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Review

Swallowing evaluation with videofluoroscopy in the paediatric population

Valutazione della funzione deglutitoria in videofluoroscopia nei pazienti pediatrici

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SUMMARY

Paediatric swallowing disorders can have several causes, from prematurity and congenital anomalies to gastro-oesophageal reflux and infective or inflammatory pathologies of the upper digestive tract. In neonates, the swallowing process is reflexive and involuntary. Later in infancy, the oral phase comes under voluntary control, while the pharyngeal phase and oesophageal phases remain involuntary. Swallowing difficulties can severely compromise pulmonary health and nutritional intake of paediatric patients. Videofluoroscopic Swallow Study (VFSS) is a radiographic procedure that provides a dynamic view of the swallowing process and is frequently considered to be definitive evaluation for objective assessment of dysphagia in paediatric patients. This review focuses on the different possible aetiologies of paediatric swallowing disorders and related videofluoroscopic swallowing study procedures and appearances.

KEY WORDS: Swallowing disorders • Videofluoroscopic swallowing study • Paediatric • Dysphagia

RIASSUNTO

I disturbi della deglutizione in età pediatrica possono essere dovuti a diverse cause, dalla condizione di prematurità e patologie malformative sino al reflusso gastro-esofageo o a patologie infettive od infiammatorie del primo tratto gastroenterico. Nei neonati il processo della deglutizione è involontario e basato su meccanismi riflessi. In seguito, nell' infanzia, la fase orale diventa volontaria , mentre le fasi faringea ed esofagea rimangono involontarie. I disordini della deglutizione possono severamente compromettere le capacità respiratorie e l'apporto nutrizionale dei pazienti pediatrici. La videofluorografia è una procedura radiologica che fornisce una valutazione dinamica della deglutizione ed è generalmente considerata come la metodica strumentale definitiva per valutare in modo obiettivo la disfagia nel paziente pediatrico. Questa review mira a descrivere le differenti eziologie della disfagia in età infantile, oltre che a focalizzarsi su i rilievi videofluorografici in queste condizioni patologiche.

PAROLE CHIAVE: *Disturbi della deglutizione • Videofluorografia • Pediatria • Disfagia*

Introduction

Children are estimated to swallow 600-1,000 times a day [1]. Feeding and swallowing are developmental phenomena involving highly complex interactions that begin in embryologic and foetal periods and continue throughout infancy and early childhood [2 3].

Swallowing enables saliva and bolus to be propelled from the mouth through the pharynx into the oesophagus [4]. When referring to swallowing, both sensory inputs (as taste, somaesthetic sensitivity, oral stereognosis, vibrotactile detection, propioception, nociception, chemical and thermal sensitivity) and motor outputs (as mastication, respiration and swallowing) are implicated [5].

"Paediatric dysphagia" is not related to a specific diagnosis but refers to any disturbance of the normal swallow sequence in infants and children, as difficulties in transporting a bolus from the oral cavity to the back of the tongue or moving food into the oesophagus, compromising safety and adequacy of nutritional intake [6-10].

Pre- and post-natal development of swallowing mechanisms

Through understanding of the development of feeding and swallowing skills, it is possible to shed light on how and why infants may demonstrate signs of oropharyngeal dysphagia.

During embryologic life, between the 4th and the 7th weeks of gestation, many processes relevant to swallowing development take place.

After the incorporation of the endoderm of the yolk sac into the embryo to form the primordial gut and rupture

of pharyngeal membrane to form primitive choanae, separation of oesophagus and trachea from the primitive foregut is essential to avoid liquid aspiration during their passage through oesophagus [11].

Thereafter, the foetal period (from the 9th week of gestation to birth) is characterised by continuous differentiation of tissues and organs [11] and by a dramatic development of swallowing, sucking and oral sensorimotor function; this latter depends from brainstem and cerebral system development and is the fundamental system for correct functioning of the former [5 12].

Sensory cranial nerve input to the brain stem swallowing centre depends on the V, VII, IX and X cranial nerves while primary motor cranial nerve output is provided primarily by the V, VII, IX, X and XII nerves and by the cervical C1-C3 nerves [5]. Correct development of cranial nerves is mandatory for adequate swallowing. Myelinisation of the roots of some cranial nerves is seen during the 20th-24th weeks of gestation, and during the 35th-38th weeks the nervous system matures sufficiently to carry out integrative functions as nipple feeding [13].

Moreover, other cerebral regions are implicated in sensory and motor system development such as the nucleus tractus solitarius, nucleus ambiguous, dorsal motor nucleus, hypoglossal nucleus and cerebral cortex [14].

Foetal swallowing is important to regulate amniotic fluid volume and composition, as well as maturation of the foetal gastrointestinal tract and renal foetal system [5 15].

Oral motor skills also develop within a system that changes during post-natal life both in structural growth and neurological control: the successful use of the suckle reflex masters suckling and its coordination with breathing, the child's motor function (mostly involving his/her tongue) masters the stabilisation of the jaw [16 17].

The swallowing anatomic components of infants are different from adult ones. In the infant, the oral cavity is smaller and teeth have not erupted. We can also typically find a smoother tongue and harder palate. The larynx and hyoid bone are higher in the neck to the oral cavity, while in adults the larynx goes down to a lower area in the neck. The epiglottis is almost attached to the soft palate so that the larynx is open to the nasopharynx [18].

The proper integration of the respiratory and feeding functions is mandatory because during feeding the time left for safe air exchange is reduced, minute ventilation is decreased, exhalation is prolonged and inhalation shortened. Thus, proper maturation and practice of the above functions during the first years of life enhances oral motor patterns, and this latter influences feeding performance [16].

Swallowing requires both voluntary and involuntary actions and can be summed up into four phases (oral, triggering of swallowing reflex, pharyngeal and oesophageal) that involve structures and muscles of the nose, mouth, throat, chest, abdomen and digestive tract [19]. The oral phase consists of both preparatory and transit phases. During the preparatory phase, food and/or liquid are prepared in the oral cavity by suckling or mastications in order to form a bolus that, in the transit phase, is moved posteriorly through the oral cavity. During the pharyngeal phase, bolus is transported through the pharynx, and then through the cervical and thoracic oesophagus into the stomach during the oesophageal phase [11 20].

In neonates, the swallowing process is reflexive and involuntary and each of the abovementioned phases may mature at different times and/or rates. Later in infancy, the oral phase is voluntary and triggering of the swallow reflex is generally an involuntary activity, but it can be commanded voluntarily, while the pharyngeal and oesophageal phases remain involuntary [6 11].

A child affected by chronic dysphagia will likely show delayed progression of normal feeding skills, recurrent respiratory disease and, consequently, growth deficiency. Aspiration is one of the abnormalities that may be encountered as an anomaly in the development during post-natal life and consists of passage of ingested material, refluxed contents, or oral secretions through the vocal folds into the lower respiratory tract. Recurrent or chronic aspiration is a serious risk factor in the paediatric population, resulting in infection, chronic lung disease and even death.

The physiological avoidance of aspiration depends not only on anatomical separation of respiratory and digestive tracts in embryologic life, but also on central neural processing. Fluids contacting the laryngeal mucosa evoke laryngeal chemoreflexes [21] resulting in many possible responses such as rapid swallowing, apnoea, laryngeal constriction, hypertension and bradycardia, or cough; as the infant matures the formers reflexes (rapid swallowing and apnoea) become less probable, while cough and laryngeal constriction become more prominent [22]. However, sex-related differences have been demonstrated between early oral, tongue, pharyngeal and laryngeal motor activities: oral and upper airway skills emerge earlier in females and the latter (pharyngeal and laryngeal movements) are less rhythmic and complete in males throughout the second semester [23].

Paediatric swallowing disorders: aetiology

An altered swallow sequence may compromise safety, efficiency, or adequacy of nutritional intake. Because

swallowing and breathing share a common space in the pharynx, swallowing difficulties can have a bad effect on pulmonary health in addition to impairing nutritional intake [24]. Swallowing disorders occur in approximately 1% of children in the general population.

Swallowing disorders in the paediatric population are often different compared to those responsible for adult dysphagia. Many aetiologies should be kept in mind during differential diagnoses [11 25-31] (Table I).

Clinical assessment

Before exposing the paediatric patient to radiation during videofluoroscopic swallowing study (VFSS), accurate clinical assessment should be made by taking clinical history, evaluating sensorimotor function of the anatomical structure for swallowing and directly observing the child during a meal [32].

A clinical evaluation of feeding should involve a speech language pathologist (SLP) with experience in feeding disorders during an individual session or during a clinical group session by a feeding team [20].

In order to assess different potential causes of peadiatric dysphagia, the clinician has to focus on physiological-medical disorders, behavioural disturbances and developmental issues [20].

Medical disorders may be chronic, temporary, or progressive and affect many systems related to swallowing including the respiratory, nervous and/or metabolic systems, digestive tract and craniofacial structures. Behavioural disorders must be considered as a possible contributing cause of dysphagia: the patient may adopt aggressive or unfit behaviour, refuse to be fed or have little motivation to engage in feeding-based activities. The paediatric patient may also develop inadequate skills for swallowing because of privation of correct practice for acquisition of mature skills or as a consequence of a medical or behavioural disorder. Schedule for Oral-Motor Assessment (SOMA) and the Dysphagia Disorder Survey are two of the more common assessment tools that the clinician can use to examine swallowing function in the paediatric population [33 34]. Nevertheless, it must be said that often clinicians do not use formal assessment tools when evaluating feeding skills in children with suspected dysphagia. Several studies also highlight the inaccuracy of clinical evaluation alone in predicting airway involvement, given that silent aspiration is not uncommon in the paediatric population. When altered swallowing function is suspected in the paediatric patient, instrumental assessment should be requested to confirm the presence of dysphagia and detect aspiration risk [11].

Videofluoroscopic swallowing study

VFSS is considered to be the best instrumental evaluation for objective swallowing assessment, and not just in paediatric patients [20 35-37].

Table I. Different aetiologies of dysphagia.

Causes of oropharyngeal dysphagia	
Neurological diseases (34.9%)	Motor neuron disease; myopathy; birth asphyxia; cerebral palsy; microcephaly; periventricular leukomalacia
Infective/flogistic pathologies	Neurosyphilis; herpetic meningoencephalitis; congenital cytomegalovirus infection; dermatomyositis; epiglottitis
Structural disorders (congenital or acquired)	Restricted lingular frenulum; cleft lip/palate; choanal atresia or stenosis (e.g. Charge syndrome); goitre; caustic injuries
Causes of esophageal dysphagia	
Motility disorders	Achalasia; scleroderma; diffuse oesophageal spasm
Intrinsic structural disorders	Diverticula; stenosis; oesophageal plications
Extrinsic structural disorders	Vertebral anomalies; foreign body: mediastinal lesions
Oesophagitis	Herpes-simplex virus; Candida; gastro-oesophageal reflux disease; Crohn's disease; eosinophilic oesophagitis; caustic agents
Causes related to prematurity (10-49%)	
Low gestational age at birth; low birth weight; comorbidities associated with prematurity	
Cardio-respiratory diseases	
Broncho-pulmonary dysplasia; laryngo-/tracheo-/bronchomalacia; cyanotic and acyanotic heart defects	
Iatrogenic complications	
Tracheostomy; feeding tube; respiratory support	

It allows concurrent visualisation of the oral, pharyngeal and oesophageal stages of swallowing [9] and is essential to confirm airway protection adequacy and exclude swallowing dysfunction after clinical evaluation of feeding [38].

Therefore, VFSS provides crucial diagnostic information [39] and leads to a reduction in chest infections risk by detecting clinically "silent" tracheal aspiration (aspiration before, during, or after swallowing in the absence of cough or visible signs of choking) [40 41], especially in neurologically-based feeding disorders.

Thus, the indications for VFSS [20 38] in the paediatric patient comprise:

- observation of oral preparatory, oral transit, pharyngeal and/or oesophageal phases of swallowing;
- patient hostility towards endoscopic examination;
- suspected or diagnosed anatomical anomalies of nasal cavities, oropharyngeal tract or upper oesophageal structures that are a hindrance to endoscopic evaluation;
- suspected swallowing disorder as a contributory cause of a persistent feeding refusal or a respiratory disorder;
- planning treatment to improve swallowing efficiency and reduce the risk of aspiration.

Contraindications for VFFS include:

- patients who have never fed orally;
- impossibility to adopt correct posture during the exam because of medical instability, agitation or lethargy;
- allergies to barium/iodine contrast;
- patient who cannot be transferred to the radiology department [20].

Another commonly used instrumental evaluation of swallowing for paediatric patients is Fiberoptic Endoscopic Evaluation of Swallowing (FEES) [20 37 42], which a sensory testing of laryngeal adductor response (LAR) can be added to (Fiberoptic Endoscopic Evaluation of Swallowing and Sensory test or FEESST).

During FEES an endoscope allows observation of dynamical changes of the larynx and pharynx during the pharyngeal phase of swallowing and passage of bolus.

FEES can be performed at the bedside and repeated in a brief period and in different clinical conditions, so that it should be considered a very valuable instrumental method in follow-up [42].

FEES, on the other hand, allows assessment of the pharyngeal phase only and make indirect considerations about the oesophageal and oral phases; it is only acceptable for either very young children or for older cooperating children and is not very helpful to assess repeated swallowing.

Therefore, the question about whether VFFS can be considered as the gold standard to assess swallowing disorders is still open. Studies have shown that both VFSS and FEES have comparable sensitivity, specificity and predictive abilities [43 44], and a valuable approach may include both examinations as complementary, when available.

Practical and radiological technique

VFSS is a fast radiographic procedure. During the exam, barium contrast agents (administered at various consistencies – from solid to liquid – according to the situation) or, if necessary, hydrosoluble no-ionic iodated agents are transported in the oro-pharyngeal cavity and oesophagus, and the sequential phases of this passage are captured in real time using fluoroscopy [45].

An optimal approach to the patient can be achieved thanks to multidisciplinary management of the procedure by radiologist, radiographer and deglutologist [45-47].

Families have to be prepared for what to expect from the procedure, and advised that for best execution of the exam and cooperation of the children, it is advisable to bring appetising foods to be mixed with the contrast agent, familiar utensils and a seating system that children usually use during meals [20 37].

Moreover, in the radiology department there should be a child-friendly environment, such as a fluoroscopy room with visual distracters (toys, boxes of rewards) and a familiar caregiver [20 37].

At present there is not a unique protocol for VFSS in infants, since the procedure is strongly influenced by individual medical conditions, feeding modality, preferred food consistencies, age and size of the paediatric patient [20 37 38].

Regarding the question of lack of a unique VFSS protocol, in 2013 the International Dysphagia Diet Standardisation Initiative (IDDSI) [48] was founded to develop globally standardised terminology to refer to thickened liquids and texture modified foods used for patients of all ages affected by dysphagia.

During a consensus meeting, a first group of descriptors of texture and flow behaviour were developed to propose a framework to > 3,100 people in 57 countries around the world, obtaining positive feedback. The final IDDSI framework consists of levels from 0 to 7 including both liquids and foods on a continuum and every level is identified by a number, colour codes and a text label. Level 1 (slightly thick liquids) has particular utility for paediatric patients, even if it cannot be always available in all healthcare.

However, during VFSS barium sulphate powder is usu-

ally mixed with different textures of liquid, semi-solid and solid food (as cookies or crackers) and administered to the patient. As some authors suggest [49], one-half cup of thin barium can be mixed either with 1½ teaspoons of thickener to obtain a nectar consistency or with 1½ tablespoons thickener to create a honey-like texture.

Density of barium sulfate suspension is often expressed in a weight/weight (w/w) ratio, which indicates the number of grams of active ingredient per 100 g of product; otherwise, it is expressed in a weight/volume (w/v) ratio which expresses the number of grams of active ingredient per 100 mL of product [49]. Varibar thin liquid (40% w/v, after reconstitution; E-Z-EM Inc., Westbury, NY) and E-Z-HD (98% w/w; E-Z-EM Inc., Westbury, NY) are barium sulphate suspensions commonly used for VFSS.

Even though nectar and honey-like consistencies can be created using thickener, several barium sulfate suspensions are commercially available such as Varibar® Thin Liquid, Varibar® Nectar, Varibar® Honey, Varibar® Pudding [49]. For infants (0-1 year), some authors [38] state that the examination should start with liquids, as this texture often results to be the prevailing one in an infants' diet, and disparate type of nipples with different flows can be used [1 50].

In patients older than 1 year, it is possible to previously evaluate their food and drink preferences [1]. However, the use of the patient's favourite food mixed with barium may facilitate cooperation to accept other types of food, resulting in a wider range of information. Finally, after having started the study, the radiologist and the SLP may change the volume and viscosity of the barium texture on the basis of patient's symptoms and signs detected [37].

The patient should not chew gum or eat for several hours prior to VFSS [51] and if the child cannot autonomously feed because of a gastrostomy or nasogastric tube (NG tube), it is recommended [37] to take small tastes of the foods for 1-2 weeks prior to the VFSS. When a NG tube is in place, its removal is not necessary in most cases, as swallowing evaluation can be performed anyway [52] and having the tube repassed is a traumatic manoeuvre for the paediatric patient [37].

Cleft lip and/or palate patients require adequate feeding methods during the VFSS. A special need feeder is a one-way valve bottle designed for infants who have sucking difficulties: it is activated by compression movements alone, so the cleft lip and/or palate patient can overcome the obstacle of sucking dysfunction during feeding [1].

During VFSS, the presence of a family member who feeds the paediatric patient should be recommended, especially in infants, using child preferred utensils, like the baby's own feeding bottle, thus contributing to make the patient seat in a friendly feeding position to achieve the optimal conditions for VFSS [20].

During the procedure, patient positioning depends on his/her size, age and medical conditions [38]. Babies, infants and children up to 3 years should be seated in usual position in their own wheelchair or a preformed seat with secure straps mounted on the X-ray equipment. When the child size exceeds preformed seat dimensions, as the fluoroscopy table is vertically positioned, the patient can sit on a step set on the lower side of the table [37 51].

