.5 ± 6.8; 22 men; BMI 28.4 ± 4.8) participated in the study. The proportion of males was lower in the patient group than in the control group (26.7% *versus* 43%, p = 0.04). One additional patient accepted to participate but declined to complete the study protocol due to difficulty to attend an appointment. All participants denied having a history and having no medical record of otology, neurology, psychiatry, or orthopaedic disorders, postural hypotension, or exposure to ototoxic medication or unsafe noise levels. All had similar access to health care, but none were seeking it due to sensory or balance deterioration. Patients were receiving primary health care for diabetes and the most frequent medication was metformin (76.4%, 95% C.I. 68.4-84.4%).

According to the occurrence of falls within the previous year, by the definition of the World Health Organization [3], patients were classified in two groups (Table I):

I. 75 patients with no history of falls (34 to 84 years old).

II. 26 patients with a history of falls (42 to 79 years old).

After clinical evaluation, including bed-side head shaking and positional tests, all participants replied to a self-administered questionnaire of symptoms related to balance, which was previously validated (Kurder Richardson 20 = 0.75, intra-class rank correlation coefficient = 0.9) [15]. The questionnaire includes nine items to report each of the balance symptoms described in Fig. 1, with yes/no answers. A "no" response was scored 0 points and a "yes" response was scored 1 point, except for vertigo which was scored 2 points; frequent falls were considered when occurring at least once per month, and frequent stumbles when occurring at least once per week. The total score is calculated by adding all the points (range 0 to 10); a score higher than 3 can be related to balance disorders [15] .

Vestibular function was evaluated by sinusoidal rotation at 0.16 Hz and at 1.28 Hz (60°/sec peak velocity), static visual vertical (average of 10 trials) and dynamic visual vertical during unilateral centrifugation (300°/sec at 3.5 cm) (I-Portal-NOCT-Professional, Neuro-Kinetics, Pittsburgh). For centrifugation, the chair was accelerated to 300°/sec in 60 sec; after 60 sec of full speed rotation the chair moved from the center position to the right in 30 sec, while in offset position the chair dwell for 60 sec, then it moved from the right position to the center in 30 sec, while in the center position it dwell for 60 sec, then it moved from the center position to the left in 30 sec, while in the offset position it dwell for 60 sec, then it moved from the left position to the center in 30 sec, and finally decelerated from 300°/sec to 0°/s in 60 sec. Postural stability was evaluated using static posturography on hard and soft surface, with the eyes either open or closed (Posturolab 40/16, Cedex).

In patients with diabetes, peripheral neuropathy was evaluated at first by the Michigan Diabetic Neuropathy Score [16] and the Semmes-Weinstein 10 g monofilament, when any of these two instruments was positive, nerve conduction studies were performed on the tibial and sural nerves (Spirit, Nicolet, Madison, U.S.A.) [17].

Bivariate analysis was performed using "t" test (either for proportions or for means, accordingly), and multivariate analysis was performed using multiple regression and analysis of covariance (Statistica, Statsoft Inc., Tulsa). The significance level was set at 0.05 for two tails.

Results

In patients with diabetes mellitus, comparison between those with/without falls showed a similar age and BMI as well as a similar frequency of peripheral neuropathy, retinopathy and other clinical characteristics (Table I).

Table I. Characteristics of 101 patients with type 2 diabetes mellitus with/without falls. Data is given as means and percentages with the 95% CI.

Characteristics of the patients	Patients no falls (n = 75)	Patients with falls (n = 26)	P*
Female/male ratio	52/24	23/3	0.001
Years of age	59.5 (57. 2-61.7)	62.6 (58.6-66.5)	> 0.1
Years of age at diagnosis	47.0 (44.7-49.2)	51.6 (48-55.2)	0.03
Years elapsed since diagnosis	9.4 (8.2-10.6)	7.5 (5.0-10.0)	> 0.1
Body mass index	29 (27.9-30)	29.5 (27.4-31.5)	> 0.1
Glycated haemoglobin	7.8 (7.0-8.7)	7.6 (7.2- 7.9)	> 0.1
Peripheral neuropathy	28% (18-38%)	34% (16-52%)	> 0.1
Retinopathy	6.5% (1-12%)	12%(0-24%)	> 0.1
Polypharmacy	34.6% (23.9-45.3%)	38.4% (29.8-57%)	> 0.1
Hypertension	48% (36.7%-59.3%)	34% (15.8-52.2%)	> 0.1
Insulin use	10.6% (3.7- 17.5%)	7.6% (0-17.7%)	> 0.1

However, patients with falls had a higher female/male ratio and were diagnosed later in life than patients with no falls (Table I).

Patients and controls had a similar gain to sinusoidal rotation at both 0.16 Hz and 1.28 Hz (Table II). However, compared to controls, patients with diabetes, either with or without a history of falls, showed an increased deviation of the static visual vertical and decreased responses to unilateral centrifugation ($p < 0.01$) (Fig. 2, Table II).

Multiple regression analysis showed a significant contribution to falls from the gender (beta 0.16, 95% C.I. -0.02-0.35) ($R = 0.35$, $p = 0.008$) and the total score of symptoms related to balance (beta 0.20, 95% C.I. 0.1-39), but no other significant relationships were observed. The frequency of patients with a total score suggesting a balance disorder (≥ 4) was almost twice that in patients with falls (57.7%, 95% C.I. 38.7-76.7%) than in patients with no falls (32.5%, 95% C.I. 22.3-42.7%) ("t" test for proportions, $p \leq 0.05$). Among the items, a significant difference between the groups was observed on a larger proportion of patients with falls reporting frequent stumbles (Fig. 1) ("t" test for proportions, $p \leq 0.05$), while in the two groups the most frequent symptoms were instability when changing posture and when moving the head rapidly (Fig. 1).

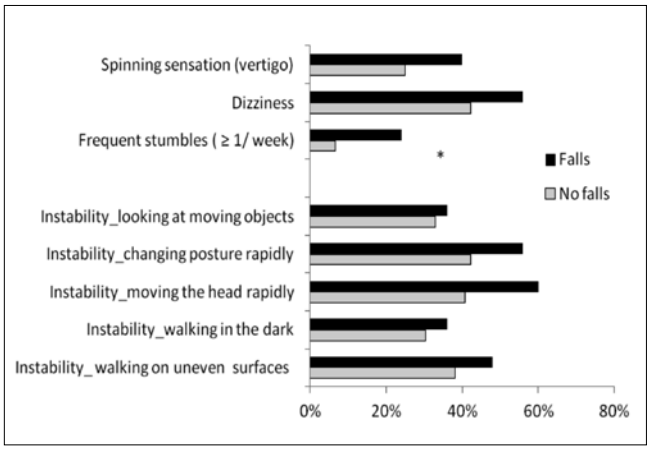


Fig. 1. Frequency of symptoms related to balance reported by 101 patients with type 2 diabetes mellitus, 26 with a history of falls and 75 with no history of falls.

Compared to healthy controls, during static posturography patients with diabetes showed a larger area of sway while standing with the eyes open either on hard or soft surface, which was accompanied by a lengthier sway path (Table III).

Among patients with diabetes, the Romberg index, either on hard or soft surface, showed no significant difference

Table II. Vestibular evaluation of 101 patients with type 2 diabetes mellitus with/without falls and 51 age-matched volunteers without diabetes. Data is given as means and 95% Confidence Intervals. Comparisons between the control group and all the patients were performed using "t" test.

		Patients (n = 101)		
Vestibular test	Controls (n = 51)	No falls (n = 75)	Falls (n = 26)	p value
Vestibulo-ocular reflex gain at 0.16 Hz	0.54 (0.48-0.59)	0.53 (0.48-0.59)	0.54 (0.46-0.61)	> 0.1
Vestibulo-ocular reflex gain at 1.28 Hz	0.96 (0.93-1.0)	0.93 (0.90-0.96)	0. 94 (0.89-0.99)	> 0.1
Static visual vertical	-0.14° (-0.3-0.03°)	1.8° (1.5-2.1°)	1.9° (1.3-2.5°)	< 0.01
Dynamic visual vertical, right	-5.0° (-5.3--4.7°)	-2.8° (-3.7--1.9°)	-1.4° (-3.3--0.4°)	< 0.01
Dynamic visual vertical, left	5.1° (4.8-5.4°)	3.5° (2.5-4.6°)	4.0° (2.3-5.7°)	0.04

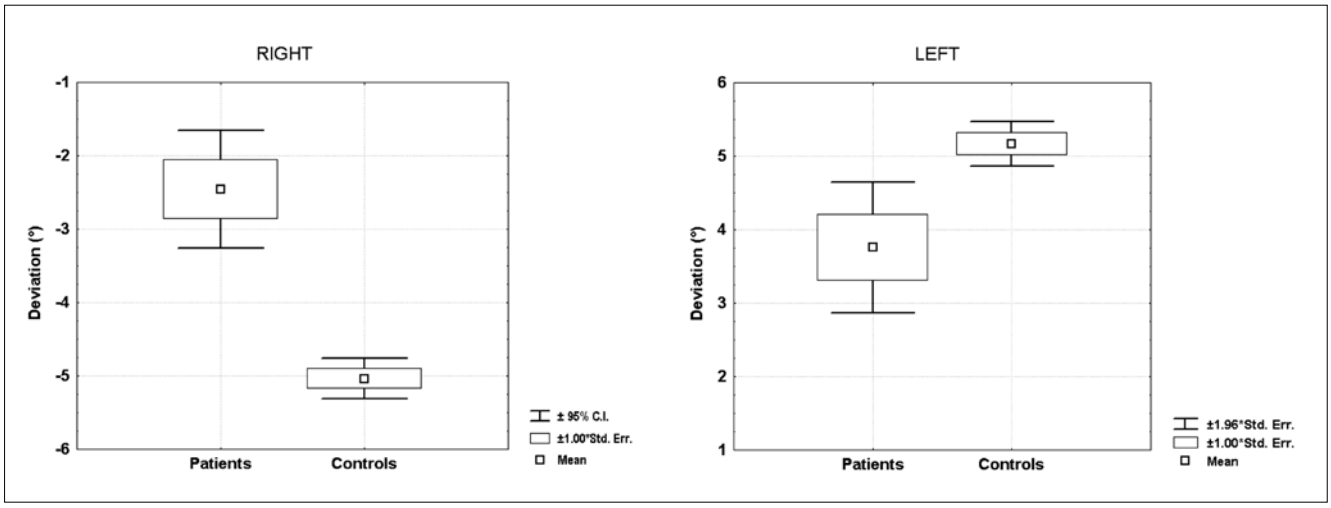


Fig. 2. Mean, standard error of the mean and 95% C.I. of the mean of the responses to unilateral centrifugation (to the right and to the left) of 101 patients with type 2 diabetes mellitus and 51 age-matched controls without diabetes.

between patients with/without falls ($p > 0.05$), and covariance analysis did not show any other significant relationship with the clinical characteristics of the patients. However, comparison between those with/without peripheral neuropathy showed that patients with no falls but neuropathy had a trend for a larger area of sway, with no lengthier sway path, while in patients with falls there was no consistent difference between those with or without neuropathy (Table III).