The child has to be primarily positioned in the lateral view to assess oro-pharyngeal cavity, larynx and cervical oesophageal region. The radiologist activates the fluoroscope for few seconds prior to the administration of barium contrast-impregnated food or liquid and keeps it on as long as the bolus reaches the cervical region of oesophagus [45]. During the oral phase, the radiologist must assess bolus containment before the swallow (Fig. 1), the rhythmicity of jaw movements and coordination of tongue movements.

The lips, nasal cavity, cervical spine column and pharyngo-oesophageal segments are, respectively, in the anterior, superior, posterior and inferior limits of the field of view [53 54].

The Antero-Posterior (A-P) view is not always routinely obtained by clinicians, since the diagnostic contribution

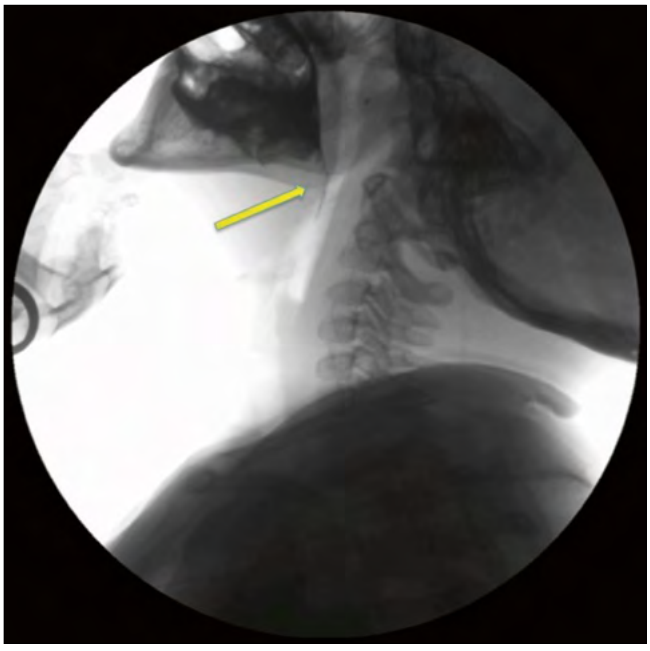

Fig. 1. Videofluorography lateral view in a 10-year-old patient. During the oral phase, a leakage of barium in the oesophagus (arrow) indicates inadequacy of bolus containment.

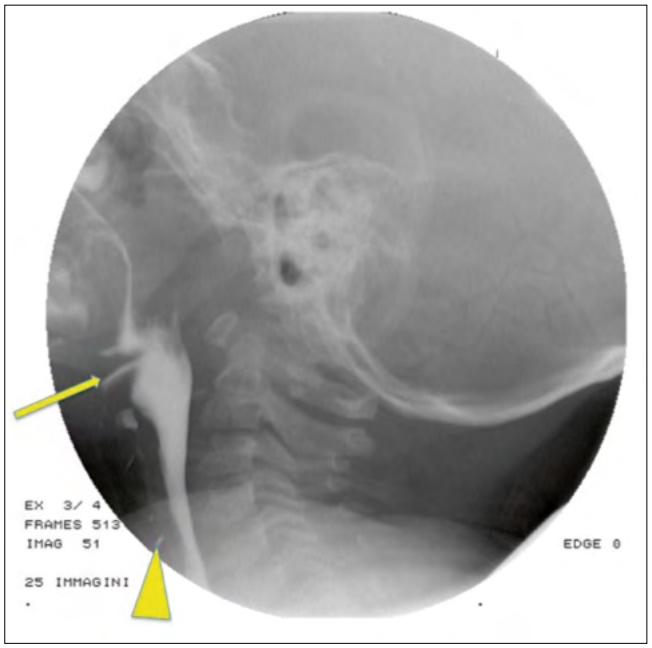

Fig. 2. Videofluorography lateral view in an 8-year-old patient with Down syndrome. During the pharyngeal phase subepiglottic penetration (arrow) and aspiration are demonstrated with persistence of contrast media in the trachea (arrowhead), in the absence of coughing.

made by an A-P view essentially concerns assessment of structural and functional symmetry and detection of unilateral abnormalities of the pharyngeal wall, as is the case with pharyngeal paresis or paralysis [45].

Milliampere (mA) and kilovolt (kV) settings are typically dependent on the patient's age, height and weight. For a 6-month-old to 5-year-old child, the usual mA and kV settings are 58-60 kVp with 1-1.1 mA, while for a 10-year-old patient these are 62 kVp and 1.5 mA [37]. As several authors state, using a pulse rate of 30 pulses/sec is essential to detect rapid aspiration and to recognise any bolus flow event related to the oropharyngeal phase of swallowing [45 55 56] (Fig. 2).

Interpreting results

During VFSS, assessment of swallowing consists in observing the orally preparatory, oral transit, pharyngeal and oesophageal phases [20 37]. Bolus formed during orally preparatory phase is held inside the oral cavity and does not move into the open larynx thanks to the base of the tongue and soft palate which close the oral cavity posteriorly [20 57].

During the oral transit phase, an anterior-to-posterior elevation of tongue push the bolus posteriorly toward the pharynx, so that pharyngeal reflex is triggered. Larynx closes by contraction of the aryepiglottic folds.

The pharyngeal phase takes place in less than a second and begins when bolus passes through the anterior faucial arch and reaches the posterior pharyngeal wall; bolus is then pushed toward the cricopharyngeal sphincter by contraction of pharyngeal constrictor muscles. Spill of bolus into the nasopharynx is prevented by elevation of the soft palate and larynx closes true and false vocal cords and aryepiglottic folds to block the way to trachea. As the oesophageal phase begins, the cricopharyngeal muscle relaxes and bolus moves through cervical and thoracic oesophagus and into the stomach thanks to oesophageal peristalsis [57].

Deterioration in swallowing function can be demonstrated by several abnormalities such as delay in the initiation of the swallowing reflex, residue of contrast-impregnated food and liquid, epiglottal undercoating, penetration and aspiration [37].

The presence of aspiration is characterised by the entry of ingested material below the level of the true vocal folds into the trachea [58] and if aspiration occurs, the material can enter the airway before, during and/or after the pharyngeal swallow [53]. When the bolus blocks the patency of the airways a chocking event occurs, exposing infants to a life-threatening condition.

Penetration is present when bolus material enters the laryngeal vestibule down to the level of the true vocal folds, but it does not cross the vocal folds [11] (Fig. 3).

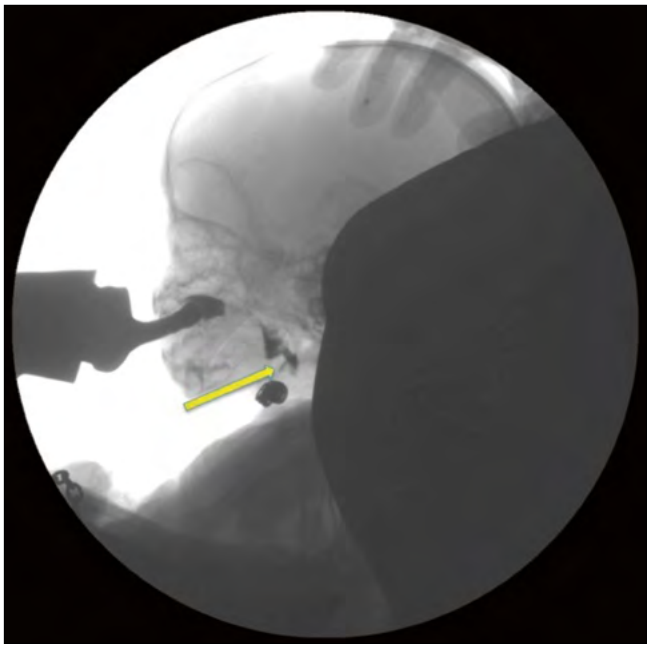

Fig. 3. Videofluorography lateral view in a 6-month-old patient with perinatal stroke shows transient sub-epiglottic penetration (arrow), in the absence of coughing.

The Penetration-Aspiration Scale [59] is a widely employed interval scale for a reliable quantification of penetration and aspiration events observed during VFSS.
The final 8-point version of the scale is multidimensional since several types of behaviours are evaluated.
Contrast-material not entering the airway is scored 1, while penetration can be scored from 2 to 5. Score 2 is given if contrast material remains above the vocal folds but no residue is visible, while score 3 is given if visible residue remains. If contrast material contacts the vocal folds but is ejected from the airway penetration this is scored 4, while if there is no ejection of material and residue is visible, penetration is scored 5.
Aspiration is a more severe event than penetration: it can be scored from 6 to 8 according to whether aspirated material is partially or totally expelled from the airway (score 6), subglottic residue is visible despite the patient's effort (score 7) or aspiration occurs without the patient's attempt to expel contrast material (score 8).
Another abnormality seen on VFSS is epiglottic undercoating which occurs when material penetrates underneath the epiglottis above the laryngeal vestibule [37].
Deteriorated swallowing can be also displayed by a swallow reflex delayed more than 1 sec [37].
On VFSS some patients show a normal swallowing process in the first few swallows but, as feeding progresses, abnormalities appear. On the other hand, certain patients may have greater difficulty during first few swallows and, as they become more organised, improve their function with additional swallows. Thus, during the procedure, multiple swallows have always to be examined [60]. If during basic examination no symptoms appear, provocative manoeuvres can be used to evoke swallowing abnormalities, always with caution, such as body position change, always keeping in mind the patient's individual history.
Protective and therapeutic manoeuvres, such as modifications regarding neck or body position, are available to prevent aspiration and limit considerable risks deriving from a sudden inability to breathe [37].
VFSS must be rapidly aborted when severe aspiration occurs, oxygen level saturation drops, or if the child does not respond to protective or therapeutic manoeuvres [37 51].
The procedure should end after having achieved all the goals of the study, trying to minimize the radiation exposure with the maximum level of clinical and radiological results [45 61].

Radioprotection issues

Videofluoroscopic analysis of swallowing is considered to be the best instrumental evaluation to objectively assess swallowing function after clinical feeding, confirming airway protection adequacy during the event [20]. However, there are limitations to the procedure such as cost, time constraints and, mostly, radiation exposure.
Although the radiation dose from VFSS is relatively low, between 0.2 and 0.85 mSv [62-66] (for a chest x-ray acquired in P-A the patient receives a radiation dose of 0.02 mSv) [67] any radiation from medical tests must be minimised to comply with the "As Low As Reasonably Achievable" principle [68]. This is particularly true in the paediatric population. Long-term effects of radiation are increasingly acknowledged, particularly in infants, since adverse effects of radiation exposure are known to be age-dependent: children are more sensitive to radiation-induced cancer than adults and the radiogenic risk of developing a radiation-related cancer is 2-3 times higher for a young child compared with an adult exposed to an identical radiation dose [69-71]. Therefore, optimisation of the procedure is important to reduce the dose using registration or fluoroscopy with low exposure data, if possible, due to intrinsic high contrast differences between barium and soft tissue. Also, specific age, weight protocols and diagnostic reference levels should be set within each department for the different ages of patients [72-76]. In order to maintain a low dose, the radiologist should make the timing of the fluoroscopy coincide with the oral and pharyngeal phases of swallowing. In VFSS, fluoroscopy time has been shown to be highly correlated with kerma area product (KAP) values and is known as a practical tool for monitoring patient radiation dose [77]. Guidelines have been adopted to limit radiation exposure times, but multiple variables may influence the duration of the exam. In particular, factors influencing radiation exposure time in VFSS include medical diagnosis category, swallowing impairment severity, the clinician's experience and use of a standardised protocol.

Conclusions

Feeding and swallowing disorders present in different manners and the underlying aetiology may be difficult to determine. An evaluation of clinical history and physical examination may screen some abnormalities, but often do not provide help in identifying the underlying cause of feeding and swallowing disorders. VFSS is considered to be the best instrumental evaluation for complete assessment from the oral to pharyngeal and oesophageal phases. In addition, the procedure strongly contributes to reducing the risk of chest infections by detecting clinically "silent" tracheal aspiration.

However, behavioural, structural and physiological disorders often coexist, complicating diagnosis and management.
For this reason, a multidisciplinary approach to diagnosis and management is helpful.

Conflict of interest statement

None declared.

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Review

Assessment of obstructive sleep apnoea (OSA) in children: an update

Valutazione critica del bambino con apnea ostruttiva notturna

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SUMMARY

OSA is a condition characterised by episodes of complete or partial obstruction of the upper airway, associated with blood-gas changes and atypical sleep patterns. Early diagnosis of OSA may reduce the occurrence of systemic complications over time, although the diagnosis of OSA is, unfortunately, often late. The aim of the work is to review the current concepts in evaluation of paediatric obstructive sleep apnoea (OSA), with an updated revision of the literature considering risk factors, clinical manifestations, and basic and advanced assessment in the paediatric population. For this narrative review, PubMed, Embase and Cinahl databases were searched for the last 10 years, according to PRISMA criteria/guidelines. Assessment of paediatric OSA remains challenging and paediatric patients should always be carefully evaluated; polysomnography is the gold standard for diagnosis of paediatric OSA.

KEY WORDS: Obstructive sleep apnoea • OSA • Children • Management • Polysomnography

RIASSUNTO

Questo lavoro vuole proporre un'attenta ed aggiornata revisione della letteratura in merito alla valutazione critica delle apnee ostruttive notturne (OSA) nel bambino, in particolare valutando i fattori di rischio implicati, le manifestazioni cliniche e l'iter diagnostico clinico-strumentale. Le apnee ostruttive notturne nel bambino si caratterizzano per la presenza di episodi di completa o parziale ostruzione delle vie aeree superiori associate a modificazioni dell'emogas-analisi e ad un riposo notturno anomalo. La corretta e precoce diagnosi di questa condizione, sebbene ancora oggi spesso sia posta in ritardo, può ridurre l'insorgenza di complicanze sistemiche. È stata eseguita una revisione della letteratura, attraverso una ricerca di articoli scientifici presenti nei database PubMed, Embase e Cinahl negli ultimi 10 anni, in base ai criteri / linee guida PRISMA. La valutazione dell'OSA pediatrica è complessa e i pazienti pediatrici dovrebbero essere sempre gestiti con molta attenzione; la polisonnografia è attualmente la tecnica "gold standard" per la diagnosi dell'OSA pediatrica.

PAROLE CHIAVE: Apnea ostruttiva notturna • OSA • Bambini • Management • Polisonnografia

Introduction

Obstructive sleep apnoea (OSA) is a condition characterised by episodes of complete or partial obstruction of the upper airway, associated with blood-gas changes and atypical sleep patterns; when present in children and if inadequately diagnosed/treated, it can be associated with behavioural problems, learning difficulties, cardiovascular complications and growth retardation [1-3]. Early diagnosis of the condition may reduce the occurrence of systemic complications over time, although the diagnosis of OSA is, unfortunately, often late [4].

During sleep, in the child, there is a moderate physiological increase in the upper airways resistance [5]. Children snore more rarely than adults, and any obstructive apnoeic episode must be considered pathological [6].

Sleep breathing disorders (SBD) include, in increasing order of severity: (i) simple snoring, (ii) syndrome of increased respiratory resistance (Upper Airways Resistance Syndrome - UARS), (iii) obstructive hypoventilation, and (iv) OSA. OSA is the most severe sleep respiratory disorder. Simple snoring (i) is characterised by vibratory noises of the soft palate during the inspiratory phase: it is described as an expression of partial obstruction of the upper digestive airway and is often associated with OSA or UARS. Until 6 years, simple snoring is present in 10% of children, under 10 years in 27% and in 47% during upper airway inflammation. Main causes of simple snoring are adeno-tonsillar hypertrophy, obesity, nasal respiratory obstructions and upper respiratory tract infections. Apart from snoring, forced oral breathing, mouth and dry lips, difficulty swallowing, halitosis and dyslalia can be present during the day.

UARS (ii) was first described in 1992 by Guilleminault [7], who observed that some children showed an increase respiratory muscle effort during sleep due to excessive resistance of the upper airway and increased negative endo-oesophageal pressure. The respiratory efforts are associated with arousal and fragmentation of sleep. Reported clinical consequences are poor weight development, reduced scholastic performance, daytime irritability and poor development in height due to reduction of growth hormone (GH) secretion, which occurs during sleep. The diagnosis of UARS can be suspected clinically, and confirmed by polysomnography (PSG).

Obstructive hypoventilation (iii) is defined as prolonged hypoventilation associated with hypoxia and hypercapnia, without complete cyclic airway obstruction [5]. In the child, there is a different pattern of recruitment of dilator muscles, characterised by greater muscular activation that is able to prevent complete collapse of the airways [8]. Another great difference between prolonged hypoventilations and true obstructive apnoea is the reduced disorder of sleep structure; in the child affected by obstructive hypoventilation, awakenings occur more rarely.

OSA (iv) in the paediatric population is characterised by a prolonged and partial obstruction of the upper airway, typical of obstructive hypoventilation, interrupted by total obstruction with hypoxaemia. In the paediatric population, any respiratory pause is considered apnoea, regardless of the duration (OSA = apnoea / hypopnea index (AHI) equal or more than 1).

Correct diagnosis of SBD is often complex, also due to the lack of differential diagnostic instrumental criteria among the various entities of infantile SBD. The incomplete instrumental codification associated with the poor correlation between severity of paediatric OSA and daytime symptomatology often leads to underestimation and late diagnosis of SBD in children.

The aim of this paper is to review the current concepts in evaluation of paediatric OSA, offering an updated revision of the literature data considering risk factors, clinical manifestations, and basic and advanced assessment in the paediatric population.

Methods

The PubMed, Embase and Cinahl databases were searched for the last 10 years (from January 2008 up to December 2017). Full-text articles were obtained in cases where the title, abstract, or key words suggested that the study may be eligible for this review. The medical subject heading (MeSH) terms included: paediatric obstructive sleep apnoea; upper airways resistance syndrome in children; obstructive hypoventilation in children, polysomnography, sleep apnoea, sleep-disordered breathing, sleep-related breathing disorders.

The search was conducted according to PRISMA criteria/guidelines (http://www.prisma-statement.org/): it was carried out independently and restricted to papers in English (Table I). Initially the total number of papers identified was 125; other papers (n = 34) were also identified from references in the published literature when all authors agreed about the reliability and importance of these manuscripts, for a total of 159 papers. Inclusion criteria were clinical series and review papers. Exclusion criteria were non-availability of full text; manuscripts not in the English language; case reports.

Therefore, the authors critically evaluated the 159 papers selected, by reading abstracts and/or texts, to decide whether the identified papers were relevant to this search or not. In this case, inclusion criteria were for clinical series, papers with an adequate group of patients studied (n > 20); for reviews, papers published on relevant journals and papers showing a rigorous methods and rigorous reporting. Finally, 48 papers resulted appropriate for this review according to all authors.

OSA risk factors in children

Snoring is reported to occur in 3-15% of paediatric population, especially between 3 and 6 years (13-35%). OSA has a reported frequency of 1-5% of the paediatric population, with a peak incidence between 2 and 6 years of age (2.5 years in males and 4 years in females), without a significant prevalence of sex [9-11]. In Italy, Brunetti et al. reported a prevalence of 4.9% for habitual snoring and 1.8% for OSA over 1200 children [12].

The main risk factors reported for OSA are:

- Adenotonsillar hypertrophy. It is the most frequent

Table I. Literature evaluation and selection, according to PRISMA criteria (http://www.prisma-statement.org/).

Total number of articles obtained by PubMed, Embase and Cinahl search	125
Other papers from references in the published literature	34
Total number of papers identified	159
Paper excluded[1]	56
Article assessed for eligibility	103
Paper excluded[2]	36
Total number of papers finally identified	67

[1] Inclusion criteria were: clinical series, review papers. Exclusion criteria were: non-availability of full text; manuscripts not in the English language; case reports.
[2] Inclusion criteria were: for clinical series, papers with an adequate group of patients studied (n >20); for reviews, papers published on relevant journals and papers showing a rigorous method and rigorous reporting.

condition associated with paediatric OSA. There is a significant correlation between tonsillar volume and SBD severity [13]. The classification of tonsil volume, according to the Brodsky scale, is based on the percentage of the oropharynx volume occupied by tonsils. Nevertheless, not all children with "kissing-tonsils" are affected, and the concept of 'airway collapsibility' has been proposed. Airway collapsibility can be evaluated by the critical closing pressure (Pcrit). Marcus et al. [14], demonstrated an increase in Pcrit in children with OSA compared to those with simple snoring; in other words, children with OSA have the most collapsible upper airway. On the other hand, isolated adenoid hypertrophy is not sufficient to determine OSA, even if may worsen SBD severity in children at risk. The impact of adenotonsillar hypertrophy in the genesis of OSA can be assessed by the success rate of adenotonsillectomy in OSA therapy (83% in children) [15].

- Obesity is an important risk factor for paediatric OSA and plays a predominant role in adolescence. In a prospective study, the prevalence of OSA was 4% in adolescents (aged between 16 and 19), most of which did not show SBD or snoring in their childhood [16]. Obesity and male sex are reported to be the greatest risks for OSA in adolescents. Another study [17] on 37 obese adolescents showed a 45% incidence of OSA. It has also been reported that obesity is an independent risk factor for OSA [18], as less than 50% of obese children undergoing adenotonsillectomy have complete resolution of their respiratory disorder during sleep [19 20].
- Inflammation. Recent studies have shown a correlation between OSA and inflammation [21]. Obesity is a condition that even in adolescents can lead to insulin resistance and hepatic steatosis [22 23], and therefore to increased production of different pro-inflammatory mediators such as leptin, interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α) [24]. Among children with asthma, those with obesity have a 4-fold increased risk of developing OSA, especially if they have poor pharmacological control. Improvement of OSA in patients treated with montelukast and nasal steroids has been reported [25].
- Craniofacial anomalies. These include dentofacial anomalies (i.e. ogival palate) and major cranio-facial malformations (i.e. maxillary hypoplasia, retro-micrognathia and macroglossia). Abnormal dentofacial lesions are frequently present in children with OSA (15-47%) and improvement of sleep disorders after orthodontic treatment has been reported [26]. However, there are studies showing improvement of the dental situation following adenotonsillectomy, suggesting the hypothesis that dento-facial anomalies may be a consequence of OSA, more than its cause [27]. Children with major cranio-facial malformations have frequent multilevel airway obstruction that must be carefully evaluated by fibroscopy and drug-induced sleep endoscopy (DISE).
- Neuromuscular disorders are characterised by insufficient central and peripheral airflow control with an increased collapsing trend of the pharyngeal-hypopharyngeal walls, reducing its muscle tone [28]. An example in which concomitant anatomical malformations and neuro-muscular disorders coexist is Down's syndrome, characterised by hypoplasia of the upper jaw, ogival palate, macroglossia and muscular hypotonia. OSA is frequently associated with Down's syndrome (81%); in fact, the American Academy of Pediatrics (AAP) recommends performing PSG in all children with trisomy 21 within four years of age [29 30].
- Other reported risk factors are a history of prematurity or multiple pregnancies [31], environmental exposure to smoking, asthma and allergic rhinitis [32].

Assessment of the paediatric OSA patient

Clinical evaluation of paediatric OSA patient consists in careful evaluation of history, clinical examination and eventually endoscopic and instrumental assessment. History and clinical examination have been reported to have positive predictive value for diagnosis of OSA of 65% and 46%, respectively [33]. Nonetheless, clinical evaluation is useful for selecting patients for instrumental tests, such as PSG.

Main reported OSA nocturnal symptoms are habitual snoring, forced oral breathing, abnormal thoracic-abdominal movements, presence of restless sleep with respiratory pauses, frequent awakenings and changes of position, dry mouth, enuresis and profuse sweating. Diurnal symptoms are difficult nasal breathing, hyperactivity and irritability, poor school/academic performance or, more rarely, sleepiness (in adolescent or obese children).

- History. There are few questionnaires available to address OSA symptoms that are suitable for the paediatric population. The Paediatric Sleep Questionnaire proposed by Chervin [34] is often used in the literature, especially in its short version composed of 22 questions, which has been validated in several languages. It has been shown that 33% of affirmative answers correlate with a high risk of paediatric SBD. Another questionnaire was proposed by Brouilette et al. [35]; it is a useful screening tool, even if not very reliable compared with polysomnographic results [36]. Recently, the

I'M SLEEPY questionnaire has been reported to be a valid screening instrument [37], as well as the paediatric version of the Epworth Sleepiness Scale (ESS) [38].

- Clinical evaluation. ENT (Ear Nose and Throat) objective examination should rule out the presence of possible tonsillar hypertrophy, which can be classified according to the Brodsky scale, evaluating the percentage of oropharynx occupied by tonsils (considered as the distance between the two anterior pillars). Another classification is based on the evaluation of tonsil size (ranging from 0 to 4: 0 indicates tonsils removed surgically, 1 intravelic tonsils, 2 extravelic tonsils, 3 extravelic tonsils not reaching the midline and 4 tonsils reaching the midline). Another frequently used classification has been reported by Friedman (Mallampati modified); it assesses the position of the tongue within the oral cavity, measuring how it obstructs the airway (grade 1: both uvula and tonsils are entirely visible, grade 2: uvula is visible but not the tonsils, grade 3: soft palate is visible but not the uvula, grade 4: only hard palate is visible) [39]. It is also useful to observe the skeletal class (retrognathic, orthognathic or prognathic), the presence of ogival palate and the facies. BMI and weight growth curve should be carefully assessed. Finally, it is also essential to measure arterial pressure and rule out eventual signs of pulmonary hypertension.
- Endoscopic assessment. Endoscopy with flexible optic fibres allows evaluating patency of nasal cavities (i.e. hypertrophy of the inferior turbinates, presence of septal deviations or choanal atresia, adenoid hypertrophy), tongue base tropism or the possible presence of laryngomalacia. In selected patients, DISE can be indicated. In children, DISE assesses the residual OSA after adenotonsillectomy [40 41]. DISE methodology is similar to that of adults, evaluating the site, entity and pattern of obstruction with particular attention to the nose, nasopharynx, oropharynx, tongue base, epiglottis and larynx. Children with multi-level obstructions show more severe OSA [42 43], as in adults. In a study on 82 children with moderate to severe OSA, lateral and/or multilevel oropharyngeal collapse was reported in most cases [44]. However, the role of DISE in the paediatric population is still controversial [45].
- Polysomnography (PSG). Presently, PSG represents the gold standard to diagnose OSA in children. The aim of PSG is to: (i) diagnose, differentiate and quantify obstructive apnoeas, mixed apnoeas, central apnoeas; (ii) identify and classify hypopneas and high-resistance syndromes; (iii) evaluate sleep fragmentation. PSG is an expensive exam; it requires specialised equipment and personnel, is time-consuming and often has long waiting lists. PSG can only be performed in a few centres, such as a sleep laboratory in a hospital setting, which allows continuous monitoring [46]. PSG should cover at least two complete nocturnal sleep cycles, without premedication or sleep deprivation, preferably at a distance from any steroid treatment. PSG recordings in children can be longer than adults, due to their sleep times: 11 to 12 hours for small and pre-school children, 9 to 10 hours for school-age children. It is useful to extend the study time in the mornings to record REM sleep (when apnoea is usually worse) [47]. Apnoea is defined as the reduction of airflow of more than 90% for at least two respiratory cycles; it is considered obstructive if during the whole period the inspiratory effort is continued or increased, it is central if the inspiratory effort is absent, and is mixed if there is a respiratory effort present only during part of the event, especially at the end. Hypopnea is defined as reduction of airflow ≥ 30% for at least two respiratory cycles; reduction of the air flow is associated with an arousal or a desaturation > 3%. In children, the detection of a single apnoea episode or hypopneas per hour is considered pathological. Three degrees of OSA severity are identified according to the AHI: mild AHI 1-4, moderate AHI 5-9, severe AHI ≥ 10. The present polysomnographic classification also allows to identify children: 1) at risk of sequelae; 2) at risk of postoperative complications, which require strict clinical and instrumental follow-up; 3) at high risk of OSA even after adenotonsillectomy, requiring further investigations and treatments.
- Nocturnal pulse oximetry. Nocturnal pulse oximetry is a valid initial diagnostic test for SBD and OSA for different reasons: its high positive predictive value (97%), its easy applicability and low cost. Therefore, it represents a good screening tool [7 8].

A positive examination (3 or more desaturation clusters and at least 3 desaturations below 90%) is considered exhaustive for OSA diagnosis. According to Brouilette criteria, desaturation is defined as a decrease in SaO2 ≥ 4% and the cluster is characterised by at least 5 desaturations that occur in a period of 10-30 min. A useful OSA severity scale is that proposed by the Canadian Brouilette group using the McGill Oximetry Score:

- Category 1, "non-conclusive examination", no desaturation, or desaturation not meeting the subsequent criteria;
- Category 2, mild OSAS: at least 3 "clusters" of desaturation < 90%;
- Category 3, moderate OSAS: at least 3 "clusters" of desaturation < 85%;

- Category 4, severe OSAS: at least 3 "clusters" of desaturation < 80%.

The diagnostic categories 2, 3 and 4 identify, respectively, three increasing classes of priority indication for adenotonsillectomy, and three increasing categories of patients at high risk of developing peri-operative complications [48 49].

- Watch Peripheral Arterial Tonometry (Watch-PAT). The AAP recommends performing alternative tests in uncomplicated cases of OSA when PSG is not available. Watch-PAT is a portable wrist-worn OSA diagnostic device that incorporates actigraphy to differentiate between wake and sleep stages and a PAT signal probe, which measures the arterial volume change (a signal of sympathetic activation) in a fingertip. Episodes of apnoea and hypopnea induce awakenings and activation of sympathetic nervous system with consequent peripheral vasoconstriction, which results in attenuation of the Watch-PAT signal. Watch-PAT records parameters continuously, including PAT (signal and amplitude), pulse rate, oxygen saturation, actigraphy, snoring, and body position. Watch-PAT is equipped with a main body (hardware) and two finger probes: the main body measures sleep time, processes the signal through specific algorithms, provides power and stores data. Remarkable features of PAT are its simplicity, accessibility and ability to measure sleep parameters, including AHI, respiratory disturbance index (RDI), total sleep time (TST) and sleep stages. One major drawback is the absence of a paediatric Watch-PAT probe, and adult devices cannot be always adapted to use in very small children (< 5 years). Several authors found that AHI and oxygen desaturation index (ODI) obtained from Watch-PAT can underestimate the degree of sleep apnoea compared to PSG, but for severe OSA (AHI > 10) the diagnostic accuracy is reported to be high. However, specific data on paediatric OSA are very limited. The development of a paediatric probe and algorithm is necessary to increase the validity and clinical application of Watch-PAT for its paediatric use. Future studies will help to clarify whether Watch-PAT could offer an alternative to PSG, which still remains the gold standard technique for diagnosing OSA in children [50].

Discussion

The percentage of paediatric patients affected by OSA is often underestimated, and a high proportion of paediatric OSA patients are not receiving correct diagnosis and timely treatment. Lack of treatment of sleep-related breathing disorders places patients at risk of developing growth delay, hyperactivity, attention deficits, learning disabilities and also increases the use of healthcare services and associated costs: it has been reported that the severity of OSA directly correlates with total annual healthcare costs and is age independent [51]. OSA is a condition that needs a clear diagnostic definition in children, and differs from the adult OSA in terms of physiology, clinical manifestation, PSG features and sequelae. It is a worldwide issue to increase clinician awareness on OSA in order to reduce the rate of late diagnosis and avoid OSA-related sequelae. Notwithstanding, the fact that only PSG has been shown to be discriminatory for OSA, any physician can easily suspect OSA clinically. Noisy breathing, mouth breathing, habitual snoring, respiratory pauses, enuresis, morning headache, excessive daytime sleepiness, attention deficit, hyperactivity and learning disorder are the symptoms that should address diagnostic suspicion. Children with suspected OSA should be evaluated by a multidisciplinary team composed of paediatricians, ENT specialists, orthodontists and speech therapists.

PSG is still the gold standard diagnostic tool, but the test is costly and clearly cannot be available in every hospital for assessment of the entire paediatric population that snores. It is likely that less expensive devices can be validated for diagnosis of children OSA in the future [11]. Screening tools, such as nocturnal pulse oximetry combined with clinical indicators, could be useful to select the most PSG deserving children, even if they are specific and not very sensitive. Identifying an ideal screening test, or a series of tests, is still challenging.

According to the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) guidelines [52], PSG should be performed prior to tonsillectomy in children affected by SBD aged 2 to 18 years. The most common indications for PSG assessment prior to tonsillectomy are: Down's syndrome, craniofacial deformities, obesity, neuromuscular diseases, mucopolysaccharidosis, sickle cell disease, symptoms discordant with physical exam and unclear medical history [53]. When OSA is confirmed, further complementary exams can be performed to obtain comprehensive upper airway evaluation: pharyngolaryngoscopy, DISE, lateral cephalograms and maxillofacial computer tomography scans [54]. As for adults, even in children a careful perioperative assessment is recommended prior to any surgical intervention, since asymptomatic OSA may be related to risk of severe perioperative morbidity or mortality, representing a surgical and anesthesiologic issue [55]. The 2014 Guidelines by American Society of Anesthesiologists Task Force on Perioperative Management of patients with OSA apply

to both adult and paediatric patients; medical history, patient/family interview, screening protocols/questionnaires and clinical examination should always be performed preoperatively. In case of suspected OSA, it may be useful to delay the intervention to obtain more detailed assessment through PSG, whenever possible. Patients affected by OSA should be prepared preoperatively, through CPAP or noninvasive positive pressure ventilation initiation (particularly in case of severe OSA), oral appliances for mandibular advancement and weight loss [55].

Management of paediatric OSA is still challenging and each task should always be carefully evaluated. Adenotonsillectomy represents the first and main step of the therapeutic program of OSA in children. Nonetheless, it is essential to provide a post-surgical follow-up to identify and evaluate subjects in which, months after adenotonsillectomy, apnoeic events re-emerge, and to investigate and evaluate other possible causes of upper airway obstruction [56 57]. Mouth breathing during sleep is very common before surgery, and can persist after surgery causing residual abnormal AHI [58-60].

Several authors have reported that pharyngeal muscle re-education, using myofunctional re-education, can play a role in reducing mouth-breathing and abnormal breathing during sleep, even after adeno-tonsillectomy [61 62]. Rehabilitative techniques, addressed by orthodontists and/or speech therapists, should include restoration of appropriate posture, appropriate tongue resting position with tongue lightly suctioned against palate, appropriate swallowing, appropriate mastication using both back molar areas (i.e., posterior chewing) and appropriate nose breathing. Such behavioural modifications can be obtained through daily re-education exercises [63 64]. Retrospective studies show that children who received adequate functional orofacial re-education can achieve long-term OSA remission compared to children treated with adenotonsillectomy and/or rapid maxillary expansion (RME) without orofacial myofunctional training [65]. Unfortunately, myo-functional exercises are difficult to achieve for children younger than 4 years who do not have sufficient attention and cannot perform them constantly and effectively. Attempts have been described to find passive re-education approaches for these young children [63-66].

As reported by many authors, upper airway collapsibility after adenotonsillectomy should also represent a therapeutic target. Abnormal collapsibility is related to sleep stages, as different sleep status can modify pharyngeal muscle tone and reflex responses. Additionally, both intrinsic and extrinsic factors have been reported to affect the risk of collapsibility of the upper airways. For instance, fat deposits can induce narrowing of the upper airway and muscle infiltration can reduce the activity and effectiveness of pharynx dilatation muscles; weight loss in children affected by OSA has been recommended in selected cases [2 67].

Continuous positive airway pressure (CPAP) has also been proposed for treatment of paediatric OSA, although its role is controversial especially after adeno-tonsillectomy [2 68-70]. In adults, CPAP represents the first-choice treatment for patients affected by OSA, according to American College of Physicians [71]. In particular, CPAP is recommended for the treatment of uncomplicated moderate to severe OSA, while it remains optional in mild OSA [72], since its use has been associated with: (i) reduction of sleep fragmentation, daytime sleepiness and cardiovascular risk, and (ii) improved neurocognitive performances and quality of life [73]. In the paediatric population, CPAP has been reported to be useful in selected cases: (i) patients not eligible for surgery, (ii) patients waiting for interventions, (iii) patients with persisting disease after surgery [74], and (iv) patients with other diseases, such as Down's syndrome or craniofacial anomalies [75].