Discussion

Evaluation of patients with type 2 diabetes mellitus receiving primary health care who were not seeking care for balance disorders, compared to healthy volunteers, showed decreased responses to utricular stimulation by unilateral centrifugation, even when horizontal canal function at 0.16 Hz and 1.28 Hz was preserved, and a larger area of sway with a lengthier sway path on static posturography. These results suggest that, in patients with diabetes mellitus receiving primary health care an underlying otolith vestibular dysfunction may contribute to postural instability, which could enhance the effect of other sensory deficits and in turn may add to the risk factors for balance decline.

The finding of decreased utricular responses to unilateral centrifugation in patients with type 2 diabetes mellitus, even when horizontal canal function was preserved, is consistent with the dissociation between the responses to cervical and ocular vestibular-evoked myogenic potentials and head thrust dynamic visual acuity in all canal planes recently reported in patients with diabetes [14]. Although in that study the head thrust dynamic visual acuity testing showed semicircular canal dysfunction in at least one plane in 70% of patients, participants were all 50 years of age and older with ≥ 10-year history of type 2 diabetes.

The different responses of the two end organs, otoliths and semicircular canals, in early stages of diabetes mellitus could be related to their metabolic and vascular characteristics. In murine models, evaluation of the local metabolic rate of glucose utilisation has shown similar results for the utricle and saccule, which were significantly higher than that for the superior, posterior, or lateral canal ampulla [18]. Compared to the posterior canal ampulla, the rat utricular macula is similar with respect to neuroepithelial volume, capillary surface area and blood flow, but the capillary diameter is smaller and the capillary length is greater [19]. This is consistent with the finding in rats with long-term experimental diabetes of increased capillary diameters along with increased vascularisation of the saccule, suggesting greater stress on the capillary wall [20]. In addition, the maculae of neither animal models nor human beings have shown microangiopathy, even if loss of type I hair cells has been described [20 21], while evidence supports that dysregulated energy metabolism could also have a role in the vestibular dysfunction due to diabetes mellitus in the context of insulin signaling networks [22].

Vestibular dysfunction is a significant differential diagnosis in patients who have unexpected falls [23], and in patients with peripheral neuropathy related to diabetes balance recovery after peripheral vestibular disease may be compromised [24]. However, in this study, the evidence of utricular dysfunction in both groups of patients (with/ without falls), with a similar frequency of peripheral neuropathy and a low frequency of retinopathy, did not allow the assessment of the interaction between sensory deficits. Likewise, the low frequency of insulin use and similar glycated haemoglobin levels in the two groups (Table I) did not allow an adequate assessment of a possible influence of these variables on vestibular function and postural control.

Although it is already known that during quiet stance patients with diabetes and peripheral neuropathy sway more

Table III. Mean and 95% confidence interval of the mean of the length of sway and area of sway of 101 patients with type diabetes mellitus with/without falls and with/without peripheral neuropathy, and 51 age-matched volunteers without diabetes mellitus.

Variables by condition	No falls no neuropathy (n = 54)	No falls with neuropathy (n = 21)	p value	Falls no neuropathy (n = 17)	Falls with neuropathy (n = 9)	p value	All patients (n = 101)	Controls (n = 51)	p value
Hard surface with eyes open									
Length of sway (mm)	366 (326-406)	356 (284-427)	> 0.1	317 (251-383)	415 (265-565)	> 0.1	364 (331- 397)	279 (259- 299)	< 0.001
Area of sway (mm^2)	108 (75-141)	205 (54-356)	0.06	89 (44-135)	105 (53-157)	> 0.1	134 (88-181)	69 (55- 83)	0.03
Hard surface with eyes closed									
Length of sway (mm)	521 (442-600)	543 (404-681)	> 0.1	444 (298-590)	531 (344-717)	> 0.1	530 (464-595)	436 (398- 474)	0.002
Area of sway (mm^2)	166 (98-233)	419 (87-751)	0.02	114 (51-176)	182 (45-319)	> 0.1	237 (135-339)	120 (96- 144)	0.09
Soft surface with eyes open									
Length of sway (mm)	473 (410-535)	487 (383-592)	> 0.1	398 (347-449)	534 (328-740)	0.07	479 (427-530)	370 (339- 400)	0.06
Area of sway (mm^2)	177 (116-239)	343 (117-568)	0.05	148 (96-199)	239 (94-385)	> 0.1	226 (151-301)	118 (96- 140)	0.01
Soft surface with eyes closed									
Length of sway (mm)	792 (664-919)	695 (563-828)	> 0.1	599 (428-770)	807 (482-1131)	> 0.1	768-(672-864)	607 (554- 660)	0.02
Area of sway (mm^2)	495 (316-674)	546 (300-792)	> 0.1	236 (146-326)	433 (177-689)	0.05	513 (372-654)	276 (217- 334)	0.02

than controls and even more so if their visual or vestibular systems are perturbed [25]. In this study, patients with diabetes, compared to healthy controls, showed a larger area of sway and a lengthier sway path. However, those with no history of falls but neuropathy had a trend for a larger area of sway, while those with falls, either with or without neuropathy, showed more variability on their sway path. This finding supports that peripheral neuropathy may interact with other sensory impairments and factors related to postural coordination underling balance decline. In this study, the sample size as well as the low frequency of retinopathy in patients with/without a history of falls may preclude further discussion on the interaction among sensory deficiencies.

Among patients with diabetes, a gender influence on falling was evident. The association between female gender and higher risk of falls has been described previously [3]. This finding could be at least partially related to muscle strength. Age-related decline in muscle quality is more pronounced in women than men [26], as well as age related hallux plantar-flexion strength decrease [27].

The results of this study should be interpreted in the context of its limitations. Since utricular hypofunction was evident in patients with/without falls, and no additional tests were performed, its contribution to postural instability cannot be assessed adequately. Since the evaluation of the occurrence of falls was by self-report, inaccuracy cannot be excluded. In this study, patients were recruited in a primary health care setting, with a low frequency of both complications and polypharmacy, with no history of otologic, neurologic, or orthopaedic disorders. Thus, in patients with more physical impairments the results may be different. According to the cross-sectional design of the study, the findings cannot exclude that patients may develop other vestibular dysfunction in the future. Longitudinal studies are needed to assess the development of the vestibular damage related to diabetes mellitus and its influence on postural control.

Conclusions

In conclusion, in patients with type 2 diabetes mellitus receiving primary health care, who are not seeking medical care due to sensory or balance decline, utricular function may be impaired even in the absence of semicircular canal dysfunction or a history of falls, and the occurrence of falls may not be independently related to vestibular function.

Acknowledgements

We thank Niels Watcher Rodarte for his valuable collaboration, as well as Rita Gómez Díaz and Anabel Meza Urquiza for their contribution to identify candidates to participate in the study and Teresa Mantilla-Ochoa and Lilia Zainos-Saucedo for their contribution to perform nerve conduction studies. The study was supported by CONACyT SALUD-2010-02-151394 and IMSS FIS/IMSS/PROT/1034.

References

1 Jáuregui-Renaud K, Kovacsovics B, Vrethem M, et al. *Dynamic and randomized perturbed posturography in the follow-up of patients with polyneuropathy.* Arch Med Res 1998;29:39-44.

2 Agrawal Y, Carey J, Della Santina C, et al. *Diabetes, Vestibular dysfunction, and falls: analyses from the National Health and Nutrition Examination Survey.* Otol Neurotol 2010;31:1445-50.

3 World Health Organization. *WHO Global report on falls prevention in older age. Epidemiology of falls.* Available at: www.who.int/ageing/publications/Falls_prevention7March.pdf

4 Roman de Mettelinge T, Cambier D, Calders P, et al. *Understanding the relationship between type 2 diabetes mellitus and falls in older adults: a prospective cohort study*. PLoS One 2013;8, e67055.

5 Yau RK, Strotmeyer ES, Resnick HE, et al. *Diabetes and risk of hospitalized fall injury among older adults.* Diabetes Care 2013;36:3985-91.

6 Schwartz AV, Vittinghoff E, Sellmeyer DE, et al. *Diabetes-related complications, glycemic control, and falls in older adults.* Diabetes Care 2008;31:391-6.

7 Gregg EW, Beckle G, Williams DF, et al. *Diabetes and physical disability among older U.S. adults.* Diabetes Care 2000;23:1272-7.

8 Herrera- Rangel A, Aranda-Moreno C, Mantilla-Ochoa MT, et al. *Awareness of sensory decline in patients with type 2 diabetes mellitus.* Int J Diabetes Dev Ctries 2015;35:s458-60.

9 Jáuregui-Renaud K, Sánchez BM, Ibarra-Olmos A, et al. *Neuro-otologic symptoms in patients with type 2 diabetes mellitus.* Diabet Res Clin Pract 2009;84:e45-7.