As for adults, in children good compliance to CPAP is crucial to obtain optimal outcomes. Conventionally, the minimum CPAC time is considered to be greater than 4 hours per night, and acceptable CPAP compliance is estimated to be greater than 70% of nights [76]. In children, the use of CPAP has been associated with improvement in attention, somnolence, school performance and global quality of life perception [75]. Nonetheless, the reported compliance rate to CPAP in children is not very high, due to the short length of CPAP use per night and the high drop-out rate; probably, the limited use of CPAP in the paediatric population can also be related to comorbidities or syndromes associated with developmental delays [75]. As in the adult population, the management of paediatric CPAP is still a multidisciplinary issue, and it has been reported that the presence of respiratory therapists may improve the CPAP compliance [75].

Conclusions

Any child with suspected OSA should be submitted for integrated clinical and instrumental evaluation. In particular:

- children with suspected OSA should also be managed by a multidisciplinary team composed of a paediatrician, ENT specialist, orthodontist and speech therapist [77-79];
- initial instrumental evaluation can be performed by nocturnal pulse oximetry;
- PSG is still the gold standard for OSA diagnosis in children;
- data on paediatric OSA should always be evaluated carefully.

Conflict of interest statement

None declared.

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Review

Clinical application of cVEMPs and oVEMPs in patients affected by Ménière's disease, vestibular neuritis and benign paroxysmal positional vertigo: a systematic review

Applicazione clinica dei cVEMPs ed oVEMPs nei pazienti affetti da malattia di Ménière, neurite vestibolare e vertigine parossistica posizionale benigna: una revisione sistematica

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SUMMARY

Vestibular evoked myogenic potentials (VEMPs) are increasingly used for different pathologies with new clinical insights. Although the study of otolithic function selectively in both its saccular (cervical VEMPs) and utricular (ocular VEMPs) parts does not represent a recent achievement, the clinical utility of this tool is still emerging. The aim of the present report is to define advances in application of VEMPs in diagnosis and clinical study of vestibular neuritis, Ménière's disease and benign paroxysmal positional vertigo. To perform a systematic review of the literature, three appropriate strings were run in PubMed to retrieve dedicated articles. A double cross-check was performed on citations and two independent investigators independently reviewed all full-text articles and performed a comprehensive quality assessment. Of 140 articles identified, 26 articles were included, comprising a total of 1,181 patients affected by vestibular neuritis (296 subjects), Ménière's disease (378 patients) and benign paroxysmal positional vertigo (507 patients). Overall, the use of both cVEMP and oVEMP appeared particularly useful in improving the topographic diagnosis of vestibular neuritis. Most (n = 8) of the studies dedicated to Ménière's disease and benign paroxysmal positional vertigo (10 overall) also reported significantly abnormal VEMP values compared to healthy controls. Although further reports will be necessary to better define normal threshold levels of VEMPs for each pathology, our review suggests that VEMPs may represent a useful aid in improving the diagnostic accuracy for these three common vestibular pathologies.

KEY WORDS: VEMPs • Ménière's disease • Vestibular neuritis • BPPV • Peripheral vertigo

RIASSUNTO

Attualmente l'applicazione dei potenziali evocati vestibolari miogenici (VEMPs) sta crescendo in molte e differenti patologie. La possibilità di studiare la funzione vestibolare in modo selettivo sia nel sacculo (VEMPs cervicali) sia nell'utricolo (VEMPs oculari) rappresenta una possibilità recentemente acquisita e l'utilità di tali indagini strumentali sta ancora emergendo e sempre meglio delineandosi. Lo scopo della nostra revisione è stato quello di definire per quanto possibile le novità nell'applicazione dei VEMPs per la diagnosi e l'approfondimento clinico di tre importanti entità patologiche: la neurite vestibolare, la malattia di Ménière e la vertigine posizionale benigna. Per realizzare questa revisione sistematica abbiamo quindi utilizzato tre differenti stringhe di parole chiave su PubMed ricercando in tal modo tutti gli articoli attinenti a queste tematiche. Una doppia verifica incrociata è stata eseguita da due degli autori prima su tutti i titoli scaturiti dalla ricerca e poi sugli specifici testi degli articoli selezionati al fine di poterne accertarne la qualità e la effettiva pertinenza. Su un totale di 140 articoli identificati, 26 studi sono stati inclusi nella revisione. Questi studi comprendevano 1.181 pazienti affetti rispettivamente da neurite vestibolare (296 soggetti), malattia di Ménière (378 soggetti) e vertigine parossistica benigna (507 soggetti). Per quanto concerne la neurite vestibolare complessivamente l'utilizzo dei cVEMPs e degli oVEMPs è apparso particolarmente utile nel migliorare l'accuratezza della diagnosi topografica della malattia. Sia per la malattia di Ménière che per la vertigine parossistica posizionale benigna ben 8 studi su 10 che comprendevano anche un gruppo controllo di pazienti sani hanno mostrato come la registrazione dei VEMPs sia risultata significativamente anormale nei soggetti patologici rispetto a quelli sani. Sebbene ulteriori studi saranno certamente necessari per meglio definire le soglie di normalità nei valori dei VEMPs per ogni singola entità patologica qui analizzata, al momento possiamo concludere che la nostra revisione indica la reale utilità della registrazione dei VEMPs. Infatti se integrata alle altre opzioni strumentali disponibili essa sembra realmente poter garantire un ulteriore innalzamento nella qualità di inquadrare clinicamente queste tre patologie vertiginose.

PAROLE CHIAVE: *VEMPs • Malattia di Ménière • Neurite vestibolare • BPPV • Vertigine periferica*

Introduction

Vestibular evoked myogenic potentials (VEMPs) are short latency electromyographic responses that can be recorded from various muscles during the contraction phase in response to acoustic stimulus. VEMPs recorded from ipsilateral sternocleidomastoid muscle known as "cervical VEMP" (cVEMP) are a clinical demonstration of the vestibulo-collic reflex. cVEMP responses are characterised by biphasic waves with initial positivity (p13) followed by a negative wave (n23). The cVEMP pathway is believed to originate in the saccular macula and continues through the vestibular nerve and nucleus, vestibulospinal tracts, spinal motor nucleus and the sternocleidomastoid muscles [1].

Recently, a myogenic response recorded from contralateral extraocular muscles in response to acoustic stimuli has been reported to be a manifestation of crossed vestibulo-ocular reflex and named ''ocular VEMP'' (oVEMP). The oVEMP pathway is thought to travel through the medial longitudinal fasciculus, oculomotor nuclei and nerves and extraocular muscles after the activation of the vestibular nerve and nucleus [2]. oVEMP responses are characterised by biphasic waves with an initial negative peak (n1) followed by a positive peak (p1) [1].

The study of otolithic function in both its saccular (cVEMPs) and utricular (oVEMPs) parts represents a milestone similar to that marked by the introduction of the caloric test, as the diagnosis and prognosis of numerous vestibular diseases can be influenced by such findings [3]. Moreover, VEMP recording is a simple and rapid method that is well tolerated by subjects, and easily implementable in a laboratory equipped for recording evoked potentials. For these reasons, the VEMP recording test has become an important diagnostic tool, particularly in evaluation of peripheral vestibular disorders.

At present, cVEMP responses have been shown to be particularly useful in assessment of patients with "superior semicircular canal dehiscence" presenting a lower-than-normal threshold for elicitation of the cVEMP response in the affected ear [4]. However, VEMPs are also thought to provide useful information about brainstem functions, as the neural pathway of both VEMPs pass through the brainstem, and several studies have described cVEMP and oVEMP abnormalities in brainstem lesions [5-7].

Undoubtedly, in recent years the popularity of this type of vestibular testing is on the increase, and different reports have been published about the utility of VEMPs in vestibular and otologic pathologies.

The aim of this systematic review was to define the advances of the application of VEMPs to three frequent vestibular pathologies, as outlined in the recent literature.

Materials and methods

In April 2017, a computerised MEDLINE search was performed using the PubMed service of the U.S. National Library of Medicine; the following 3 search strings were run:

1. "Ménière Disease"[Mesh] OR "Endolymphatic Hydrops"[Mesh] AND "Vestibular Evoked Myogenic Potentials"[Mesh];
2. "Vestibular Neuronitis"[Mesh] OR "Vestibular neuritis"[Mesh] AND "Vestibular Evoked Myogenic Potentials"[Mesh];
3. "Benign Paroxysmal Positional Vertigo"[Mesh] AND "Vestibular Evoked Myogenic Potentials"[Mesh].

Overall, the initial search returned a total of 140 results. Abstracts and titles obtained were screened independently by two of the authors (F.M.G. and M.R.), who subsequently met to discuss disagreements on citation inclusion.

Inclusion criteria for citations were:

- articles reporting sufficient number of patients (> 10 subjects).

Exclusion criteria for citations were:

- analysis including cohorts of patients affected by others vestibular pathologies;
- articles concerning different instrumental methods than cVEMPs or oVEMPs.

Of the 140 articles, 36 met initial inclusion criteria according to both authors (FMG and MR), and were thus obtained and reviewed in detail by the same two authors, who met and discussed disagreements on article inclusion.

Inclusion criteria for full text articles identified were:

- sufficient and accurate description of VEMPs recording system;
- sufficient and accurate description of pathologies and clinical features.

Exclusion criteria were:

- lack of sufficient analysis and presentation of data;
- inclusion of patients with probable or not definite diagnosis.

A total of 12 studies were excluded because of insufficient data about recording VEMPs (n = 4), lack of sufficient analysis of presented data (n = 6), or patient redundancy (n = 2).

An additional manual check was performed on the references included in the articles and two additional studies were identified and confirmed to meet the inclusion criteria. The main information was extracted and analysed for all included studies.

Results

After an initial check, full-text retrieval and manual cross-

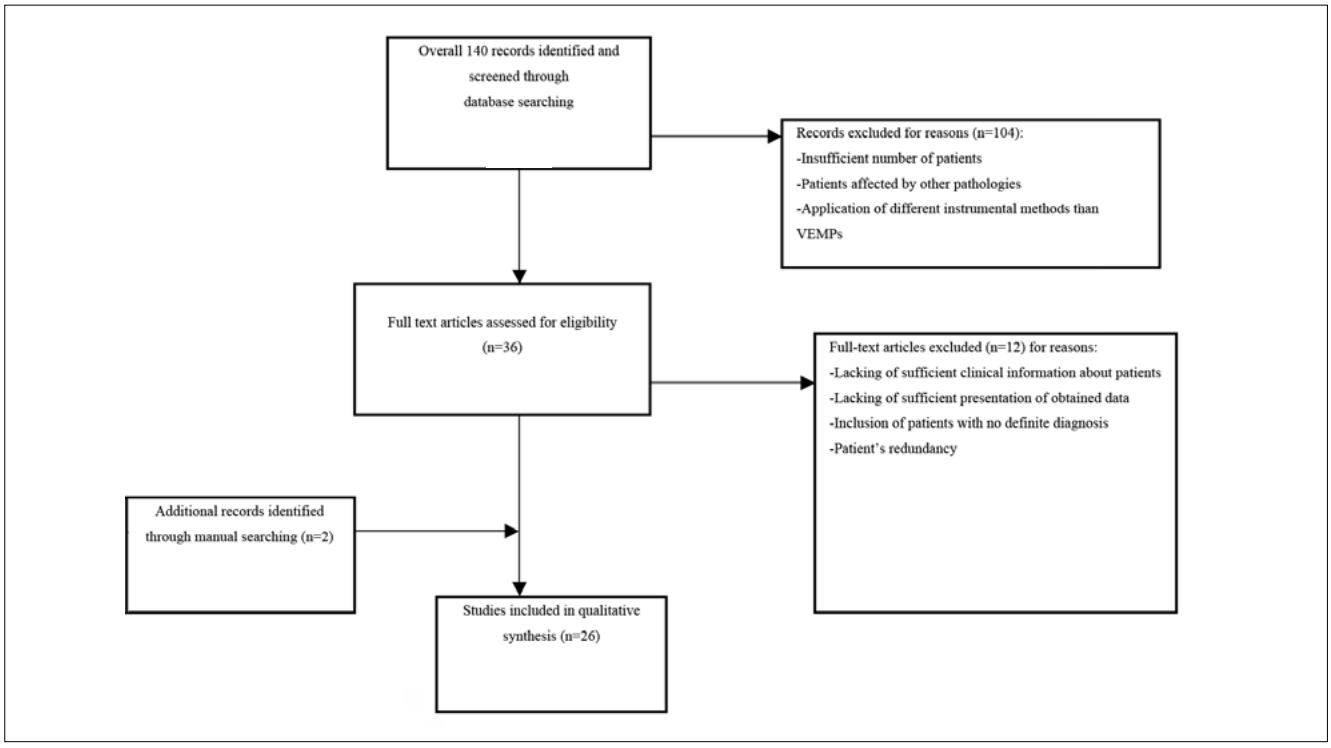

Fig. 1. Flowchart showing studies' selection.

checking of references included in the articles, a total of 26 studies, including 1181 subjects, clearly met the inclusion criteria and were chosen for analysis (Figure 1). The main characteristics of these selected studies are outlined in Tables I, II and III.

Overall, the number of patients in each study included in this analysis varied from 12 to 134. There were 6 studies (including 296 patients) investigating VN, 10 studies (including 378 patients) dedicated to MD and 13 studies (including 507 patients) investigating BPPV.

All VN dedicated studies performed cVEMPs, while oVEMPs responses were recorded in only 3 of the studies. Of the 10 MD studies, cVEMPs was performed in 7 and oVEMPs in 3 studies. Of the 13 articles analysing BPPV patients, 8 investigated cVEMPs while only 1 study reported recording oVEMPs.

Overall, abnormal VEMPs recording rates for VN ranged from 36.6% to 80% (Table I). A significant correlation between the presence of VEMPs abnormalities and pathology was reported in 5 of the MD studies; amplitude reduction was the most frequently observed alteration (Table II). Furthermore, half of the BPPV articles (4/8) found a significant correlation between affected patients and VEMP abnormalities compared to control groups (Table III).

Vestibular neuritis

The vestibular nerve is composed of the superior vestibular nerve (utricular nerve and superior and lateral ampullary nerves) and the inferior vestibular nerve (saccular nerve and posterior ampullary nerve) [8]. Vestibular neuritis (VN) is a clinical entity defined by an episode of prolonged vertigo associated with unilateral peripheral vestibular hypofunction [9]. It may affect either the entire vestibular nerve or each division of the vestibular nerve separately [10].

In patients who present selective involvement of the superior vestibular nerve (superior VN), the function of the horizontal and anterior canals is impaired, as shown by abnormal calorics and deficient head-impulse tests in the plane of the involved horizontal and anterior canals [11].

In such patients, the utricular afferents that traverse the superior vestibular nerve are likely to have absent or reduced function. However, the function of the inferior division of the vestibular nerve is spared, as shown by normal head-impulse tests during stimulation of the posterior canal and normal cVEMP [12 13].

By contrast, VN selectively affecting the inferior division may show reduced or absent ipsilesional cVEMP in the presence of functioning horizontal and anterior semicircular canals and utricle, as determined by normal calorics and horizontal head-impulse tests [14].

Table I. Main characteristics of the studies analysed with correlations between vestibular neuritis (VN) and VEMPs responses.

Authors	Year	No. of patients with definite VN	No. of healthy subjects in control group	Type of VEMPs	Sound conduction	Stimuli	Stimulation intensity	Stimulation frequencies	Significant findings in VEMPs responses
Hong et al. [17]	2008	134	None	cVEMP	ACS	Clicks	95 dB	2,000 Hz	Abnormal values in 49 (36.6%) patients
Vinciana and Lopez-Escamez [18]	2010	41	None	cVEMP	ACS	Tone bursts	129 dB	500 Hz	Abnormal values in 21 (51%) patients
Nola et al. [19]	2011	20	None	cVEMP	ACS	n.a.	130 dB	500 Hz	Abnormal values in 9 (45%) patients
Shin et al. [14]	2012	41	60	cVEMP	ACS	Tone bursts	100 dB	1,000 Hz	n.a.
				oVEMP	ACS	Tone bursts	100 dB	1,000 Hz	Abnormal values in 30 (73.1%) patients
Walther and Blodow [20]	2013	20	None	cVEMP	ACS	Tone bursts	100 dB	500 Hz	Abnormal values in 9 (45%) patients
				oVEMP	ACS	Tone bursts	100 dB	500 Hz	Abnormal values in 12 (60%) patients
Magliulo et al. [3]	2014	40	None	cVEMP	ACS	Logon	130 dB	500 Hz	Abnormal values in 19 (47.5%) patients
				oVEMP	BCS	n.a.	n.a.	n.a.	Abnormal values in 32 (80%) patients

ACS: Air-Conducted Sound; BCS: Bone-Conducted Sound; n.a.: not available.

Functional impairment of the entire vestibular nerve (superior and inferior division) and a single superior division involvement in VN are the most common conditions [15], and selective inferior vestibular nerve damage has recently been described [16].

Some authors have investigated the role of VEMPs recording in improving the diagnostic accuracy for patients affected by VN. Hong et al. [17] studied 134 patients with VN. Overall 49 (36.6%) showed an abnormal cVEMP response. In particular, a prolonged p13 latency was noted in 29 patients, while 25 patients presented a n23 prolonged latency. Increased cVEMP asymmetry was found in 27 patients. The authors speculated that 36.6% of all subjects in their study had lesions in the labyrinth or inferior vestibular nerve.

Vinciana et al. [18] analysed 41 patients diagnosed with VN. cVEMPs were performed and resulted abnormal in 21 (51%) of 41 cases, the most common finding was an increase in ipsilateral latencies for p1 and n1 peaks.

Further, Nola et al. [19] performed cVEMP recording in a cohort of 20 patients affected by VN. Nine patients, presenting a torsional nystagmus and bilateral normoreflexia after caloric labyrinth stimulation, had no cVEMP response on the affected side (while the response was present on the contralateral side). The authors concluded that these nine patients were affected by inferior VN.