10 Perez R, Ziv E, Freeman S, et al. *Vestibular end-organ impairment in an animal model of type 2 diabetes mellitus.* Laryngoscope 2001;111:110-3.

11 Myers SF. *Myelin-sheath abnormalities in the vestibular nerves of chronically diabetic rats.* Otolaryngol Head Neck Surgery 1998;119:432-8.

12 Özel HE, Özkiriş M, Gencer ZK, et al. *Audiovestibular functions in noninsulin-dependent diabetes mellitus*. Acta Otolaryngol 2014;134:51-7.

13 Abdul Razzak R, Hussein W. *Postural visual dependence in asymptomatic type 2 diabetic patients without peripheral neuropathy during a postural challenging task.* J Diabetes Complications 2016;30:501-6.

14 Ward BK, Wenzel A, Kalyani RR, et al. *Characterization of vestibulopathy in individuals with type 2 diabetes mellitus.* Otolaryngol Head Neck Surg 2015;153:112-8.

15 Jáuregui-Renaud K, Gutiérrez MA, Viveros RL. *Síntomas de inestabilidad corporal y enfermedad vestibular.* Rev Med Instit Mex Seguro Soc 2003;41:373-8.

16 Feldman EL, Stevens MJ, Thomas PK, et al. *A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy.* Diabetes Care 1994;17:1281-9.

17 England JD, Gronseth GS, Franklin G, et al. American Academy of Neurology; American Association of Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. *Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation.* Neurology 2005;64:199-207.

18 Olds MJ, Lyon MJ. *Glucose utilization of the rat vestibular end organs: a quantitative 2-deoxyglucose study.* Ann Otol Rhinol Laryngol 1997;106:145-50.

19 Payman R, Lyon MJ. *Rat utricular macula: blood flow and stereological assessment of capillary morphology.* Ann Otol Rhinol Laryngol 1993;102:893-9.

20 Myers SF, Ross MD, Jokelainen P, et al. *Morphological evidence of vestibular pathology in long-term experimental diabetes mellitus. I. Microvascular changes.* Acta Otolaryngol 1985;100:351-64.

21 Kocdor P, Kaya S, Erdil M, Cureoglu S, et al. *Vascular and neuroepithelial histopathology of the saccule in humans with diabetes mellitus*. Otology Neurotol 2016;37:553-7.

22 Degerman E, Rauch U, Lindberg S, et al. *Expression of insulin signalling components in the sensory epithelium of the human saccule.* Cell Tissue Res 2013;352:469-78.

23 Pothula VB, Lesser THJ, Sharma AK. *Falls and vestibular impairment.* Clin Otolaryngol All Sci 2004;29:179-82.

24 Aranda-Moreno C, Meza A, Rodriguez R, et al. *Diabetic polyneuropathy may increase the handicap related to vestibular disease.* Arch Med Res 2009;40:180-5.

25 Bonnet CT, Ray C. *Peripheral neuropathy may not be the only fundamental reason explaining increased sway in diabetic individuals.* Clin Biomech 2011;26:699-706.

26 Doherty TJ. *The influence of aging and sex on skeletal muscle mass and strength.* Curr Opin Clin Nutr Metab Care 2001;4:503-8.

27 Menz HB, Zammit GV, Munteanu SE, et al. *Plantar flexion strength of the toes: age and gender differences and evaluation of a clinical screening test.* Foot Ankle Int 2006;27:1103-8.

Received: May 20, 2016 - Accepted: January 15, 2017

Address for correspondence: Kathrine Jáuregui-Renaud, Unidad de Investigación Médica en Otoneurología, Planta baja del Edificio C-Salud en el Trabajo, Centro Médico Nacional siglo XXI, IMSS, Av. Cuauhtémoc 330, Colonia Doctores, 06720 México D.F. Tel. 5255 5627 69 00. E-mail: kathrine.jauregui@imss.gob.mx

ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:436-443; doi: 10.14639/0392-100X-1081

Maxillofacial surgery

Our experience in the surgical management of craniofacial fibrous dysplasia: what has changed in the last 10 years?

La nostra esperienza nel trattamento chirurgico della displasia fibrosa cranio-maxillo-facciale: cosa è cambiato negli ultimi 10 anni?

V. VALENTINI[1], A. CASSONI[1], V. TERENZI[1], M. DELLA MONACA[1], M.T. FADDA[1], O. RAJABTORK ZADEH[1], I. RAPONI[1], A. ANELLI[2], G. IANNETTI[1]

[1] Odontostomatological Science and Maxillofacial Surgery Department, "Sapienza" University of Rome. Policlinico Umberto I, Rome, Italy; [2] Otolaryngology-Head and Neck Surgery Dept, National Cancer Institute "Regina Elena", Rome, Italy

SUMMARY

The mainstay of treatment of craniofacial dysplasia (CFD) remains surgery once clinical observation has been excluded. Nevertheless, disagreement remains about the type of surgical intervention (remodelling versus radical resection). The aim of this paper is to present our experience until 2013 comparing CFD management between 1980 and 2002 and between 2003 and 2013 and to propose our surgical algorithm. From January 2003 to December 2013, 41 new patients (18 males and 23 females) with histologically demonstrated CFD presented to our Department. Data were compared with those of 95 patients observed and/or treated between 1980 and 2002. Considering the last period, we noted that observation (26/41 patients) was the most used method; radical resection was performed in most cases (8/15 patients), but in proportion the numbers of patients undergoing bone shaving has increased (6% between 1980 and 2002 vs 15% between 2003 and 2013), while a decrease in the number of patients undergoing excision was seen (63% between 1980 and 2002 vs. 19% between 2003 and 2013). On this basis, we believe that radical resection is the only technique to obtain resolution of fibrous dysplasia. Wait-and-see is indicated in case of stable lesions. Reconstructive techniques allow obtaining adequate aesthetical and functional results; nevertheless, in most cases adjunctive surgical refinements are required and recovery time is higher than with surgical shaving, so that most patients prefer to perform remodelling. Nevertheless, in case of aggressive lesions radical resection is mandatory, except in paediatric patients with residual large defects in which it can be acceptable to try to resolve symptoms via bone shaving, reserving more aggressive treatments in case of relapse or after skeletal maturity.

KEY WORDS: Craniofacial fibrous dysplasia • Free flap • Paediatric reconstruction • Surgical treatment

RIASSUNTO

Nonostante la chirurgia rimanga l'opzione di scelta nel trattamento della displasia cranio-facciale (CFD) una volta che l'osservazione clinica sia stata esclusa, resta controverso il tipo di intervento (rimodellamento contro resezione radicale). Lo scopo di questo lavoro è di rivedere criticamente la nostra esperienza fino al 2013 confrontando la gestione CFD tra il 1980 e il 2002 e tra il 2003 e il 2013 e di proporre il nostro algoritmo chirurgico. Dal gennaio 2003 al dicembre 2013, 41 nuovi pazienti (18 maschi e 23 femmine) con diagnosi di CFD sono stati considerati. I dati sono stati confrontati con quelli di 95 pazienti che sono stati osservati e / o trattati tra il 1980 e il 2002. Considerando l'ultimo periodo abbiamo notato che l'osservazione clinica (26/41 pzt) è stato il metodo più utilizzato; una resezione radicale è stata eseguita in molti casi (8/15 pzt), ma in proporzione il numero di pazienti sottoposti a rimodellamento è aumentato (6% vs 15%), mentre è stato osservato una diminuzione del numero di pzt sottoposti escissione (63% vs 19%). Su queste basi, riteniamo che la resezione radicale rimanga l'unica tecnica per ottenere la risoluzione della displasia fibrosa. L'osservazione clinica è indicata in caso di lesioni stabili. Le moderne tecniche ricostruttive consentono di ottenere adeguati risultati estetici e funzionali in caso di resezione radicale; tuttavia, nella maggior parte dei casi si rendono necessarie ulteriori procedure ed i tempi di recupero sono superiori, cosicchè la maggior parte dei pazienti preferiscono eseguire il rimodellamento. Nonostante tutto, in caso di lesioni aggressive la resezione radicale è mandatoria, tranne che in pazienti pediatrici in cui tale intervento comporterebbe estesi difetti residui: in tali casi può essere accettabile effettuare un rimodellamento riservando trattamenti più demolitivi in caso di recidiva o dopo la maturità scheletrica.

PAROLE CHIAVE: *Displasia fibrosa cranio-maxillo-facciale • Lembi liberi • Ricostruzione in età pediatrica • Trattamento chirurgico*

Acta Otorhinolaryngol Ital 2017;37:436-443

Introduction

Fibrous dysplasia (FD) is a non-malignant bone lesion characterised by replacement of normal bone with fibro-osseous connective tissue. It was first described by Von Recklinghausen in 1981 as "osteitis fibrosa generalisata" [1 2]. In 1938, Lichtenstein and Jaffe introduced the term "fibrous dysplasia", differentiating between the monostotic and polyostotic types (MFD and PFD, respectively) [3]. The McCune-Albright syndrome (MAS) was described in 1937 [4 5]; in these cases, the polyostotic form is associated with precocious puberty and areas of cutaneous pigmentation (*cafè au lait* spots). The term craniofacial dysplasia (CFD) has been introduced to describe forms arising in the contiguous bones of the cranium and facial skeleton; therefore, it cannot be defined as either a monostotic or polyostotic type [6]. In cases of MFD, the zygomatic-maxillary complex is reported to be the region most commonly involved. In cases of PFD and MAS, the anterior cranial base is involved in the disease in more than 95% of cases [7 8]. Even if medical therapy has a role in the management of symptoms, the mainstay of treatment remains surgery (radical or conservative). Clinical observation is recommended in cases of asymptomatic, slow-growing lesions that do not compromise the quality of life.

We present our experience in 95 patients affected by FD involving craniofacial bones (1980-2002). Among these, we performed surgery in 68 cases. We present an update of our experience and propose our surgical algorithm in which we critically review our experience prior to 2013, and then compare FD management between 1980-2002 and 2003-2013.