The cVEMP examinations were then repeated after 8 days, 1 month and 3 months. After 8 days, seven of the patients diagnosed with inferior branch VN showed an improvement of cVEMP values while a complete reappearance of cVEMP after 1 month was noted in all nine patients.

The findings of Shin et al. [14] strongly support the hypothesis that oVEMPs response is mediated by the superior vestibular nerve. The authors examined 41 patients with acute VN, and on the basis of clinical findings (appearance of mixed horizontal and torsional nystagmus; impaired horizontal SCC function on head-impulse test and caloric paresis > 25%; normal cVEMP and normal head-impulse test for posterior SCC) 30 subjects affected by neuritis of the superior vestibular nerve were identified. Interestingly, all these patients presented normal cVEMP responses in the affected ear, indicating that the saccular otolithic receptors and their afferents, in the inferior vestibular nerve, were completely functional. In contrast, all 30 patients had an asymmetric oVEMP response with the p10 component either absent, markedly reduced or delayed, beneath the eye opposite to the affected ear.

In a recent study, Magliulo et al. [3] prospectively evaluated 40 patients affected by VN employing both cVEMPs and oVEMPs. Thirty-two of the 40 patients showed absent or abnormal oVEMPs at the first control, while only 19 of the 40 patients showed absent or abnormal values of cVEMPs. With the aid of the video head impulse test (vHIT) the authors were able to classify the various pathological findings with regards to the location of vestibular damage and number of vestibular organs involved. The superior vestibular nerve VN (30%), followed by the total VN (25%), were the most frequently involved entities.

Table II. Main characteristics of the studies analysed with correlations between Ménière's disease (MD) and VEMPs responses.

Authors	Year	No. of patients with definite MD	No. of healthy subjects in the control group	Type of VEMPs	Sound conduction	Stimuli	Stimulation intensity	Stimulation frequencies	Significant findings in VEMPs responses
Akkuzu et al. [34]	2006	20	17	cVEMP	ACS	Tone bursts	100 dB	500 Hz	Abnormal values ($p < 0.001$)
Hong et al. [17]	2008	29	None	cVEMP	ACS	Clicks	95 dB	2,000 Hz	Abnormal values in 20 (69%) patients
Kim-Lee et al. [42]	2009	24	20	cVEMP	ACS	Tone bursts	90 dB	500-1,000 Hz	Elevated frequency peak amplitude ($p < 0.001$)
Winters et al. [37]	2011	37	55	oVEMP	ACS	Tone bursts	120 dB	500-4,900 Hz	Lower response rate ($p < 0.05$)
									Higher asymmetry ratio ($p < 0.05$)
									Lower amplitude ($p < 0.05$)
Kingma and Wit [36]	2011	22	None	cVEMP	ACS	Tone bursts	100 dB	250-500 Hz	Lower amplitude in the affected ears ($p < 0.05$)
Taylor et al. [38]	2011	60	35	cVEMP	ACS	Clicks	140 dB	500 Hz	Abnormal values in 24 (40%) patients
					BCS	Vibration pulses	n.a.	n.a.	Abnormal values in 13 (22.8%) patients
				oVEMP	ACS	Clicks	140 dB	500 Hz	Abnormal values in 30 (50%) patients
					BCS	Vibration pulses	n.a.	n.a.	Abnormal values in 6 (10.2%) patients
Sandhu et al. [41]	2012	12	8	cVEMP	ACS	Tone bursts	120 dB	250-500-750-1,000-1,500-2,000-3,000-4,000 Hz	Lower amplitude ($p < 0.05$)
				oVEMP	ACS	Tone bursts	120 dB	250-4,000 Hz	Lower amplitude ($p < 0.05$)
Egami et al. [35]	2013	114	None	cVEMP	ACS	Clicks/ Tone bursts	95 dB	500 Hz	Abnormal values in 57 (50%) patients
Silva et al. [61]	2016	30	30	Combined cVEMP-oVEMP	ACS	Tone bursts	120 dB	500 Hz	Mean latency values of n10 - p15 waves were higher than control group
Chen et al. [62]	2016	30	30	cVEMP	ACS	Tone bursts	90 dB	500 Hz	Abnormal responses in 12 (40%) patients
				oVEMP	ACS	Tone bursts	95 dB	500 Hz	Abnormal responses in 5 (16.7%) patients

ACS: Air-Conducted Sound; BCS: Bone-Conducted Sound; n.a.: not available.

Similary, Walther and Blodow [20] analysed 20 patients affected by VN using both oVEMPs and cVEMPs in combination with vHIT. The authors were able to differentiate 4 types of VN (entire VN; superior VN; inferior VN; ampullary VN); entire VN and superior VN were the entities most frequently observed.

Ménière's disease (MD)

Ménière's disease (MD) is characterised by fluctuating hearing loss, tinnitus, aural fullness and episodic vertigo [21 22]. The histopathological correlate, endolymphatic hydrops, is observed most frequently in the cochlea and the saccule, followed by the utricle and the semi-circular canals [23-25].

Table III. Main characteristics of the studies analysed with correlations between benign paroxysmal positional vertigo (BPPV) and VEMPs responses.

Authors	Year	No. of patients with definite BPPV	No. of healthy subjects in control group	Type of VEMPs	Sound conduction	Stimuli	Stimulation intensity	Stimulation frequencies	Significant findings and correlations in VEMPs responses
Akkuzu et al. [34]	2006	25	17	cVEMP	ACS	Tone bursts	500 dB	500 Hz	Abnormal values (p=0.012)
Boleas-Aguirre et al. [50]	2007	19	None	cVEMP	ACS	Clicks	70-100 dB	n.a.	Absent responses in 10 (52.4%) affected ears vs 5 (26.3%) healthy ears
Hong et al. [17]	2008	62	None	cVEMP	ACS	Clicks	95 dB	500 Hz	Abnormal values in 24 (40%) patients
Yang et al. [51]	2008	41	92	cVEMP	ACS	Clicks	95 dB	n.a.	No response in 11 (27%) patients; Prolonged latencies (p<0.001)
Korres et al. [52]	2011	27	30	cVEMP	ACS	Tone bursts	95 dB	500 Hz	Abnormal values (p<0.005)
Longo et al. [55]	2011	23	24	cVEMP	ACS	Logon	127 dB	500 Hz	Abnormal values (p<0.001)
Lee et al. [53]	2013	16	None	cVEMP	ACS	Tone bursts	90 dB	500 Hz	Abnormal values in 5 (31.3%) patients
				oVEMP	ACS	Tone bursts	95 dB	500 Hz	Abnormal values in 4 (25%) patients
Yetiser et al. [54]	2014	102	15	cVEMP	ACS	Tone bursts	95 dB	500 Hz	Abnormal values in 24 (23.5%) patients
Xu et al. [56]	2016	30	30	cVEMP	ACS	Tone bursts	90 dB	500 Hz	Abnormal values in 9 (30%) BPPV patients vs 2 (6.6%) healthy patients
				oVEMP	ACS	Tone bursts	95 dB	500 Hz	Abnormal values in 17 (56.7%) BPPV patients vs 1 (3.3%) healthy patient
Singh et al. [57]	2015	31	31	cVEMP	ACS	Tone bursts	125 dB	500 Hz	No significant group difference on any cVEMP parameters
				oVEMP	ACS	Tone bursts	125 dB	500 Hz	Peak-to-peak amplitude significantly smaller in the affected ears
Chang et al. [58]	2017	65	None	cVEMP	ACS	Tone bursts	95 dB	500 Hz	Decreased interaural amplitude difference ratio at the affect side associated with persisting BPPV after manoeuver
Hoseinabadi et al. [59]	2015	30	None	cVEMP oVEMP	ACS	Tone bursts	95 dB	500 Hz	QoL is more compromised in patients with cVEMP and oVEMP abnormalities
Karatas et al. [60]	2016	36	20	cVEMP	ACS	Tone bursts	100 dB	500 Hz	Normalised amplitudes of BPPV patients significantly lower than those in the control group

QoL: Quality of Life; ACS: Air-Conducted Sound; n.a.: not available.

The diagnosis of MD relies upon clinical presentation and pure tone audiometry, which in the early stages of the disease shows low frequency hearing loss in a "rising configuration" that later progresses to a flat hearing loss of moderate severity [26-29].

Current standard vestibular testing consists of caloric stimulation of both ears using nystagmography to evaluate the ear's functionality. However, this test highlights disturbances in only 1 (the horizontal canal) of the 3 semicircular canals. Moreover, in patients with MD, the calorigram can show variable responses, and in many cases, test results are normal [30].

Initial reports using a standard fixed acoustic stimulus showed that a significant number (35%-54%) of patients with MD did not have cVEMPs present [31-33], so that authors began to compare VEMPs values in patients affected by MD with those recorded in normal ears.

Akkuzu et al. [34] found 10 (50%) abnormal cVEMP responses in 20 patients with MD. In particular, there were 4 ears with no response while six ears presented a prolonged latency at p13. Among 29 subjects diagnosed with MD, Hong et al. [15] observed an abnormality of cVEMP in 20 (69%) of them. In particular, increased cVEMP asymmetry was noted in 14 (70%) patients followed by a prolonged p13 latency (9 patients, 45%).

Egami et al. [35] measuring cVEMP in 144 patients affected by MD and found abnormal values in 57 (50%) of them. It must be noted that among the same patients only 43 (37.7%) showed no or decreased caloric responses on the affected side.

Kingma et al. [36] measured cVEMP in 22 patients affected by MD. On average, significantly lower VEMP amplitudes were measured at the side of the affected ear for both stimulus frequencies (250 and 500 Hz).

Winters et al. [37] evaluated the changes of the oVEMP in a group of 37 patients with MD. The data showed that the oVEMP response rates in ears of patients with MD were dramatically lower (54% at 120 dB SPL; 29% at 115 dB SPL) than in normal subjects (98.2% at 120 dB SPL).

Taylor et al. [38] investigated the prevalence of cVEMP and oVEMP on 60 patients with MD reporting 50% of abnormality for oVEMP and 40% of abnormality for cVEMP responses.

Some authors [39 40] reported a shift in dominant frequency away from the typical 500 to 1000 Hz for VEMPs recorded in patients with MD. On the basis of these observations, Sandhu et al. [41] confirmed the presence of this shift in dominant frequency for both cVEMP and oVEMP in patients with MD. Interestingly, the authors were able to evoke myogenic potentials in all ears tested: in healthy volunteers, the acoustic stimulus frequency at which the response amplitudes were largest was 500 Hz, while in subjects affected by MD this value shifted to higher frequencies.

Similar results were observed by Kim-Lee et al. [42] who analysed the cVEMP responses in a group of 24 subjects with MD. Overall, cVEMP were present in 83% of affected ears, but were most reliably elicited at a tone burst stimulation frequency of 1,000 Hz. Moreover, the frequency peak amplitude ratios (FPA) in the MD group were significantly elevated compared with those of the control group. The authors concluded that FPA is elevated in MD and thus may represent a useful diagnostic criterion in the diagnosis of this pathology.

Another interesting study was published by Katayama et al. [43] who investigated the relationship between the presence of endolymphatic hydrops and cVEMP in patients with MD. Intratympanic injection with gadolinium diluted with saline was performed in 49 affected ears and after one day, 3 Tesla MRI and cVEMP were performed. Overall, cVEMP was present in 21 ears and absent in 28 ears. Endolymphatic hydrops was significantly associated with the absence of cVEMP.

Benign paroxysmal positional vertigo (BPPV)

Benign paroxysmal positional vertigo (BPPV) is the most common disorder of the peripheral vestibular system and characterised by episodes of vertigo associated with head movements [44 45]. Although BPPV generally responds well to treatment, there is a significant rate of recurrence after the initial resolution [46]. The recurrence rates during a 1-year follow-up period have been reported to range from 10% to 18% [47 48].

In explaining the pathophysiology of BPPV, the concept of a degenerative process that affects the macula of the utricle causing detachment of otoliths has gained popular support [49]. However, in 30 affected ears with BPPV Akkuzu et al. [34] found 9 (30%) ears showing abnormal cVEMP values. This finding suggested that the degenerative process involved in BPPV might also affect the macula of the saccule.

Similarly, Boleas-Aguirre et al. [50] analysed 19 patients diagnosed with BPPV of the posterior semi-circular canal. The authors found a lack of cVEMP response in 52% of the affected ears. When adjusted for bilateral absence, cVEMP response was absent in 20.3% of ears. The authors concluded that some patients with BPPV show a certain degree of saccular dysfunction.

Among 62 subjects diagnosed with BPPV, Hong et al. [15] reported an abnormality of cVEMP in 16 (25.8%) of them. Yang et al. [51] investigated the clinical significance of cVEMP in a group of 41 patients affected by BPPV

in comparison to 92 healthy volunteers. Overall, 11 (27%) patients in the BPPV group showed no response in VEMPs in the affected ear. Moreover, VEMPs showed prolonged p13 and n23 latencies in BPPV subjects compared with those of the control group.

Korres et al. [52] analysed 27 BPPV patients and noted that the percentage of abnormal cVEMP in the BPPV population was significantly higher than in the ears of control group.

Lee et al. [53] investigated the usefulness of VEMP in patients presenting recurrent BPPV and reported interesting results. The authors analysed 16 subjects presenting recurrent BPPV and 20 patients with non-recurrent BPPV by cVEMP and oVEMP. Among the group of patients with recurrent BPPV, abnormal cVEMP responses were detected in 5 (31.3%) subjects, while abnormal oVEMP responses resulted in 4 (25%) subjects. Between the 20 patients with non-recurrent BPPV, only 3 (15%) subjects overall showed abnormal cVEMP or abnormal oVEMP.

Yetiser et al. [54] recently analysed a cohort of 102 patients affected by BPPV and reported similar findings. In total, 24 (23.5%) patients presented a gross cVEMP abnormality (absence of VEMP in 6 and greater than 25% depression of the amplitude in 18). Abnormality of VEMPs was not correlated with age, severity of nystagmus or the site of canal involvement, but was significantly correlated with persistence or recurrence of symptoms.

Finally, Longo et al. [55], in their prospective study of 23 patients affected by BPPV and 24 healthy volunteers, found that the cVEMP among BPPV patients were altered in 14 ears (30.4%) and absent in 5 (10.9%) affected ears and in 2 (4.3%) non-affected ears. This value was significantly higher than the comparative control groups.

Conclusions

Although official standard measurement parameters of normality must still be defined for VEMPs, it seems clear that this instrument will represent a novel and important vestibular examination for VP, MD and BPPV. In VN, VEMPs (cVEMP together with oVEMP) may represent a useful tool in improving topographic diagnosis, offering key information about prognosis and therapy. In MD, both cVEMP and oVEMP showed better sensitivity and specificity compared with the caloric test, but a wide variety of described alterations in VEMPs recordings among the studies analysed were noted, with amplitude reduction representing the most frequent finding. For this reason, additional studies are needed to accurately identify specific anomalies in VEMPs recording associated with MD. In VPPB, VEMPs may also be important in predicting pathological recurrences.

Conflict of interest statement

None declared.

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Head and neck

Barbed suture in oral cavity reconstruction: preliminary results

La sutura barbed nella ricostruzione del cavo orale: risultati preliminari

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SUMMARY

The purpose of this study is to evaluate the efficacy and safety of unidirectional barbed suture (V-Loc) compared to a standard monofilament stitch (Vicryl) in suturing of a free flap to local tissue after head and neck surgery for squamous cell carcinoma of the oral cavity. Complication rates, operative closure time, length of hospitalisation and costs were evaluated. The study cohort (group A) of 20 consecutive patients reconstructed using barbed stitches for suturing was prospectively compared to a control cohort (group B) of 20 consecutive patients reconstructed using conventional vicryl stitches. All patients were affected by squamous cell carcinoma of the tongue and underwent different types of glossectomy and reconstruction with free flaps. This analysis demonstrates the efficacy of the barbed suture compared with a standard monofilament stitch in terms of lower complication rate (15% group A, 30% group B), intra-operative closure times (486 minutes group A, 517 minutes group B), and length of hospitalisation (average length of hospitalisation 14.60 days group A, 16.85 days group B). These factors coupled with the use of a lower number of stitches compared with the standard stitches may compensate the increased cost of the barbed suture. In conclusion, this study demonstrates that the use of unidirectional barbed stitches for suturing of a free flap to the recipient site reduces the complication rate, principally in terms of dehiscence and fistula incidence, and reduces intra-operative time and length of hospitalisation. Based on these results and on the literature, the use of unidirectional barbed stitches can be considered as a safe and efficient alternative to conventional stitches for suturing of free flaps to local tissue.

KEY WORDS: Barbed suture • Free flap • Head neck reconstruction • Oral cavity cancer

RIASSUNTO

Il presente studio ha lo scopo di analizzare le potenzialità e la sicurezza della sutura unidirezionale barbed (V-Loc) rispetto alla sutura convenzionale monofilamento (vicryl) nella chirurgia ricostruttiva del cavo orale con lembo libero. Sono stati valutati i seguenti parametri: percentuale di complicanze, tempi intra-operatori, tempi di ospedalizzazione e costi della procedura. La coorte di studio (gruppo A), costituita da 20 pazienti consecutivi in cui è stata utilizzata la sutura barbed per suturare il lembo libero alla mucosa del cavo orale, è stata confrontata con la coorte di controllo (gruppo B), costituita da 20 pazienti consecutivi, in cui è stata invece utilizzata la sutura convenzionale Vycril. Tutti i pazienti, affetti da carcinoma squamocellulare della lingua, sono stati sottoposti a chirurgia compartimentale della lingua e successiva ricostruzione con lembo libero radiale di avambraccio o antero-laterale di coscia. La nostra analisi dimostra l'efficacia della sutura barbed se confrontata con quella convenzionale, in termini di minore percentuale di complicanze post-operatorie (15% gruppo A, 30% gruppo B), tempi intraoperatori di chiusura (486 minuti gruppo A, 517 minuti gruppo B), e tempi di ospedalizzazione (tempo medio di ospedalizzazione: 14,60 giorni gruppo A, 16,85 gruppo B). Questi fattori, associati al minor numero di fili barbed utilizzati durante la sutura, potrebbero compensare il costo maggiore della sutura barbed rispetto a quella convenzionale. In conclusione, questo studio dimostra che l'utilizzo della sutura unidirezionale barbed nella sutura del lembo libero alla mucosa del cavo orale riduce la percentuale di complicanze post-operatorie, principalmente in termini di deiscenza e fistola, i tempi intra-operatori e la durata dell'ospedalizzazione. Basandosi su questi risultati e sulla letteratura, si può concludere che l'utilizzo della sutura barbed rappresenta un'alternativa sicura ed efficace rispetto alla sutura convenzionale nella chirurgia ricostruttiva del cavo orale.

PAROLE CHIAVE: *Sutura barbed • Lembo libero • Ricostruzione cervico-cefalica • Carcinoma del cavo orale*

Introduction

Since the introduction of reconstruction in head and neck oncology in the 1970s as a mainstay of surgical practice, the use of free flaps has progressively evolved, reaching success rates ranging between 90% and 98%. To date, microvascular flaps represent the gold standard for reconstruction of complex three-dimensional composite defects in the head and neck district. The main advantages of microvascular reconstructive techniques, compared to less sophisticated ones, are the possibility to choose the best

defect-adapted tissue, tailor the flap in a three-dimensional fashion to minimise postoperative functional defects and, most importantly, to bring well vascularised tissue into the surgical field to accelerate the healing process. Although in recent decades, surgeons' experience, quality of anaesthesiology techniques and postoperative care have consistently improved, free flap reconstruction of head and neck cancer (HNC) defects remains a complex procedure involving many aspects that can increase the perioperative complication rate (general and local) and potentially affect the final outcome, especially in elderly patients with important comorbidities [1].

Regarding local complications, the incidence of flap dehiscence and fistula reported in the literature is high. The sutures commonly used to fix the free flap to local tissue in the recipient site include conventional absorbable monofilament, such as vicryl. In recent years, our centre has adopted the barbed suture, a relatively new device with cutting barb that gives tensile strength without the need for tying. There is increasing evidence that knotless, barbed, self-anchoring suture devices are as safe and well tolerated as conventional stitches in tissue suturing and that their use seems to be associated with reduced surgical closure times, local complications and costs [2].

In our study, we evaluated the efficacy and safety of the unidirectional barbed suture (V-Loc) compared to a standard monofilament stitch (Vicryl) in suturing of free flaps to local tissue after head and neck surgery for squamous cell carcinoma of the oral cavity. Complication rates, operative closure times, length of hospitalisation and costs were evaluated. To our knowledge, this study represents the first analysis of outcomes of barbed sutures applied in reconstructive head and neck surgery.

Materials and methods

A prospective study was carried out on the use of the barbed suture in the reconstruction of patients affected by squamous cell carcinoma of the tongue who were submitted to different types of glossectomy (subtotal, hemi-glossectomy, marginal glossectomy) and reconstructed with free flaps (radial forearm free flap (RFFF) or anterolateral tight free flap (ALT)).

The study cohort (group A) included 20 consecutive patients treated between 2016 and 2017 in the ENT Department of San Luigi Gonzaga Hospital, Orbassano (Turin) and in the ENT Department of FPO-IRCCS Candiolo Cancer Institute. All patients were reconstructed using barbed stitches for suturing (V-Loc, Covidien, Mansfield, VA, USA).

The control cohort (group B) included 20 consecutive patients treated by the same surgeons between 2014 and 2016 in the ENT Department of Turin, the Martini Hospital and San Luigi Gonzaga Hospital, and reconstructed using conventional Vicryl stitches (vicryl 3.0, Ethicon, Cincinnati, OH, USA).

The characteristics of patients in group A are reported in Table I, and those in group B are reported in Table II. Nine of 40 patients were affected by diabetes mellitus (DM) (6 in group A and 3 in group B). Seven patients were pretreated with radiotherapy (RT) (4 in group A and 3 in group B). All patients gave oral and written informed consent preoperatively, following the principles of the Helsinki Declaration, developed in 2013 by the World Medical Association (WMA) as a statement of ethical principles for medical research involving human subjects [3].

Clinical assessment was performed during the 3 weeks before surgery. This involved clinical examination, biopsy with histological exam, evaluation of nutritional status, Maxillo-Facial and Neck CT /MRI and total body PET scan in the case of advanced stage disease.

Nutritional status of the patients was evaluated with the subjective global assessment (SGA) [4]. The SGA consists of a brief nutritional history (weight loss during the last 2 weeks and 6 months, dietary change, and a short physical examination of subcutaneous fat, muscle mass and fluid balance). It categorises patients as being well nourished (SGA A), moderately (or suspected of being) malnourished (SGA B), or severely malnourished (SGA C).

Surgery

All patients underwent different types of glossectomy by a submandibular approach, en bloc with ipsilateral/bilateral neck dissection, followed by reconstruction with RFFF or ALT. The types of glossectomy were classified into three categories [5]: partial glossectomy (less than one third of tongue), hemi-glossectomy (from one third to half of tongue) and sub-total glossectomy (from half to three quarters of tongue).

A variety of surgical approaches are available for resection of a primary tumour in the oral cavity. At the present time, the submandibular approach, combined with the use of the harmonic pincer for resection of the tongue, is currently accepted as an oncologically-viable alternative to the conservative trans-mandibular approach, reducing the rate of complications (dehiscence, fistula, plate exposure, osteitis, lack of osteosynthesis, osteonecrosis) [6].

The surgeon performs a tracheostomy to bypass the transoral intubation and to isolate the oral cavity. Ipsilateral or bilateral selective/radical neck dissection is performed, depending on the site of the tumour (lateral, median or paramedian) and nodal status. The continuity between T

Table I. Patient demographics, group A (barbed suture).

N	Sex	Age (years)	Comorbidities	SGA	TNM	Pre-treatment	Type of reconstruction	Intraoperative length (minutes)	Length of hospitalisation (days)	No. of stitches
1	M	64	None	B	cT4aN2c	None	ALT	600	13	4
2	M	68	DM	B	cT4aN1	None	ALT	570	12	4
3	M	51	None	B	rT4aN1	RT	ALT	570	14	4
4	M	46	None	A	rT2N0	RT	RFFF	520	11	3
5	F	65	DM	B	rT3N2b	RT	ALT	480	15	4
6	M	51	None	B	cT3N2b	None	RFFF	510	11	3
7	F	67	DM	C	cT3N2b	None	ALT	440	13	4
8	M	53	None	B	cT2N0	None	RFFF	450	16	3
9	M	54	None	B	cT2N0	None	RFFF	430	14	3
10	F	54	None	B	cT3N2a	None	RFFF	435	11	2
11	M	58	None	B	cT2N1	None	RFFF	490	22	3
12	M	47	None	A	cT2N1	None	RFFF	495	15	3
13	F	60	None	B	cT2N0	None	ALT	410	15	4
14	M	72	DM	C	cT3N0	None	ALT	510	18	4
15	F	63	None	B	cT3N3b	None	ALT	500	17	4
16	M	30	None	C	cT2N0	None	ALT	415	12	3
17	M	78	None	C	cT3N1	None	ALT	470	17	3
18	F	76	DM	C	cT3N0	None	ALT	480	15	3
19	M	61	None	B	cT3N0	None	RFFF	485	13	3
20	M	64	DM	B	rT3N0	S-RT	ALT	460	18	3

DM: diabetes mellitus; RT: radiotherapy; SGA: subjective global assessment; S: surgery; RFFF: radial forearm free flap; ALT: anterolateral tight flap.

Table II. Patient demographics, group B (conventional suture).

N	Sex	Age (years)	Comorbidities	SGA	TNM	Pre-treatment	Type of reconstruction	Intraoperative length (minutes)	Length of hospitalisation (days)	No. of stitches
1	M	75	None	C	cT2N0	None	RFFF	540	13	15
2	M	42	None	A	cT2N2c	None	RFFF	540	13	17
3	F	73	None	B	cT2N0	None	RFFF	510	14	14
4	M	76	None	C	cT2N0	None	RFFF	600	16	14
5	M	58	None	B	cT3N0	None	ALT	510	19	18
6	F	66	None	B	rT3N1	RT	ALT	450	20	21
7	M	58	DM	B	cT2N2c	None	ALT	510	22	17
8	F	62	None	B	cT2N0	None	ALT	420	17	15
9	F	51	None	B	cT4aN0	None	RFFF	420	17	14
10	M	56	None	B	cT3N2b	None	RFFF	540	21	15
11	M	48	None	A	cT2N0	None	RFFF	500	13	15
12	F	47	None	A	rT2N0	RT	RFFF	480	12	13
13	M	60	DM	B	cT4aN2c	None	ALT	555	21	17
14	M	65	None	C	cT2N2b	None	RFFF	490	16	15
15	M	61	None	B	rT4aN2b	RT	ALT	705	18	18
16	F	43	None	A	cT1N2b	None	RFFF	600	15	14
17	M	49	None	A	cT2N0	None	RFFF	465	21	15
18	F	65	DM	C	cT4aN0	None	ALT	465	21	21
19	M	52	None	B	cT3N1	None	ALT	555	17	15
20	M	21	None	A	cT2N1	None	RFFF	480	11	16

DM: diabetes mellitus; SGA: subjective global assessment; RT: radiotherapy; RFFF: radial forearm free flap; ALT: anterolateral tight flap.

and N is preserved sectioning the mylohyoid muscle. With a transoral approach, resection should include at least a 1.5- to 2 cm margin from the macroscopic border of the cancer. Cold instruments may be inadequate for haemostasis owing to the vascularity of the tongue. Therefore, an ultracision device (Harmonic Focus + Shears, Ethicon) is preferred. Frozen sections are obtained from the mucosal margins and from the depth of the surgical defect to ensure that an adequate excision of the primary tumour has been accomplished.

The intraoral defect is then reconstructed with a radial forearm free flap (RFFF) or anterolateral free flap (ALT), depending on the extent of the intraoral defect, patient characteristics and donor site.

Only two surgeons (GS, EC) performed all of the procedures.

Suture technique

In group A, the suture between local tissue and free flap was performed with a continuous barbed suture. Using the barbed suture, the closure was started by taking the stitch, passing it into the tissue in the opposite direction from the splay of the barb, allowing the suture to pass easily and running the V-Loc device through the welded loop. When a force is applied in the opposite direction, the barb of the suture grasps the surrounding tissue and ensures that the tissue is retained in place (Fig. 1). Images of the V-Loc suture between lingual tissue and free flap (ALT) after partial glossectomy and the healing process are shown in Figures 2-5.

In group B, the suture was performed with a single interrupted knot, using a conventional vicryl stitch (vicryl 3.0, Ethicon, Cincinnati, OH, USA).

Statistical analysis

The following parameters were evaluated: complication rates, intraoperative time, length of hospitalisation, number of stitches used and cost of the procedure.

Postoperative complications were divided into major complications requiring surgical re-intervention (partial/total necrosis, haematoma, haemorrhage) and minor complications (fistula, suture dehiscence) requiring only medical dressing.

Intraoperative time, length of hospitalisation and cost of the procedures were evaluated with a t-test. The incidence of complications between the two groups was evaluated with a chi-squared test.

Statistical analysis was performed using PRIMIT Software, version 3.03 (McGraw-Hill. Inc.) with $p < 0.05$ considered as statistically significant.

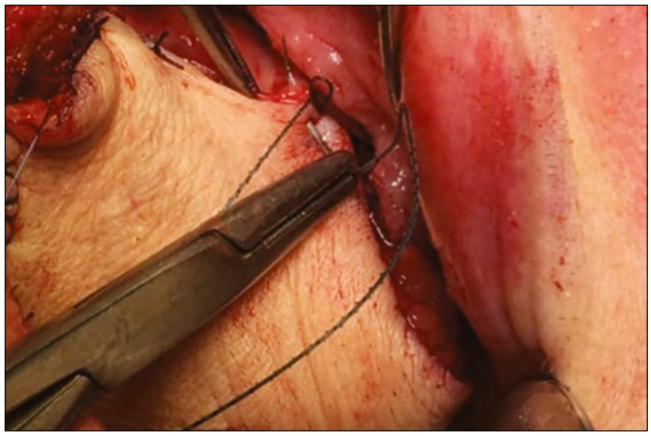

Fig. 1. V-Loc barbed suture.

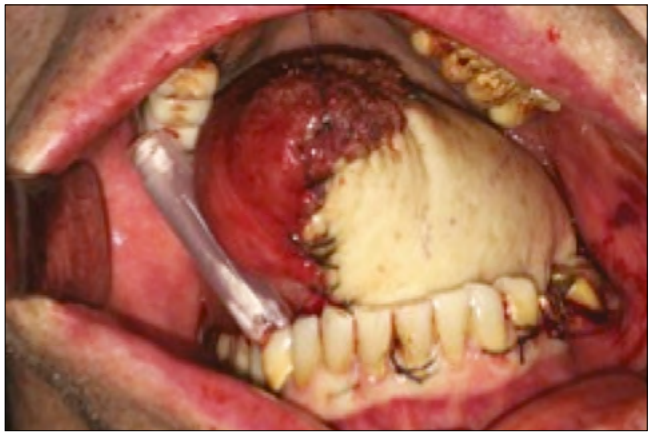

Fig. 2. Intraoperative suture with barbed stitch between lingual tissue and free flap (ALT) after partial glossectomy.

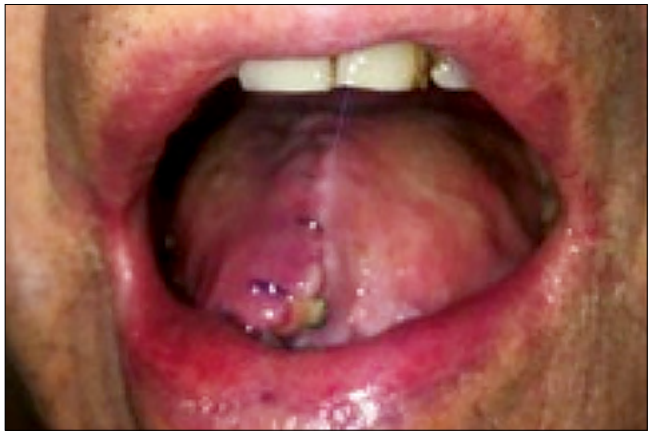

Fig. 3. Barbed suture: 20 days after partial glossectomy.

Results

A total of 40 patients were treated (27 male, 13 female); the median age of group A was 59.1 years (range 21-76 years) and 56.4 years in group B (range 30-78 years).

20 patients were reconstructed with RFFF (8 in group A and 12 in group B), and 20 patients with ALT (12 in group A and 8 in group B).

Intraoperative time

The average intraoperative time was 486 minutes for group A and 516.75 minutes for group B. There was no significant difference between groups (t-test, p = 0.113; Table III).

Length of hospitalisation

The average length of hospitalisation was 14.60 days in group A and 16.85 days in group B. There was a significant difference between groups (t-test, p = 0.03; Table III).

Cost of the procedure

The cost of a V-Loc stitch was about € 26.60, while for a vicryl stitch, the cost was € 2.50. The median number of stitches used in the barbed suture was 3.35, while in the conventional suture was 15.95. The median cost of the procedure in group A was € 89.11, in group B it was € 39.88 (Table III).

Complication rate

The incidences of fistula and flap dehiscence were analysed, not considered flap necrosis since this complication could not be related to the type of suture. Subsequently, fistula and dehiscence rates were correlated with three factors: diabetes mellitus, preoperative treatment and nutritional status.

In group A, three patients developed a complication (15%): two minor complications (10%) (suture dehiscence with orocutaneous fistula), and one major complication (total necrosis of the flap) (5%). One of the patients with postoperative fistula was treated with RT before surgery. No patient suffered from diabetes mellitus. The two patients who developed postoperative fistula were moderately (or suspected of being) malnourished (SGA B).

In group B, six patients developed only minor complications (30%) (suture dehiscence with orocutaneous fistula): one of these patients was affected by diabetes mellitus, and none were pretreated before surgery. Three of these patients were well nourished (SGA A), and three were moderately (or suspected of being) malnourished (SGA B).

The overall percentage of procedures without minor complications was 80%: 90% in group A and 70% in group B. Using the chi-squared test, there was no significant difference between the two groups (p-value = 0.114) (Table III). The results are summarised in Table IV.

Discussion

The goal of head and neck reconstruction is the recovery of important functions (swallowing, speech, chewing) and appearance. Microvascular free tissue transfer techniques have become accepted for head and neck reconstructions because of their increased success rates (95-99%) and good functional and aesthetic outcomes [7]. Despite progress, the incidence of complications in the literature has continued to be reported as high. Analysing the outcomes after reconstructive surgery in HNC, Pohenz et al. and Bianchi et al. have evaluated the incidence of minor complications of the receiving site and found: flap partial necrosis (29.3%), dehiscence (27.2%), haematoma (23.2%), seroma (13.4%) and fistula (6.9%) [8 9].

In the literature, the reported incidence of fistula is about 20%. In our study, flap dehiscence and fistula were the most common minor complications (17.5% overall, 10% in group A and 30% in group B). The main risk factors associated with fistula are ascribable to patient-related factors, such as poor nutritional status, systemic conditions that compromise wound healing (diabetes mellitus), previous treatments (radiotherapy and/or chemotherapy) and to surgical site-related factors, such as the clean/contaminated environment of the oral cavity (saliva and bacterial flora), infections, size of the defects after extensive resection and ischaemic complications of the flap [10]. Flap dehiscence with orocutaneous fistula after microvascular tongue reconstruction is a complication that decreases the patient's quality of life, with prolonged hospitalisation and delayed start of adjuvant treatment. Treatment of fistula consists of

Table III. Statistical analysis.

		Group A	Group B	P-value
Average intra-operative time (min)		486	517	0.113
Average length of hospitalisation (days)		14.6	16.85	0.03
Cost of procedure	Cost of a stitch (euro)	26.60	2.50	
	Average no. of stitches	3.35	15.95	
	Average cost (euro)	89.11	39.88	
Rate of minor complications	Yes	2	6	0.114
	No	18	14	

Table IV. Summary of results.