Materials and methods

From January 2003 to December 2013, 41 new patients (18 males and 23 females) with histologically demonstrated fibrous dysplasia located in the cranio-maxillofacial area presented to our department. Medium follow-up was 51 months (range: 9-108 months). The average patient age was 29 years (range: 8-72 years). In 35 cases (85%), patients presented with MFD as specified in our previous study; forms affecting two contiguous segments of bone were classified as monostotic, and thus, monostotic should be understood as meaning monofocal. Five patients (12%) had PFD, while only one patient (3%) was diagnosed with MAS. Considering the two periods examined (1980-2002 versus 2003-2013), differences between distribution of the FD type in the patient populations are illustrated in Figure 1A.

Results

Among these 41 patients, 15 (36.5%) underwent surgery. When considering 95 patients that presented to our department between 1980 and 2002, a higher percentage (71.2%) were surgically treated (68 patients). Management of FD according to the patients' group is illustrated in Figure 1B. Observation (26/41 patients) was the most widely used method in the last 10 years. This group consisted of 17 females and nine males with a median age of 31.5 years (range: 8-72). Of particular interest was that nine paediatric patients (34.6%) were present. In 22/26 patients, MFD was observed. Specific data are reported in Table I. None of these patients received treatment, since stable/low growing lesions were present and were not causing functional and/or important aesthetical discomfort.

In patients who underwent surgical treatment, radical resection was performed in most cases (8/15 patients). However, the proportion of patients undergoing bone shaving increased (6% versus 15%), while a decrease in the number of patients undergoing radical surgery was seen (63% versus 19%). Optic canal nerve decompression was performed in one only long-standing symptomatic patient, and a small amount of visual improvement was observed. Radical resection of a mandibular lesion was performed in two cases of relapse (2/7 patients) after bone shaving (one case was performed at

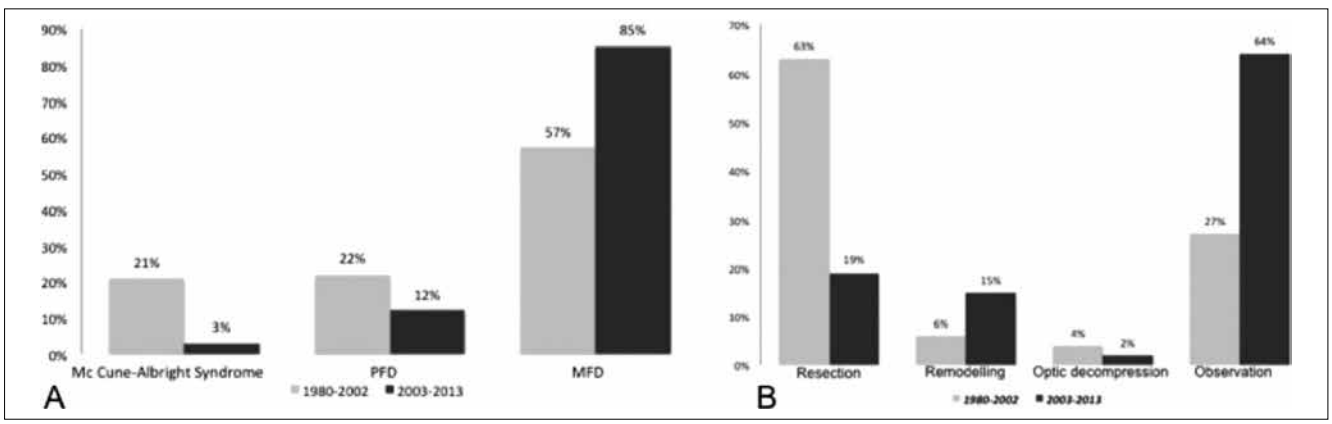


Fig. 1. Changes between 1980 and 2002 and between 2003 and 2013 in the treatment of FD. A) Distribution of FD type; B) Management of FD.

Table I. DF characteristics in the observational group.

Involved Area	Monostotic	Polyostotic	Patient Number
Mandible	7	1	8
Maxillary bone	4	2	6
Maxillary+Cheekbone	1	1	2
Ethmoid	0	3	3
Sphenoid	6	3	9
Frontal	3	3	5
Temporal	0	1	1
Total patients: 26			

another centre). As previously reported, no relapse was observed after radical treatment.

Discussion

FD represents about 2.5% of all bone lesions and 7% of all benign bone tumours, with an incidence of 1:4000-1:10,000 with a slight female predilection; usually the disease arises in the first three decades of life and stabilises when patients reach skeletal maturity [9]. In most cases of CFD, the first clinical manifestation is a slow growing, eventually painful mass causing facial asymmetry. Pathological fractures, orbital dystopia, diplopia, proptosis, blindness, epiphora, strabismus, facial paralysis, loss of hearing, tinnitus and nasal obstruction, may also be evident. These lesions can infrequently present rapid growth and can be associated with other pathological lesions such as mucoceles or aneurysmal bone cysts, while malignant transformation is very rare (< 1% of cases) [8]. On the basis of clinical behaviour, lesions can be classified as:

- quiescent (stable with no growth);
- non-aggressive (slow growing);
- aggressive (rapid growth +/- pain, para-aesthesia, pathologic fracture, malignant transformation, and association with secondary lesions).

Diagnosis can be made with X-ray and CT-scan, but an incisional biopsy is mandatory. Once FD is confirmed, it is important to exclude PFD and MAS. Serum alkaline phosphatase is an important marker in detecting recurrence of FD [10].

Surgery is considered the mainstay of treatment once clinical observation has been excluded. In our experience over the last 10 years, we noted that observation has been the therapy of choice in cases of FD (63.5% observational cases versus 28.8% surgery). In the last several years, medical therapy with biphosphonate (such as zoledronic acid) or an antibody to RANKL (such as denosumab) has been used to attempt to control pain and stabilise lesions, but long term effects are controversial [10-15]. Radiotherapy is excluded because of the high risk of malignant transformation [8]. At present, the main discussion is about the type of surgery, since radical resection is the only curative technique, while bone shaving allows achieving adequate aesthetic-functional results but is burdened by a higher recurrence rate [7]. In a previous study, we stated that "we prefer conservative treatment of fibrous dysplasia only in cases involving the cranial base, polyostotic forms, and McCune-Albright syndrome. On the other hand, in the majority of cases of MFD or monofocal fibrous dysplasia of the craniofacial region, we conclude that modern surgical techniques allow an aggressive but definitive treatment with good functional and aesthetic results." [7].

In principle we still agree with this statement, but analysing the data on FD management (Figure 1B), we observed that in the last 10 years the number of patients undergoing bone shaving has increased (6% versus 15%), while a decrease in number of patients undergoing radical surgery was seen (63% versus 19%). On this basis, we propose a more detailed surgical algorithm in which we specify that clinical observation is the first option. A first proposal for FD classification was suggested by Chen in 1990 [16]. He differentiated treatment on the basis of involved sites and defined four zones:

- Zone 1: fronto-orbito-malar regions of the face. Radical excision and reconstruction are recommended.
- Zone 2: hair bearing scalp. Intervention is optional.
- Zone 3: central skull base including the sphenoid, pterygoid, petrous temporal bone, and mastoid. Observation is recommended.
- Zone 4: tooth bearing portions of the skull, the maxilla and mandible. Conservative management is recommended.

As previous reported, we only partially agree with the algorithm proposed by Chen, since free flaps allow optimal results in the recontruction of Zone 4 defects; nevethless, at present, we have partially changed our opinion about the treatment of stable lesions involving Zones 1 and 4 [7]. Another detailed description of CFD management according to anatomical sites has been recently proposed by Lee et al [8]. In this study, we present our algorithm based on pathological behaviour and symptoms.

a) Facial deformities

Most patients affected by CFD present a slow growing, indolent mass, and facial deformity is the only symptom. In most cases, disease progression stops once skeletal maturity has been achieved, but reactivation of the disease has been observed in adulthood and during pregnancy [17 18]. Even in MAS cases, skull lesions preferentially do not progress after puberty. Deformities are more disfiguring than in MFD and PFD, particularly if GH excess is untreated or inadequately treated [19]. Management of FD depends on the anatomical site as well as on clinical and biological characteristics of lesions, but, especially in younger patients, it is impossible to predict it since no biomarkers or specific histological characteristics exist. In those latter cases, watching carefully and attentively is the best option. It is preferable to perform any