		Group A (barbed suture)	Group B (conventional suture)
No. of patients		20	20
Gender	Male	14	13
	Female	6	7
Median age (years)		59.1	56.4
Comorbidities		6	3
Pre-treatment (RT)		4	3
SGA	A	2	6
	B	13	10
	C	5	4
Free flap	RFFF	8	12
	ALT	12	8
Median intra-operative duration (min)		486	517
Median hospitalisation (days)		14.60	16.85
Complications	Minor	2	6
	Major	1	0
No. of stitches (median)		3.35	15.95
Median cost (euro)		89.11	39.88

RT: radiotherapy; SGA: subjective global assessment; RFFF: radial forearm free flap; ALT: anterolateral tight flap.

drainage, no oral intake, dressings and antibiotic therapy [11]. Prevention of fistula must focus on meticulous preoperative multidisciplinary evaluation of the patient. In addition, in our opinion, efforts should be made to improve the suturing technique of the flap to the local tissue, with the goal of providing a watertight closure and therefore better endurance of the suture, and to suture areas that are not easily accessible, such as the base of the tongue, the retromolar area or spaces close to teeth.

In recent years, our centre has used barbed sutures to fix free flaps to local tissue. This is a relatively new device, introduced by John Alcamo in 1964. In recent years, this innovative suture has gained popularity as an alternative to conventional materials, since its approval by the US Food and Drug Administration for soft tissue application in 2005 [12 13].

The advent of barbed sutures has given surgeons a new tool for soft tissue suturing. These stitches have begun to revolutionise the field of orthopaedics, plastic surgery, gynaecology, urology and other specialties; however, it has not yet found widespread application in head and neck surgery, apart from pharyngoplasty for obstructive sleep apnoea [14 15].

This particular stitch consists of a permanent suture that has directional projections (or barbs) along its entire length, which imparts tensile strength without the need for tying. The stitch is passed into the tissue in the opposite direction to the splay of the barb, allowing the suture to pass easily. When a force is applied in the opposite direction, the barb of the suture grasps the surrounding tissue and secures the tissue in place [16]. A continuous knotless suture can immediately provide excellent waterproof tightness, reducing saliva infiltration between tissues of different thickness and type. Theoretically, in addition to the closing power of an appropriate flap's volume, the good 3D adaptability and greater vascularisation of the flap, this advantage should represent a substantial improvement over conventional sutures.

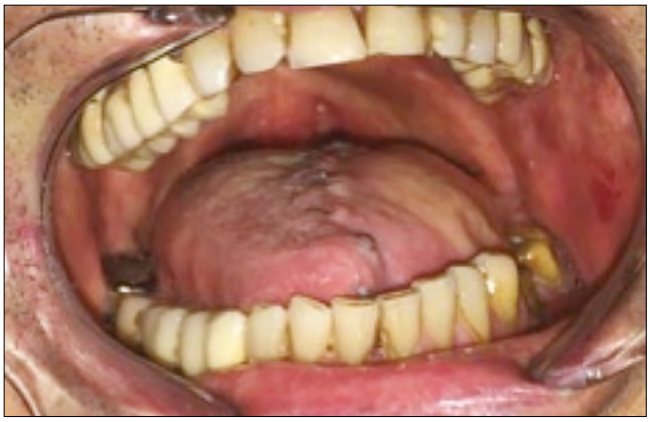

Fig. 4. Barbed suture: Two months after partial glossectomy.

Currently, three types of barbed suture are commercially available: the Quill Self-Retaining System (SRS) bidirectional barbed suture (Angiotech, Vancouver, BC, Canada), V-Loc unidirectional barbed suture (Covidien) and Stratafix unidirectional and bidirectional barbed suture (Ethicon) [17]. In our study, we compared the V-Loc barbed suture (group A, study group) with the vicryl 3.0 conventional suture (group B, control group) to suture a free flap to the lingual mucosa. V-Loc is a unidirectional suture with evenly spaced, circumferentially distributed barbs, with a needle on one end and a welded loop on the other.

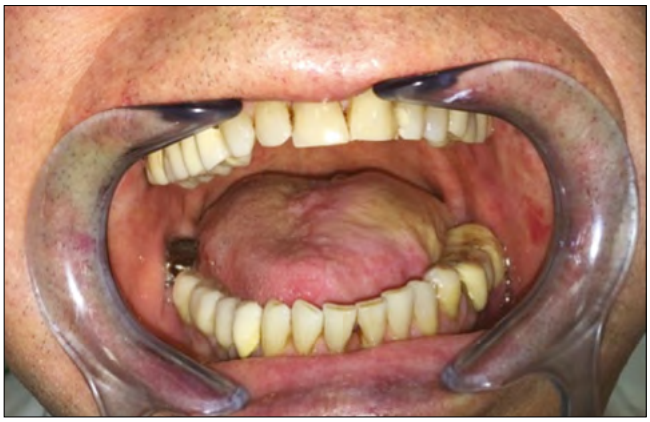

Fig. 5. Barbed suture: six months after partial glossectomy.

Comparisons between the two groups demonstrated the efficiency of the barbed suture: minor complication rates (suture dehiscence with orocutaneous fistula) were 10% in group A and 30% in group B. It is undeniable that the barbed suture shows a trend towards a fewer minor complications, even though our results did not show a significant difference between the two cohorts. This is probably due to the small number of patients in our study.

The advantages of the barbed suture may be due to different factors. This suture could decrease the potential chance of knot-related complications. In conventional stitches, the spaces between filaments of braided sutures act as a nidus for bacteria, exacerbating the risk of infection, ischaemia and necrosis. On the other hand, barbed stitches decrease the potential for knot slippage or dehiscence secondary to knot breakage, suture extrusion or splitting, necrosis caused by tissue strangulation and micro-infarction. Furthermore, the barbed suture provides a continuous suture with multiple anchoring points at each needle entry point, allowing resistance even after an eventual discontinuity, a more uniform distribution of force along the entire length of the stitch, better tissue apposition and better wound healing due to reduction of ischaemia. The tension is more uniformly distributed along the wound and approximation of the tissues is better than with conventional stitches [17-19].

In addition, the more straightforward and intuitive use of barbed stitches compared with conventional ones allows the surgeon to easily suture even those areas that are difficult to reach, such as the base of the tongue, the retromolar area, or a flap near teeth. Based on these considerations, intraoperative closure times could also be reduced after a normal learning curve, with consequent reduction of intraoperative length, as Paul and colleagues have underlined [20]. Our results confirmed this, with an average intraoperative period of 486 minutes for group A and 516.75 minutes for group B, even though the difference between the two groups was not significantly different (p-value = 0.113). With a lower incidence of complications and a faster recovery of oral intake, the length of hospitalisation was significantly reduced (p-value = 0.03).

It is reasonable to think that the learning curve for the barbed suture for skilled surgeons and for those in training is easier and shorter than the conventional one. Vicini et al. studying the learning curve and operative time of the surgical team during pharyngoplasty for OSAHS observed a decrease of these parameters over the course of the study with an initial steep ascent in technical skill acquisition followed by more gradual improvement, and a steady decrease in operative time. The minimally required manipulations and the knotless technique represent for the non-experienced surgeon a technique that is easy to learn, quick and safe to perform, including inside a simultaneous multilevel procedure if required [21 22].

The main limitation of the barbed suture is its cost; the cost of a vicryl stitch is about € 2.50, while it is € 26.60 for a V-Loc stitch (median cost of the procedure in group A was € 89.11, whereas it was € 39.88 in group B); however, the reduction in intraoperative time, reduction in length of hospitalisation and use of fewer stitches compared with standard ones may offset this increased cost. This idea is supported by a report by Massoud et al. [23], who performed a cost-effectiveness analysis of robotic-assisted radical prostatectomy using the unidirectional suture compared with the traditional suture and found the former to be more economical [22].

Obviously, the drawbacks of the barbed device are related to the possibility of extrusion of the suture with its slowly absorbable profile. Furthermore, once the barbs have engaged the tissue, it is almost impossible to remove the stitch, and there is still no recognised procedure for correcting a misplaced suture other than cutting it and starting over again [12]. The barbed suture is stiffer than the conventional one, and this could represent an inconvenience for the patient; for this reason, in our experience, to prevent the patient from feeling discomfort in the oral cavity, it is preferable not to leave the extremity of the thread unrestrained but rather to go back with the suture.

Despite the relevance of our findings, the present study has some limitations. It represents two-surgeons and single-institution non-randomised series, so our results cannot be generalised. Moreover, due to the small sample size, statistical analysis is inconclusive and the data will have to be verified in larger, multi-institutional series.

Conclusions

To our knowledge, this study is the first analysis on the use of the barbed suture compared to conventional ones in the suturing of a free flap to local tissue in head and neck reconstructive surgery, in terms of intraoperative times, costs and complication rates.

The study has demonstrated that the use of unidirectional barbed stitches during the suturing of a free flap to the recipient site reduces the complication rate, principally in terms of dehiscence and fistula incidence. Moreover, the barbed suture is technically easy and safe and may reduce the intraoperative time and consequently the length of hospitalisation. Based on these results and on the findings in the literature, the use of unidirectional barbed stitches can be considered as a safe and efficient alternative to conventional stitches for suturing of free flap to local tissue.

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Conflict of interest statement

None declared.

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Head and neck

Recurrent Bell's palsy: outcomes and correlation with clinical comorbidities

Paralisi di Bell recidivanti: risultati clinici e correlazione con comorbidità

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SUMMARY

Recurrent Bell's palsy (RBP) has been reported to range from 2.6 to 15.2% of primary Bell's palsy (BP) and has been associated with systemic comorbidities such as diabetes and hypertension. A retrospective analysis of patients affected by BP and RBP were performed to define the signs and symptoms associated with recurrence and the outcomes. Clinical and subjective characteristics of 341 patients affected by facial palsy were analysed. Facial function was assessed via House-Brackmann and Sunnybrook grading system. Characteristics of the palsy and systemic comorbidities (diabetes, hypertension, herpetic infections, autoimmunity disorders, audio-vestibular symptoms) were analysed in BP and RBP patients applying Fisher exact and the Mann-Whitney U tests, while time to recovery was explored with univariate and multivariate analysis. Twenty-four patients presented two or more episodes of facial palsy, representing a recurrence rate of 7%. Associated symptoms (e.g. retroauricular pain, taste disorder, dry eye etc.) were similar between BP and RBP patients. RBP occurred at older age than primary episode ($p = 0.03$). Recurrence was a risk factor for delayed recovery ($p = 0.02$), although final facial function was similar between the two groups. In conclusion, no significant differences were found between primary BP patients and RBP patients in terms of symptoms, palsy severity and presence of comorbidities. Delayed facial nerve function recovery in RBP did not affect the final outcome. Treatment of facial nerve recurrences must be the same of the primary episode, although the presence of prodromal symptoms may alert the patient and early corticosteroid treatment may be commenced even before the onset of paresis.

KEY WORDS: Recurrent • Alternating • Bell's palsy • Facial paralysis • Outcomes

RIASSUNTO

Dati di letteratura riportano che una recidiva di paralisi di Bell (RBP) si presenta nel 2,6-15,2% dei pazienti che hanno già sviluppato in precedenza una paralisi di Bell (BP); la RBP è stata associata a comorbidità come diabete e ipertensione. Questo studio riporta un'analisi retrospettiva dei pazienti affetti da BP e RBP per definire i segni e i sintomi associati alla recidiva e i risultati clinici a lungo termine. Sono state analizzate le caratteristiche cliniche e soggettive di 341 pazienti affetti da paralisi facciale. La funzione facciale è stata valutata tramite il sistema di classificazione House-Brackmann e Sunnybrook. Le caratteristiche della paralisi e delle comorbidità sistemiche (diabete, ipertensione, infezioni erpetiche, disordini autoimmuni, sintomi audio-vestibolari) sono state analizzate nei pazienti con BP e RBP con i test di Fisher Exact e Mann-Whitney U, mentre il tempo di recupero è stato esplorato tramite analisi statistica univariata e multivariata. Ventiquattro pazienti (7%) hanno presentato una paralisi recidivante. La prevalenza e tipologia dei sintomi associati (ad esempio dolore retroauricolare, disturbi del gusto, secchezza oculare ecc.) erano simili tra i pazienti con BP e RBP. I pazienti con recidiva di paresi risultavano più anziani dei pazienti con paralisi primaria ($p = 0,03$), mentre i due gruppi non differivano in termini di sesso, gravità della paralisi e presenza di comorbidità. La recidiva è risultata essere un fattore di rischio per un recupero tardivo ($p = 0,02$), sebbene la funzione facciale finale fosse simile tra i due gruppi. In conclusione, non sono state riscontrate differenze significative tra i pazienti con BP primaria e quelli con BP recidivante in termini di sintomi, gravità della paralisi e presenza di comorbidità. Il recupero ritardato della funzione del nervo facciale in RBP non influenzava l'esito finale. Il trattamento delle recidive del nervo facciale deve essere trattato con le stesse modalità dell'episodio primario, tuttavia la presenza di sintomi prodromici può allertare il paziente e un trattamento precoce con corticosteroidi può essere iniziato anche prima dell'esordio della paresi.

PAROLE CHIAVE: *Ricorrente • Recidivante • Paralisi di Bell • Paralisi facciale • Risultati*

Introduction

The sudden onset of facial palsy is most commonly due to stroke or Bell's palsy (BP). BP is the most frequent form of peripheral palsy of the facial nerve and represents about 60% of all aetiologies, with a diversely reported annual incidence between 8 and 52.8 new cases per 100,000 individuals [1-3]. It is believed that reactivation of Herpes viruses in the endonevrium of the geniculate ganglion can play a role in the onset of peripheral idiopathic facial nerve palsy [4-6], but the aetiology is not yet completely defined. Medical treatment is based on high-dose of corticosteroids and antiviral agents, even if there is limited evidence of the efficacy of the latter [7 8].

Recurrent Bell's palsy (RBP), either ipsilateral or contralateral to the side affected in the primary episode, is a relatively rare disease. The incidence of recurrent facial palsy has been reported to range from 2.6 to 15.2 % of patients who already had a primary episode [9-17]. It was first reported to occur by Devriese and Peltz [10], who first identified alternating or recurrent palsies as those recurrences that affect the contralateral or ipsilateral facial nerve.

The data regarding prognosis of RBP, when compared to primary BP, are conflicting, partly because classification of degree of palsy is not uniform across studies. It is, therefore, not clear whether the pathogenetic mechanisms underlying RBP are the same as BP, and consequently if the therapeutic approaches should be different.

In the present study, subjects presenting with recurrent facial palsy were selected from all patients presenting with unilateral idiopatic facial palsy visited in a tertiary referral centre; the clinical characteristics and prognosis of patients with primary and recurrent BP were compared to define the signs and symptoms associated with recurrence and prognosis of outcomes.

Materials and methods

Subjects

This study was designed as a retrospective cohort study on subjects treated at Policlinico Umberto I University Hospital of Rome, between May 2010 and March 2018. The protocol was approved by the ethics committee of the University (authorisation number # 29-05-08/1432) and written informed consent was administered to each patient before commencing any study-related procedure. In order to obtain a homogeneous cohort of subjects, the eligibility criteria were: age 14 to 89 years; unilateral Bell's Palsy diagnosed by clinical ENT and neurological assessment; treatment within 48 hours after the onset of the initial symptoms of BP; standardised oral pharmacological treatment with prednisone 1 mg/kg for 10 days plus valacyclovir 500 mg TID for 6 days. Exclusions criteria included: pregnancy; palsy due to metabolic, neurological, infective, neoplastic, toxic or iatrogenic disease; traumatic injury to the facial nerve, VZV infection (Ramsay-Hunt syndrome), Melkersson-Rosenthal syndrome.

Study procedures

Two routinely scale systems were used to assess the facial palsy severity in the clinical practice: the House-Brackmann facial grading (HB) scale [18] and the Sunnybrook facial (SB) grading system [19]. The HB scale measures the global degree of paresis/paralysis, ranging from grade I (normal function) to VI (complete paralysis). It was chosen for its simplicity of assessment, most frequent use and robustness. Nevertheless, this scale lacks accuracy on synkinesis and regional asymmetry; therefore, the SB scale system, with a score ranging from 0 to 100, was added as it provides regional scores at rest and motion also in addition to accurate information on synkinesis.

Each patient was evaluated at his/her first visit and 10 days - 1, 3, 6 months post onset. Patients were interviewed to gather information on diabetes, hypertension, previous herpetic infections, systemic infections, autoimmunity disorders, audio-vestibular symptoms and family history of facial palsy. For the palsy itself, information about the presence and side of recurrence and time lapse between episodes, and all associated symptoms, were collected.

Patients who at first examination had HB ≥ IV or who had no improvements to HB II-III grade after 10 days underwent the following: brain MRI with gadolinium, audiometric and impendence tests, and electrophysiological tests (electromyography, electroneurography and blink reflex). Furthermore, patients with HB grade > IV, who did not show improvement at the second clinical assessment and were negative for secondary palsy, were referred to physical rehabilitation [20].

Statistical analysis

Data are presented as proportion and mean ± standard deviation or median (interval), as appropriate. Differences between patients with BP and RBP were tested by Fisher's exact test and Mann-Whitney U test for categorical and continuous variables, respectively. Time to recovery was explored with univariate (Log-Rank

test) time-to-event analyses. To further verify if the time to recovery was truly different in patients with BP and RBP, we ran a Cox proportional hazards regression model in a stepwise fashion to obtain hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). The main time variable was defined as the period (days) elapsed from palsy onset and the last available visit or outcome reached (i.e. recovery to a HB equal or less than grade II). Demographic and clinical variables were included Aa covariates of interest: sex, age, HB and SB grades (entered as multilevel variable), first BP or RBP episode, familial history and presence or absence and type of comorbidity (hypertension, diabetes, audio-vestibular symptoms, autoimmunity, herpetic infections). Two-tailed p-values < 0.05 were considered as significant, without correction for multiple comparisons considering the exploratory nature of the present study. Data were analysed using the Statistical Package for Social Sciences, version 16.0 (IBM SPSS Inc., Chicago, Ill., USA).