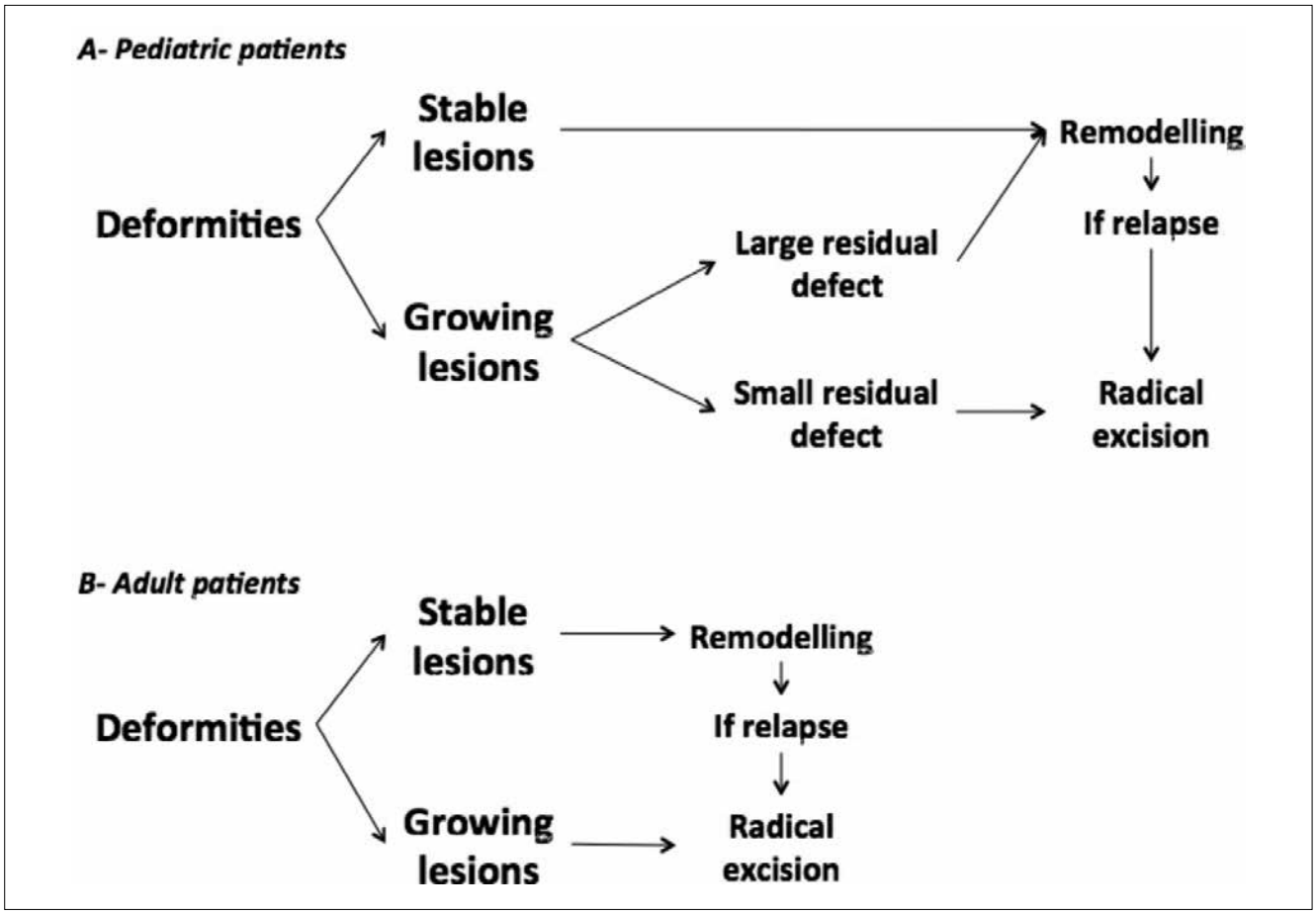


Fig. 2. Surgical management of facial deformities in adults (A) and children (B).

kind of surgery only after puberty, but sometimes it is necessary to operate on the patient earlier.

One of the main question concerns is the treatment choice and whether it is easier to treat an adult or a child. In our previous paper, we recommended wide resection and contemporary reconstruction in cases of Zones 1 and 4 lesions even in younger children [7]. While in cases of Zone 1 defects, reconstruction can be achieved in most cases using bone grafts and/or local flaps; in cases of Zone 4 defects, free flaps are preferential as they can assure adequate reconstruction, but in younger patients their use should be discussed [20 21]. It is clear that it is more important to distinguish between adult (> 14 years) and paediatric (< 14 years) patients than between stable (quiescent/non-aggressive) and growing (aggressive) lesions. Considering both adult and paediatric populations with cases of stable lesions, we currently recommend remodelling as the primary treatment (Figs. 2A and B). It is true that a major rate of recurrence is reported after bone shaving, but it can be repeated.

An adequate follow-up (annual CT scan for the first two years and then based on of clinical findings) makes it possible to identify relapse and to treat it early. Obviously, in those latter cases the treatment of choice is surgical resection and contemporary reconstruction. The change in the treatment of stable lesions in adult patients is due to the fact that wide resection always requires reconstruction; this can lead to higher post-operative morbidity in terms of recovery time when compared to surgical shaving, even if the aesthetical and functional results are considered better.

Based on our advice, it is mandatory to inform the patient about the therapeutic options. In most cases, remodelling is the favoured choice. This is probably due to the fact that most patients prefer to try to obtain aesthetical and functional improvements with a less complex surgical intervention, knowing that in case of a relapse radical surgery can be performed.

In previous studies, reports on recurrence do not differentiate between stable and growing lesions; it can be hypothesised that in the first cases the expected recurrence rate would be lower. In paediatric patients, remodelling permits the clinician to avoid influencing craniofacial growth and asymmetry. Currently, surgical shaving can be optimised using computer-assisted navigation [22]. Mirroring techniques permit achieving optimal aesthetic results, but there appear to be some disadvantages. The main one is the absence of instruments in some centres. Due to the low use in maxillofacial surgery, operative time is higher than with conventional techniques [23].

In cases of aggressive lesions, it seems the best therapeutic option is surgical resection and contemporary reconstruction; nevertheless, in the case of paediatric patients each case has to be carefully evaluated according to several parameters:

- wide resection (mostly if altering occlusion) leads to some degree of facial asymmetry regardless of reconstruction;
- donor site morbidity must be considered.

We have to distinguish between two main situations:

- *Small residual defects:* Reconstruction can be achieved using local flaps or bone grafts, so that a radical resection can be considered. Since radiotherapy is not considered, treatment for CFD, complications related to bone grafts and absorption due to irradiation can be excluded. The best option in cases of mandibular reconstruction is the use of an autogenous rib graft. Such cases may require further surgical intervention (eventually with a free flap reconstruction) once skeletal maturity has been reached in order to permit implanto-prosthetic rehabilitation [24]. In this group with Zone 1 defects, in which bone graft reconstruction leads in most cases to adequate results, can be included [16 25 26].
- *Large residual defects:* Even an adequate reconstruction can lead to facial asymmetry, and remodelling as the first choice should be considered, eventually delaying a more aggressive surgical intervention after puberty. Currently, free-tissue transfer has become the preferred treatment option for reconstruction of extensive tissue; iliac crest and fibula free flaps appear to be the best options in cases of Zones 1 and 4 defects in adults. Nevertheless, some considerations have to be made in younger patients, since the recipient vessels are much more prone to vasospasm compared to those in adults. In addition, one must consider growth alteration at the donor site. Iliac crest free flap is not considered before skeletal maturity has been reached [20]. Fibula free flaps are the best choice, and donor-site morbidity can be minimised in most cases with attention to technical details of fibular flap harvesting and use of aggressive physical therapy [27]. Nevertheless, even if some authors advocate its use also in younger patients (< 9 years), we think that in cases of surgical resection for malignant lesions immediate reconstruction using fibula free flap can be justified, but in FD cases this option has to be considered only after failure of primary reconstruction using bone grafts or in case of relapse after remodelling has occurred.

b) Trigeminal nerve impairment

Growing lesions can result in compression of the adjacent structure such as the trigeminal nerve; patients refer hypo-anaesthesia or para-aesthesia, but in some cases they complain of hyperaesthesia. In such cases, surgical decompression of the canal nerve has been described [28]. Nevertheless, this procedure cannot be definitive; in such cases, more aggressive intervention consisting of nerve interruption at the Spix or infraorbital foramen may be required. In order to restore sensitivity of the lip and teeth, a microsurgical anastomosis with the contralateral mandibular nerve can be performed at the same surgical time (Fig. 3). In cases of infraorbital nerve impairment, anastomosis can be performed using a nerve graft [29].

c) Sinusitis

Between the paranasal sinuses, the sphenoid sinus is the most frequently affected by FD [8 30]. Nevertheless, the incidence of sinusitis in patients affected by FD is the same when compared with the general population [8]. The treatment is the same and consists of a combination of surgery and medical therapy (Fig. 4A); obviously, surgery is necessary to correct anatomical alterations causing obstruction or associated lesions such as mucocele [18]. A preferential approach, as in the general population, is an endoscopic one [31]. If aesthetical corrections are needed,

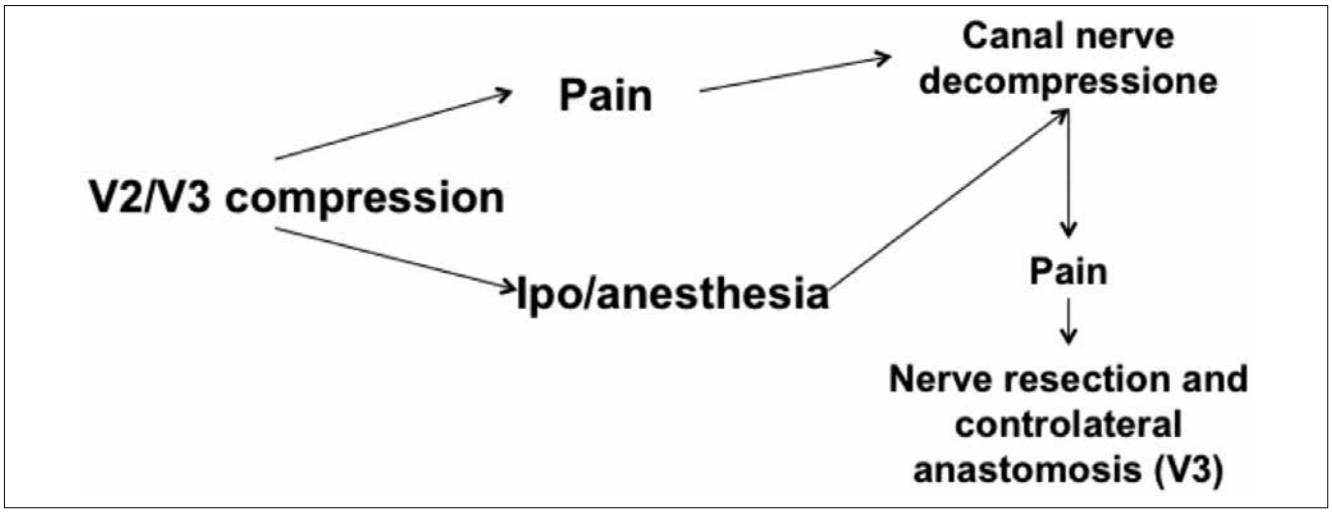


Fig. 3. Surgical management of V2/V3 impairment.

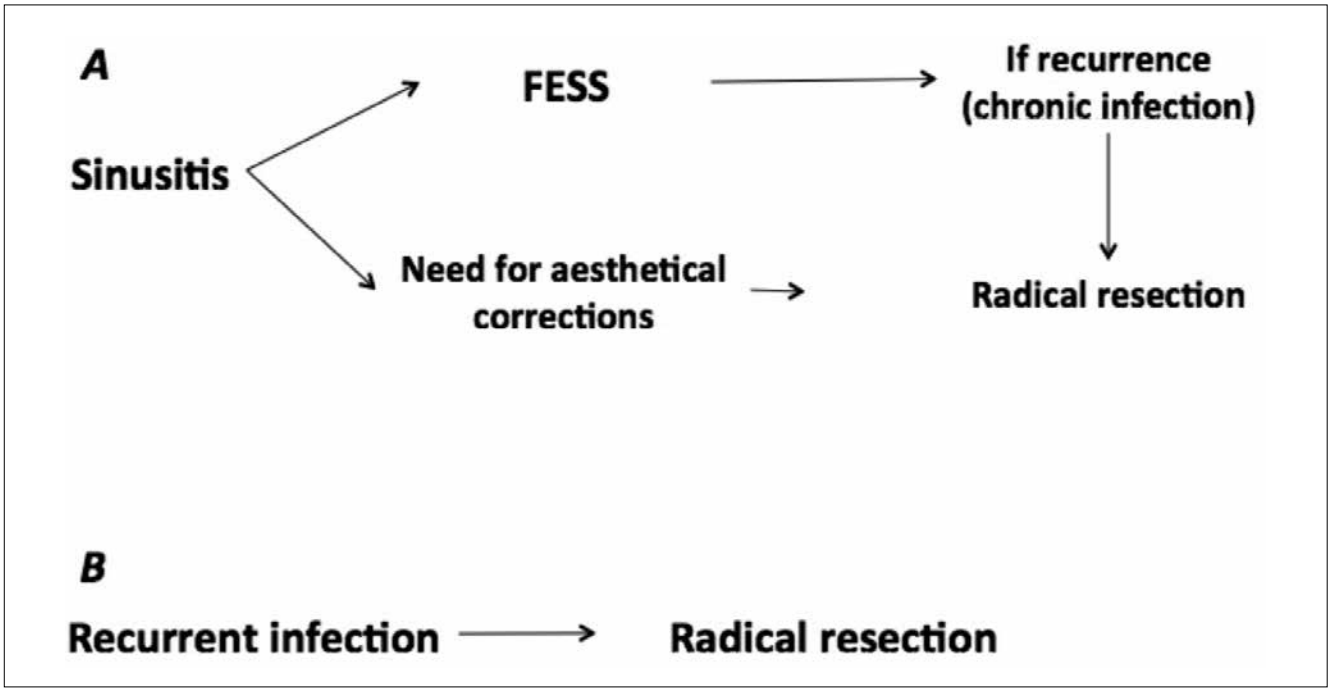


Fig. 4. Surgical management of sinusitis and of recurrent infections.

these should eventually be made in association with open access. In cases of recurrent sinonasal infection, particular attention must be paid to avoid complications such as osteomyelitis. In such cases, surgical resection is required.

d) Osteomyelitis

In patients affected by FD, osteomyelitis is one of the complications that can arise. It is most frequent in case of lesions involving the maxilla and mandible derived from dental infections or recurrent sinusitis. Diagnosis can be difficult, since only histological examination can confirm it in most cases. It is very challenging to treat. Medical therapy is mandatory, but to resolve the pathology, surgical resection (Fig. 4B) is usually required [8]. It is known that caries index scores are higher in patients affected by FD, and this has been attributed to enamel hypoplasia and hypomineralisation, and also to limited dental care. In cases of dental infection, it is mandatory to extract or treat the teeth, but in these cases healing can be altered thus increasing the risk of osteomyelitis [8].

Diplopia/exophthalmos

Orbital bone involvement in cases of CFD can lead to midfacial asymmetry or hypertelorism, exophthalmos and proptosis (in cases of anterior skull base and frontal bone involvement); diplopia can be referred. In the first case, treatment is described in the section "Facial deformities" and consists of remodelling in cases of stable lesions and wide resection in cases of aggressive ones. When massive involvement of the orbital bones is observed, an interdisciplinary approach is mandatory to evaluate the presence of ophthalmological complications such as diplopia and visual impairment [32]. In surgical treatment of exophthalmos consequent to FD, it must be considered that remodelling of maxilla and zygoma can lead to a worsening of symptoms. In those cases, surgical osteotomies to improve orbital volume should be performed (Fig. 5A). If only a 2-wall decompression is required, an endoscopic approach has to be considered [33]. Obviously, maxillo-zygomatic correction must be considered at the same surgical time. In order to treat diplopia, the first step is to correct orbital dystopia; eventually, eye muscle realignment surgery can be performed.

e) Optic nerve compression (ONC)

CFD involving the anterior cranial base and sphenoid bone can encase the optic nerve, but does not always result in visual loss. It is already accepted that loss of vision consequent to optic canal nerve involvement can be due to several factors, including direct compression, optic nerve traction (proptosis), haemorrhage/injury of the optic nerve and FD-associated cystic lesions [34].

Recently, a meta-analysis concluded that most patients affected by CFD with radiographic optic nerve compression are asymptomatic and will remain that way, so that "...surgical decompression should be reserved for symptomatic patients, the majority of whom will show improvement and good long-term results after optic nerve decompression. Expectant management, repeated ophthalmologic exams, and long-term radiologic follow-up are indicated in asymptomatic FD patients who have optic nerve encasement." [35]. In cases in which decompression is required, we agree with Schreiber et al (Fig. 5B), who stated that "... endoscopic optic nerve decompression has become wide-

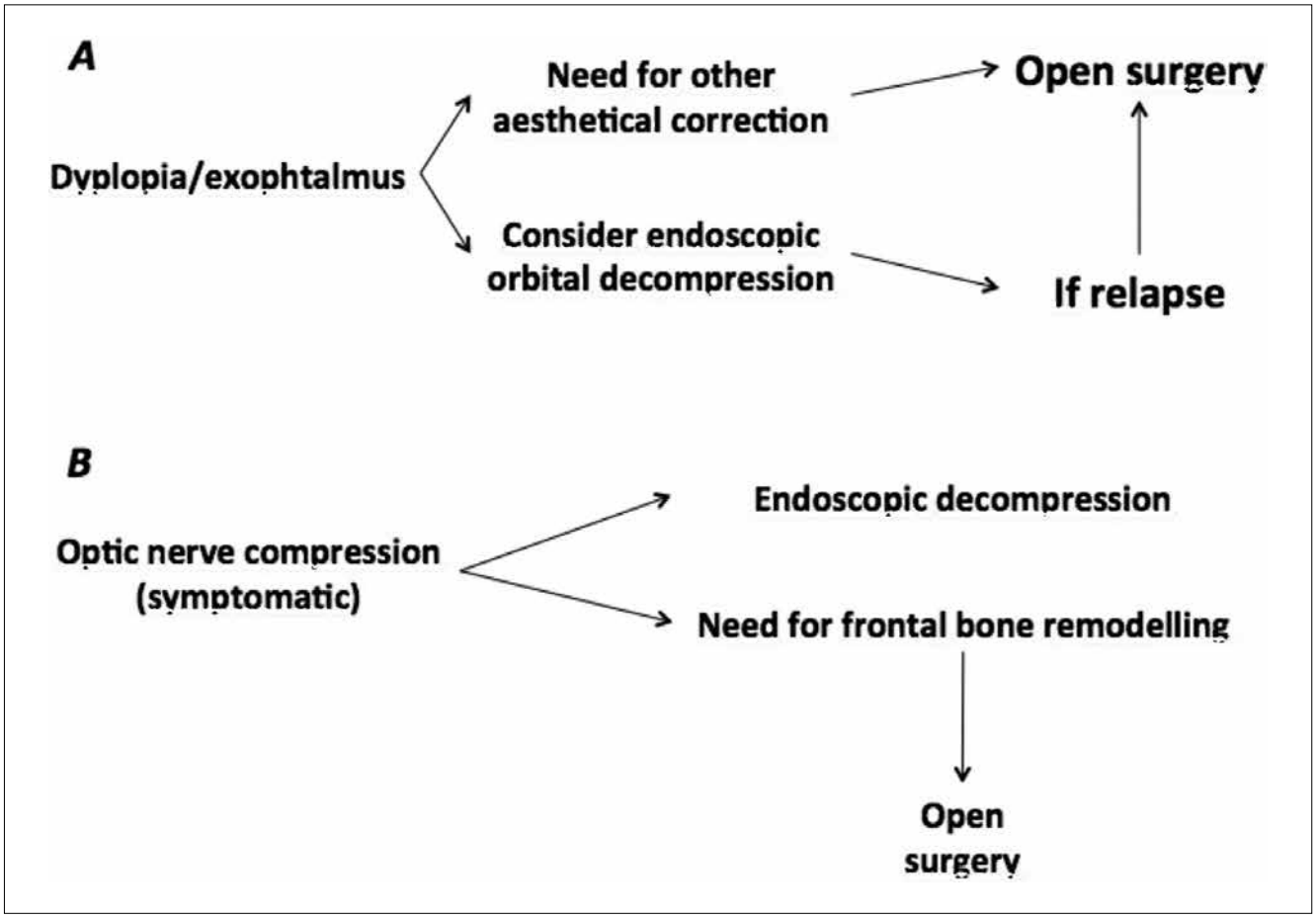


Fig. 5. Surgical management of diplopia/exophthalmos and optic nerve compression.

ly accepted as the approach of choice for post- traumatic injuries and subsequently for benign lesions compressing the nerve and accessible through the nose, such as fibrous dysplasia" [18]. Open surgery is reserved for cases in which a need for frontal bone or other anterior cranial base remodelling is required; obviously, a combined approach should eventually be considered.

Conclusions

Fibrous dysplasia is a benign disease and radical resection (if possible) is the only technique to obtain resolution of the disease. Watching carefully and attentively is indicated in cases of stable lesions, and based on our experience, it is the best therapeutic option if possible. Current reconstructive techniques allow achieving adequate aesthetic and functional results; nevertheless, in most cases adjunctive surgical refinements are required and recovery times are higher than in cases of surgical shaving, so that most patients prefer to undergo remodelling. Nevertheless, in cases of aggressive lesions we think that radical resection is mandatory, except in paediatric patients with residual large defects. In these cases, we think that it is acceptable to try and resolve symptoms by performing bone shaving, reserving more aggressive treatment for cases of relapse or after skeletal maturity.

References

1 Ozek C, Gundogan H, Bilkay U, et al. *Craniomaxillofacial Fibrous dysplasia*. J Craniofac Surg 2002;13:382-9.

2 Von Recklinghausen. *FD: Die fibrose oder deformierende Ostitis, die Osteomalacie, und die ostoplastische Carcinose in ihren gegenseltgen Beziehungen*. Berlin: Festschr, Rudolf Virchow; 1891.

3 Lichtenstein L, Jaffe HL. *Fibrous dysplasia of bone: a condition affecting one, several or many bones, tha graver cases of which may present abnormal pigmentation of skin, premature sexual development, hyperthyroidism or still other extraskeletal abnormalities*. Arch Pathol 1942;33:777.

4 McCune DJ. *Osteitis fibrosa cystica: the case of a nine year old girl who also exhibits precocious puberty, multiple pigmentation of the skin and hyperthyroidism*. Am J Dis Child 1936;52:743.

5 Albright F, Butler AM, Hampton AO, et al. *Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females: report of five cases*. N Engl J Med 1937;216:727.

6 Eversole LR, Sabes WR, Rovin S. *Fibrous dysplasia: A nosologic problem in the diagnosis of fibro osseous lesions of the jaws*. J Oral Pathol 1972;1:189-220.

[7] Valentini V, Cassoni A, Marianetti TM, et al. *Craniomaxillofacial fibrous dysplasia: conservative treatment or radical surgery? A retrospective study on 68 patients*. Plast Reconstr Surg 2009;123:653-60.

[8] Lee JS, FitzGibbon EJ, Chen YR, et al. *Clinical guidelines for the management of craniofacial fibrous dysplasia*. Orphanet J Rare Dis 2012;7Suppl1:S2.

[9] Menon S, Venkatswamy S, Ramu V, et al. *Craniofacial dysplasia: literature review*. Ann Maxillofac Surg 2013;3:66-71.

[10] Park BY, Cheon YW, Kim YO, et al. *Prognosis for craniofacial fibrous dysplasia after incomplete resection: AGE and serum alkaline phosphatise*. Int J Oral Maxillofac Surg 2010;39:221-6.

[11] Chapurlat RD, Gensburger D, Jimenez-Andrade J, et al. *Pathophysiology and medical treatment of pain in fibrous dysplasia of bone*. Orphanet J Rare Dis 2012;7Suppl1:S3

[12] Wu D, Ma J, Bao S, et al. *Continuous effect with long-term safety in zoledronic acid therapy for polyostotic fibrous dysplasia with severe bone destruction*. Rheumatol Int 2015;35:767-72.

[13] Ganda K, Seibel MJ. *Rapid biochemical response to denosumab in fibrous dysplasia of bone: report of two cases*. Osteoporos Int 2014;25:777-82.

[14] Thomsen MD, Rejnmark L. *Clinical and radiological observations in a case series of 26 patients with fibrous dysplasia*. Calcif Tissue Int 2014;94:384-95.

[15] Boyce AM, Chong WH, Gafni RI, et al. *Denosumab treatment for fibrous dysplasia*. J Bone Miner Res 2012;27:1462-70.

[16] Chen YR, Noordhoff MS. *Treatment of craniomaxillofacial fibrous dysplasia: How early and how extensive?* Plast Reconstr Surg 1990;86:835-42.

[17] Lee, Davies ML, Macpherson P. *Fibrous dysplasia of the skull: disease activity in relation to age*. Br J Radiol 1991;64:576-9.

[18] Schreiber A, Villaret AB, Maroldi R, et al. *Fibrous dysplasia of the sinonasal tract and adjacent skull base*. Curr Opin Otolaryngol Head Neck Surg 2012;20:45-52.

[19] Lala R, Matarazzo P, Andreo M, et al. *Impact of endocrine hyperfunction and phosphate wasting on bone in McCune- Albright syndrome*. J Pediatr Endocrinol Metab 2002;15:913-20.

[20] Genden EM, Buchbinder D, Chaplin JM, et al. *Reconstruction of the pediatric maxilla and mandible*. Arch Otolaryngol Head Neck Surg 2000;126:293-300.

[21] Weizman N, Gil Z, Wasserzung O, et al. *Surgical ablation and free flap reconstruction in children with malignant head and neck tumors*. Skull Base 2011;21:165-70.

[22] Yu H, Shen SG, Wang X, et al. *The indication and application of computer-assisted navigation in oral and maxillofacial surgery-Shanghai's experience based on 104 cases*. J Craniomaxillofac Surg 2013;41:770-4.

[23] Nowinski D, Messo E, Hedlund A, et al. *Computer-navigated contouring of craniofacial fibrous dysplasia involving the orbit*. J Craniofac Surg 2011;22:469-72.

[24] Eckardt A, Swennen G, Barth EL, et al. *Long-term results after mandibular continuity resection in infancy: the role of autogenous rib grafts for mandibular restoration*. J Craniofac Surg 2006;17:255-60.

[25] Gabbay JS, Yuan JT, Andrews BT, et al. *Fibrous dysplasia of the zygomaticomaxillary region: outcomes of surgical intervention*. Plast Reconstr Surg 2013;131:1329-38.

[26] Valentini V, Cassoni A, Marianetti TM, et al. *Reconstruction of craniofacial bony defects using autogenous bone grafts: a retrospective study on 233 patients*. J Craniofac Surg 2007;18:953-8.

[27] Crosby MA, Martin JW, Robb GL, et al. *Pediatric mandibular reconstruction using a vascularized fibula flap*. Head Neck 2008;30:311-9.

[28] Bessho K, Tagawa T, Murata M, et al. *Monostotic fibrous dysplasia with involvement of the mandibular canal*. Oral Surg Oral Med Oral Pathol 1989;68:396-400.

[29] Meyer RA, Bagheri SC. *Microsurgical reconstruction of the trigeminal nerve*. Oral Maxfac Surg Clin N Am 2013;25:287-302.

[30] DeKlotz TKH. *Otologic and sinonasal manifestations of PFD/MAS.* Presented at the Combined Otolaryngology Spring Meeting Chicago, IL 2011.

[31] Re M, Magliulo G, Romeo R, et al. *Risks and medico-legal aspects of endoscopic sinus surgery: a review*. Eur Arch Otorhinolaryngol 2014;271:2103-17.

[32] Goisis M, Biglioli F, Guareschi M, et al. *Fibrous dysplasia of the orbital region: current clinical perspectives in ophthalmology and cranio-maxillofacial surgery*. Ophtal Plast Reconstr Surg 2006;22:383-7.

[33] Choi JW, Lee SW, Koh KS. *Correction of proptosis and zygomaticomaxillary asymmetry using orbital wall decompression and zygoma reduction in craniofacial fibrous dysplasia*. J Craniofac Surg. 2009;20:326-30.

[34] Lee JS, FittzGibbon E, Butman JA, et al. *Normal vision despite narrowing of the optic canal in fibrous dysplasia*. N Engl J Med 2002;347:1670-6.

[35] Amit M, Collins MT, FitzGibbon EJ, et al. *Surgery versus watchful waiting in patients with craniofacial fibrous dysplasia-a meta-analysis*. PLoS ONE 2011;6:e25179.

Received: September 1, 2016 - Accepted: October 18, 2016

Address for correspondence: Valentina Terenzi, viale del Policlinico 155, 00100 Rome, Italy. E-mail: v.terenzi@libero.it

ACTA OTORHINOLARYNGOLOGICA ITALICA 2017;37:444-446; doi: 10.14639/0392-100X-1193

CASE SERIES AND REPORTS

Injection laryngoplasty through a transoral approach using the Guedel oral airway

Laringoplastica iniettiva mediante approccio transorale con l'utilizzo della cannula di Guedel

A.L. HAMDAN[1], M. RIZK[2], C. AYOUB[2], G. ZIADE[1]

[1] Department of Otolaryngology, Head & Neck Surgery, American University of Beirut Medical Center, Beirut-Lebanon; [2] Department of Anesthesiology, American University of Beirut Medical Center, Beirut-Lebanon

SUMMARY

Injection laryngoplasty has gained popularity as a treatment modality for glottal insufficiency. Several approaches have been described, specifically transcutaneous, transoral and transnasal. The authors describe a novel technique performed successfully on three subjects, namely endoscopic injection laryngoplasty using the modified Guedel oral airway. There was marked improvement in dysphonia, maximum phonation time and closed quotient in all three subjects with a decrease in the Voice Handicap Index-10 score. This new approach is a viable approach for the treatment of glottal insufficiency.

KEY WORDS: Glottic insufficiency • Laryngoplasty • Endoscopy

RIASSUNTO

Le laringoplastiche iniettive hanno ottenuto notevole popolarità come modalità di trattamento per l'insufficienza glottica. Numerosi approcci sono stati descritti: transcutaneo, transorale, transnasale. Gli autori descrivono una nuova tecnica, eseguita con successo in tre pazienti: la laringoplastica iniettiva endoscopica con l'utilizzo la cannula di Guedel modificata. C'è stato un marcato miglioramento della disfonia, del tempo massimo fonatorio e del quoziente di chiusura glottica, insieme ad un decremento del Voice-Handicap Index-10 score. Questo nuovo valido approccio è applicabile per il trattamento dell'insufficienza glottica.

PAROLE CHIAVE: *Insufficienza glottica • Laringoplastica • Endoscopia*

Acta Otorhinolaryngol Ital 2017;37:444-446

Introduction

Injection laryngoplasty has gained popularity among otolaryngologists as a treatment modality for glottic insufficiency. The main approaches are the transcutaneous, transoral and transnasal. The transoral approach is primarily limited by the presence of hyperactive gag reflex and/or inadequate oral opening, whereas the transcutaneous approach is limited by unfavourable neck anatomy. In both approaches two routes are used, one for visualising the larynx and the other for introducing the injecting needle. In addition, there is a need for an experienced assistant to perform the flexible endoscopy [1 2]. On the other hand, transnasal injection laryngoplasty as described by Ricci Maccarini A et al. is a safe procedure with limited discomfort to the patient [3]. Nevertheless, it has limited application in cases of a narrow nasal passage, especially in patients who are on anticoagulants [3].

The authors describe a novel approach, namely fibre optic endoscopic injection laryngoplasty through the transoral approach using the modified Guedel oral airway [4] (Fig. 1). This approach can be used as alternative to the aforementioned conventional approaches.

This investigation was exempted from the Institutional Review Board Approval. While the patient was seated in the examination room, the oral cavity, oropharynx and larynx were anesthetised by applying xylocaine spray and gel to the dorsum of the tongue, following which the modified Guedel oral airway was inserted. The fibre optic scope with working channel (Ref 11001UD1 by Karl Storz) was then gently introduced thru the oral airway until the laryngeal structures were visualised (Fig. 2). Similar to the transnasal approach, once the fibre optic scope was in place, a 19 gauge fibre optic needle (Endoline Securline – BTC Medical Europe S.R.L., made in Italy) was then introduced through the working channel of the endoscope and its blunted tip was used to palpate the posterolateral and mid aspect of the vocal cord to ensure complete anaesthesia. The needle was then engaged at the desired injection site and filling material was injected until voice quality was satisfactory. The scope is usually handled with the right hand and the injecting needle in the left hand. The sy-

Fig. 1. The modified Guedel oral airway with the roof of the convex curvature removed.

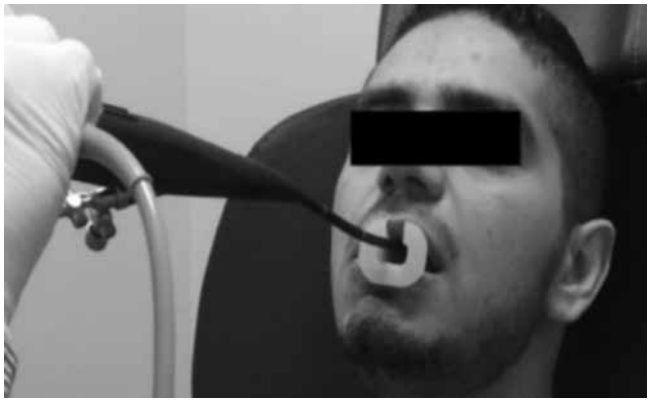


Fig. 2. Patient in the sitting position and the fiberoptic scope introduced through the modified Guedel oral airway.

ringe containing the filling materiel can be either pressed by the surgeon or by the assistant. Patients were instructed to resume oral intake one hour after the procedure to avoid risk of aspiration. Pooling of secretions in the larynx was reduced by administering intramuscular glucopyrrolate (200 micrograms/1 ml) prior to the procedure.

Case series

Patient selection for this approach was based on the presence of either a strong gag reflex (patient 1), intake of anticoagulants and/or the presence of a narrow nasal passage (patients 2 and 3). The first patient was a 23-year-old man with dysphonia and aspiration secondary to an immobile right vocal cord and impaired mobility of the left cord following prolonged intubation that resulted in subglottic scarring. The second patient was a 60-year-old woman with dysphonia and dysphagia secondary to an immobile right vocal cord post resection of a right cerebellopontine angle tumour. The third patient was a 65-year-old woman with dysphonia and dysphagia secondary to a left immobile vocal cord following total thyroidectomy. In all three patients, 0.2 to 0.6 cc of Restylane® (hyaluronic acid stabilised solution 20 mg/ml) was injected lateral to the vocal process and/or at the mid vocal cord. Perceptual evaluation, maximum phonation time, as well as closed quotient and Voice Handicap Index-10 [5] were used as outcome measures.

This novel approach was well tolerated by all patients with no complications. In all three subjects, there was marked improvement in all perceptual parameters (Table I) with an increase in the maximum phonation time by 8 seconds in the first patient, 7 seconds in the second patient and 5.5 seconds in the third. There was also a noticeable decrease in the Voice Handicap Index-10 score in the three subjects (Table II).

The mean closed quotient, measured by computing the ratio of closed frames to the total number of frames, improved from 0 to 0.4 in subject one, from 0.3 to 0.5 in subject two and from 0.4 to 0.5 in subject three.

Discussion

Injection laryngoplasty as an office procedure has become the gold standard treatment of glottic insufficiency [2]. There are ubiquitous reports on the added value of the different approaches used with the main focus being on tolerance, safety and improvement in voice quality and swallowing. As a novel approach, we have combined the usage of the transnasal fibre optic endoscope/working channel with the modified Guedel oral airway primarily used in gastroscopy and bronchoscopy. The added values of this novel approach are; 1, the use of only one route for visualisation of the larynx and introduction of the injecting needle unlike the transoral and transcutaneous approaches; 2, the

Table I. Perceptual evaluation, GRBAS classification.

GRBAS classification	Subject 1		Subject 2		Subject 3	
	Before injection	After injection	Before injection	After injection	Before injection	After injection
Grade	3	1	3	1	3	1
Roughness	3	1	3	2	3	2
Breathiness	3	1	3	1	3	1
Asthenia	3	2	3	2	3	1
Strain	0	0	0	0	0	0

Table II. Voice Handicap Index (VHI-10).

VHI-10	Subject 1		Subject 2		Subject 3	
	Before injection	After injection	Before injection	After injection	Before injection	After injection
F1. My voice makes it difficult for people to hear me	4	1	4	0	4	0
P2. I run out of air when I talk	4	2	3	1	4	0
F3. People have difficulty understanding me in a noisy room	4	1	4	1	3	1
P4. The sound of my voice varies throughout the day	4	2	4	2	2	1
F5. My family has difficulty hearing me when I call them throughout the house	4	1	4	0	4	0
F6. I use the phone less often than I would like to	4	2	4	1	4	1
E7. I'm tense when talking to others because of my voice	4	2	3	1	2	1
F8. I tend to avoid groups of people because of my voice	4	1	4	0	3	1
E9. People seem irritated with my voice	3	0	3	0	1	0
P10. People ask, "what's wrong with your voice?"	4	1	4	1	4	1
Total score	39	13	37	7	31	6

use of the modified oral airway facilitates the introduction of the fibre optic endoscope and guides its pathway to the laryngeal inlet with no difficulty or discomfort to the patient as the scope slides on the lingual surface of the oral airway with little if any contact with the mucosa; 3, the fibre optic scope secures the passage of the injection needle through the endoscope working channel thus preventing inadvertent injury to the pharyngeal mucosa; 4, it allows the surgeons to use both hands with no need for an experienced assistant to do the fibre optic endoscopy or for the patient to hold his or her tongue. The scope is usually held by the surgeon's left hand and the fibre optic needle is held in the right hand. It is important to note that the fibre optic scope can be easily maneuvered through the oral airway because of the enhanced rotation along its longitudinal access achieved by the removal of the dorsal convex roof. Another advantage is the lack of risk for the patient to bite the scope by accident.

Conclusions

This approach is a viable alternative to the transoral, transcutaneous and transnasal approaches. It is of particular added value to the transcutaneous approach in patients with unfavourable neck anatomy, to the transoral approach in patients with a strong gag reflex and to the transnasal approach in patients with narrow nasal passages and/or are on anticoagulants.

References

1 Courey MS. *Injection laryngoplasty*. Otolaryngol Clin North Am 2004;37:121-38.

2 Sulica L, Rosen CA, Postma GN, et al. *Current practice in injection augmentation of the vocal folds: indications, treatment principles, techniques, and complications*. Laryngoscope 2010;120:319-25.

3 Ricci Maccarini A, De Rossi G, Pieri F, et al. *Injection Laryngoplasty Under Fiberoptic Endoscopy*. Injection Laryngoplasty 2015:51-65. Springer International Publishing.

4 Ayoub C, Itani MM, Lteif A, et al. *A modified Guedel airway for continuous oxygenation and suctioning during fibreoptic bronchoscopy*. Anaesthesia 2000;55:455-7.

5 Rosen CA, Lee AS, Osborne J, et al. *Development and validation of the voice handicap index-10*. Laryngoscope 2004;114:1549-56.

Received: April 2, 2016 - Accepted: December 23, 2016

Address for correspondence: Abdul-Latif Hamdan, American University of Beirut, Department of Otolaryngology, 11-0236 Beirut-Lebanon. Tel. 961-1-350000. E-mail: ah77@aub.edu.lb

ECHNO 2018

ROME Italy
11-12-13-14
April 2018

8th EUROPEAN CONGRESS ON HEAD AND NECK ONCOLOGY

PRECONGRESS EVENT 11 April 2018
AIOCC - IHNS Italian Head and Neck Society National Congress

SCIENTIFIC COMMITTEE:

Giuseppe Spriano
ECHNO Chairman

C. René Leemans
EHNS President

Wojciech Golusinski
EHNS Secretary

Piero Nicolai
AIOCC - IHNS President

EUROPEAN ORGANIZER:

EHNS
www.ehns.org
European Head and Neck Society

LOCAL COMMITTEE:

AIOCC - IHNS
Associazione Italiana Oncologia Cervico Cefalica

IAOO 2019

ROME Italy
3 - 4 - 5 - 6
July 2019

7th WORLD CONGRESS OF THE INTERNATIONAL ACADEMY OF ORAL ONCOLOGY

www.iaoo2019.com