Results

A total of 341 patients (198 men, 143 women, mean age 50.2 ± 17.9 years, range: 14 to 89) attended the Emergency Department due to BP from May 2010 to March 2018.

Of these 341 patients, 30 were lost to follow-up and 22 had incomplete data collection, and we thus analysed the data of 289 patients. The mean HB grade was 3.7 ± 1.07, the Sunnybrook score was 40.7 ± 20.8. Twenty-four patients (7.0%) had a RBP. All patients with RBP were included in the analysis with exception of one patient at his third episode of facial palsy with clinical characteristics of Melkersson-Rosenthal syndrome (oedema of the lips, lingua plicata and relapsing facial palsy). Table I shows the characteristics of patients according to either a first BP episode (n = 265) or RBP (n = 24). Patients with RBP were older than the other patients (p = 0.03). The two groups did not differ in terms of sex, BP severity (HB and SB), or presence of comorbidities.

Eleven patients presented the palsy on their right side, and 13 on their left side. In RBP subjects, the median time from the previous episode was 6 years (interval: 2-33); the paresis involved the ipsilateral and contralateral side in 12 and 7 cases, respectively, while the remaining 5 cases were not able to report the previously affected side. The time elapsed from the previous BP episode and the previously affected side (ipsilateral or contralateral) did not influence the outcome. Interestingly, we found that patients with recurrent BP in the contralateral side were more likely to have hypertension (6 of 7) than those presenting a further ipsilateral BP episode (1 of 12) (p = 0.02) in the absence of other significant differences. Nevertheless, we do not think that this finding has a clinical correlation.

Considering the symptoms associated at onset of paresis among patients affected by RBP, 10 presented retroauricular pain, 4 dysgeusia, 4 dry eye, 4 hyperlacrymation and 3 patients had dry mouth; these symptoms were present alone or in combination. All the patients except one were at their second palsy; 15 palsies were ipsilateral and 8 contralateral. The patient affected by Melkersson-Rosenthal syndrome already presented 1 palsy on his left side and 3 on the right side. Five patients reported a family history of BP. Three patients, already treated in our clinic for BP, came to our observation with prodromal symptoms (retroauricular pain, dry eye, dysgeusia) before the onset of paresis that occurred within the next following days [21].

A total of 224 patients (78%) recovered from BP after a mean time of 63.4 days (interval: 2 to 357), while the remaining 65 (22%) did not completely recover after 6 months of follow-up.

Figure 1 shows the Kaplan-Meier curve displaying time to recovery from BP according to study group (first BP episode versus recurrent BP). Patients with first BP episode recovered faster than those with RBP (p = 0.04 by the Log-Rank test). No difference in terms of final facial function was found between the two groups.

Table I. Main characteristics of study sample (n = 289) according to the presence of a first BP episode or a recurrent BP.

	First BP episode	Recurrent BP	P-value
N	265	24	-
Gender (female:male)	113:152	10:14	1.00
Age, years	49.4 ± 18.1	57.2 ± 14.0	**0.03**
HB score	3.95 ± 0.65	3.83 ± 0.92	0.68
SB score	40.7 ± 21	40.4 ± 20.2	0.60
Presence of comorbidity	186	19	0.48
Hypertension	83	11	0.17
Diabetes	28	5	0.17
Autoimmunity disease	18	0	0.38
Infectious disease	5	2	0.11
Audio-vestibular abnormal	37	4	0.76
Herpes virus infection	108	12	0.39
Familial history of BP	27 (10%)	5 (20%)	0.16
Follow-up, days	60 ± 58	70 ± 59	0.34

Values are presented as means ± SD or N as appropriated. Significant values are in bold. BP: Bell palsy; HB: House-Brackmann.

Table II. Cox regression model (stepwise fashion) showing variables predictive for BP recovery.

	N	HR	95% CIs	p
HB grade				
III	117	1.00	-	-
IV	85	0.61	0.42-0.88	**0.01**
V or VI	87	0.42	0.29-0.60	**< 0.001**
First BP episode	265	1.00	-	-
Recurrent BP	24	0.52	0.29-0.91	**0.02**

HR < 1.0 indicates a greater risk of not recovering from BP. Significant values in bold. BP: Bell palsy; HB: House-Brackmann; HR: hazard ratio; 95% CIs: 95% confidence intervals.

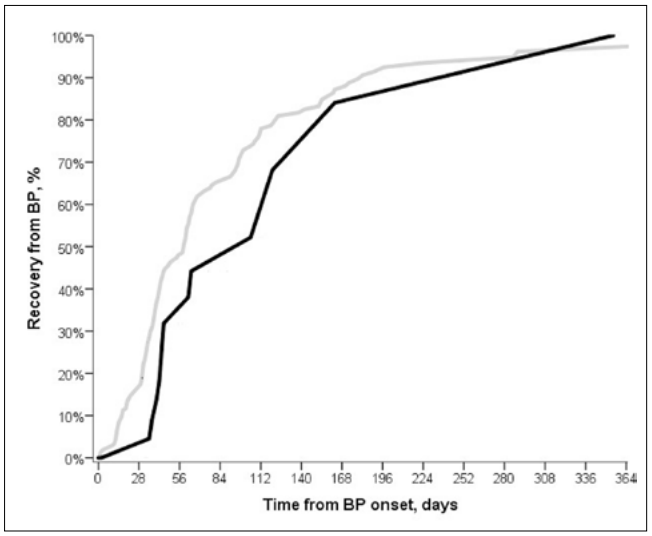

Fig. 1. Kaplan-Meier curve showing the time to Bell's Palsy recovery in patients with a first episode (BP) (n = 265; grey line) and in those with recurrence (RBP) (n = 24; black line).

Findings from the Cox regression model are shown in Table II. As expected, higher HB grades were associated with delayed recovery (HR: 1.00 for grade III, 0.61 for grade IV, 0.42 for grade V or VI; $p < 0.001$). Also, RBP was a risk factor for delayed recovery (HR: 0.52; $p = 0.02$). The remaining clinical variables, including sex, age and comorbidities, did not contribute to fit the model.

Discussion

Recurrence of peripheral facial palsy is well known and has been reported by several studies; physicians and rehabilitation therapists should inform patients presenting with a primary episode that recurrence may occur even after several years. In the present study, 24 of 289 patients (7%) developed a second episode of facial palsy, a percentage that is in accordance with data present in the literature [9-17]. Although RBP has been associated with systemic comorbidities such as diabetes and hypertension [9 10 22-25], our results did not show such a correlation. Findings in the literature are often discordant as far as correlation of comorbidities with severity of outcomes, mainly due to composition and homogeneity of study groups, follow-up times and differences in classification of severity of palsy.

Many studies have addressed the incidence of recurrence with respect to the side, ipsilateral or contralateral. Ralli et al. [14] found an increased incidence in the contralateral side compared to the ipsilateral side, while Navarrete et al. [22] found a major incidence on the right side, regardless if ipsilateral or contralateral. Almost all studies agree in judging ipsilateral RBP as being worst in terms of long-term prognosis. Nevertheless, no clear follow-up timing has been established, and clinical evaluation of degree of palsy and systematic statistical approaches have been used. In their study, Ralli et al. [14] evaluated 35 patients with recurrent unilateral BP. The incidence of recurrence was higher in younger patients, with a poorer prognosis for palsies occurring on the same side of the primary episode. Similarly, Navarrete et al. [22] found worse recovery in patients where recurrence occurred ipsilaterally to the primary episode. On the contrary, Cirpaciu and coauthors [13] did not find differences in the recurrence rate between RBP presenting in the ipsilateral or contralateral side respect to the primary BP. The authors reported a prevalence of incidence in young females (68% of the cases), in subjects with age between 21 and 30 years and with a family history of multiple episodes of RBP. In our study, a family history of BP was present in 5 patients (20%) suggesting a genetic predisposition for this pathology. Indeed, some studies found an association of certain human leukocyte antigens (HLAs) with the palsy, although these findings were not confirmed by other studies [26 27].

The association between recurrent facial palsy and diabetes mellitus has been reported with an incidence between 5.6% and 28.6% [10 11 15 23 25]. However, other authors have found no difference in diabetes incidence between primary and recurrent BP [9].

The study of Chung et al. [9] analysed the differences between primary and recurrent BP as far as the role of degree of palsy, side and comorbidities over palsy prognosis. The authors have studied a large population (1,257 subjects) affected by BP correlating the degree of palsy, assessed via House-Brackmann classification, electrophysiologic tests and MRI. In their study, the incidence of RBP was 5.7%. The study group was

homogeneous as far as treatment with steroids and antivirals, and outcomes were evaluated after a minimum of 6 months follow-up. The rate of recovery for BP was significantly higher (88.4%) than RBP (72.2%). Interestingly, while diabetes did not seem to influence incidence of RBP, recurrence was significantly higher in subjects who were pregnant or affected by hypertension, although these factors were no longer signicant after logistic regression analysis.

Some studies have shown that the peak of incidence was in a younger age [10 13 14 23] and described women as most susceptible to recurrence (68%) [13]. In the present study, a higher incidence was found in elderly patients, which is probably was due to a time factor that increased the probability to develop a second episode of paresis. Moreover, in our study, synkinesis did not seem to have higher prevalence in RBP. One possible reason is that synkinesis was found to have a prevalence at a younger age [28], due to functional and structural changes related to aging that reduce recovery of the peripheral nervous system after injury.

No difference was found between BP and RBP concerning SB score and HB grade as far as palsy severity, although in the Kaplan-Meier analysis primary BP showed a significant faster recovery.

As far as RBP characteristics are concerned, time elapsed from the previous palsy episode did not differ between ipsilateral and contralateral presentation. Concerning symptoms associated with paresis, their distribution was not significantly different between the two groups. Nevertheless, the previous experience of a primary BP episode led 3 of our patients to attend our facial palsy centre before onset of the paresis when only retroauricular pain and taste disorder were present, which allowed us to begin corticosteroid treatment in the very early stage of the paresis.

In the present study, no significant difference was found between the incidence of RBP in ipsilateral or contralateral recurrence, although there was a mild prevalence for the ipsilateral side.

Recurrence and higher HB grades were risk factors for delayed recovery, confirming the findings of Chung and al. [9]. Patients with primary BP recovered faster than patients with RBP ($p = 0.05$). Nevertheless, despite the delayed recovery in RBP, no difference was found in final facial function. Other studies found different recovery rates between the two groups [9 10 15], possibly because of the presence of other confounding factors such as incidence of comorbidities and differences in therapeutic approaches.

Conclusions

In conclusion, no significant difference in terms of symptoms, palsy severity and presence of comorbidities was found between primary BP patients and RBP patients. Final facial nerve function, even if delayed in recurrences, was similar in the two groups. The management of a recurrent facial palsy must be the same as the primary episode; nevertheless, the presence of prodromal symptoms may alert the patient to go to emergency department, allowing the beginning of corticosteroid treatment in the very early stage of the paresis.

Conflict of interest statement

None declared.

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HEAD AND NECK

Radial vs ulnar forearm flap: a preliminary study of donor site morbidity

Lembo d'avambraccio radiale vs lembo d'avambraccio ulnare: uno studio preliminare sulla morbilità del sito donatore

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SUMMARY

The objective of this study was to compare donor site morbidity after reconstructive surgery with Ulnar Forearm Free Flap (UFFF) and Radial Forearm Free Flap (RFFF) with subjective methods. The UFFF and the RFFF were applied for reconstruction of soft tissue defects of the head and neck region in 30 patients (20 M and 10 F; age range 28-75 years) affected by head and neck squamous cell carcinoma. The Disability of Arm, Shoulder and Hand (DASH) questionnaire was used to assess morbidity of the donor site. Analysis of the patients' DASH scores showed an overall median DASH total score of 9.17. No significant differences were observed for median values of the RFFF and UFFF groups (7.14 vs 10 respectively) or for the values in males and females (5 vs 13.3 respectively). The UFFF can be considered a valid alternative to the RFFF for reconstruction of soft tissue defects of the head and neck area; it is safe, easy to harvest and is not associated with major morbidities of the donor site as demonstrated by the DASH questionnaire.

KEY WORDS: Fasciocutaneous flap • Ulnar • Radial • Donor site morbidity • DASH questionnaire

RIASSUNTO

L'obiettivo di questo studio era di confrontare la morbilità del sito donatore dopo chirurgia ricostruttiva con il lembo libero d'avambraccio ulnare (UFFF) e il lembo libero d'avambraccio radiale (RFFF) con metodiche soggettive. Il UFFF e il RFFF sono stati utilizzati per la ricostruzione del difetti dei tessuti molli della testa e del collo in 30 pazienti (20 M e 10 F; range d'età 28-75 anni), affetti da carcinoma squamocellulare della testa e del collo. Il questionario sulla disabilità per l'arto superiore DASH è stato usato per valutare la morbilità del sito donatore. L'analisi del punteggio DASH dei pazienti ha dimostrato una mediana del punteggio totale DASH di 9,17. Non sono state osservate differenze significative per i valori mediani dei gruppi RFFF e UFFF (7,14 vs 10, rispettivamente) e per i valori ottenuti dai maschi e dalle femmine (5 vs 13,3, rispettivamente). Il UFFF può essere considerato una valida alternativa al RFFF per la ricostruzione dei difetti dei tessuti molli del distretto testa-collo; è affidabile, semplice da trapiantare e non causa maggiori morbilità del sito donatore come dimostrato dal questionario DASH.

PAROLE CHIAVE: *Lembo libero d'avambraccio • Ulnare • Radiale • Morbilità del sito donatore • Questionario DASH*

Introduction

Head and neck reconstructive surgery often requires thin and pliable tissues to achieve optimal surgical and functional outcomes. There are several reconstructive options, but forearm free flaps, since their introduction in the '80s, have been used with great success. The skin of the forearm can be harvested based on either the radial or ulnar artery; both flaps are technically easy to harvest and offer long pedicle and large calibre [1]. Nevertheless, while the radial forearm free flap (RFFF), proposed for the first time by Soutar et al. [2], was immediately considered an easy and versatile flap, the use of the ulnar forearm free flap (UFFF), first described by Lovie in 1984 [3], gained less popularity than the RFFF, because of the incorrect assumption that the ulnar artery provides the dominant vascular supply for the hand [4]. Fortunately, the use of the UFFF in the reconstruction of head and neck region has recently increased and some authors have underlined its advantages, namely less wound-healing problems and better aesthetic outcomes of the donor site, in comparison with the RFFF, since the surface of the donor site consists of muscle bellies instead of tendons [5 6].

However, the donor site of both flaps, especially if har-

vested in the dominant arm, may be unsatisfactory in terms of aesthetic and functional outcomes.
The aim of this study was to evaluate donor site morbidity with subjective methods and to verify the impact of the two harvesting techniques on the daily activities of patients who underwent oncological reconstructive head and neck surgery with RFFF and UFFF, in order to evaluate which of the two flaps can be considered preferable in terms of minor morbidities.

Materials and methods

We performed a retrospective analysis of medical charts and follow-up visits of 30 patients affected by primary cancer of head and neck region who underwent surgery and reconstruction with RFFF (15 patients) or UFFF (15 patients).
All procedures were performed in two Institutions, the Department of Otolaryngology Head and Neck Surgery of the University of Pavia, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy, and the Department of Otorhinolaryngology Head and Neck Surgery of the University Vita-Salute San Raffaele, San Raffaele Hospital, Milan, Italy, in the period between April 2012 and March 2016; the reconstructive procedure was carried out synchronous to ablative surgery.
Allen's test (the only mandatory test) and US Doppler were routinely performed before surgery to demonstrate adequate blood flow from the radial or ulnar artery to the hand.

Surgical technique: RFFF

The harvesting of the RFFF was conducted according to the initial description of Soutar [2] (Fig. 1). The flap is designed on the forearm to include both the lateral intermuscular septum and the cephalic vein. The flap is centred on the radial artery and the course of the artery is marked on the forearm.
The upper limb is exsanguinated with a bandage and a tourniquet is applied at 250 mmHg.
The dissection is started laterally, then the circumference of the skin flap and the extension towards the cubital fossa are incised. The flap is elevated in a deep subcutaneous plane. The cephalic vein, lying deep in the subcutaneous fat, is identified, skeletonised and elevated towards its proximal course. Proceeding over the extensor and abductor tendons, the superficial branch of the radial nerve is identified, lateral to the brachioradialis tendon. Dissection is extended medially over the epitenon covering the radial nerve. Epitenon was always maintained. Medial edge of the brachioradialis muscle is retracted, underlining the

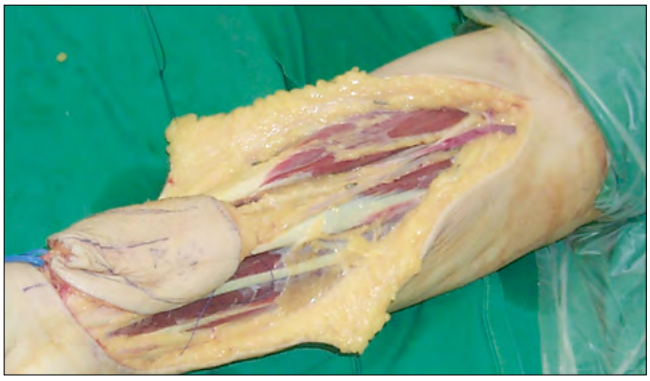

Fig. 1. Radial forearm flap harvested.

lateral intermuscular septum. Sharp dissection of the septum allows identification of the radial artery, usually running below the tendon. The fascia of the brachioradialis muscle is incised, protecting the pedicle, and the muscle is mobilised, allowing the complete visualization of the course of the radial artery. Muscle perforator branches are ligated. Next, the dissection moves to the medial side of the flap, elevating the deep fascia over the flexor muscles tendons, whose epitenon is preserved. The radial artery is identified distally to the flap, transected and ligated, together with the venae comitantes. Dissection can finally proceed from distal to proximal until enough vessel length is achieved.
Tourniquet is deflated and recipient vessels are identified and prepared for anastomotic suturing. Flap vessels are divided and the flap is transferred and inset.
RFFF was always harvested as a fasciocutaneous flap, never incorporating part of radius nor palmaris longus tendon.
Reconstruction of the donor site can be performed with a simple suture of a full thickness skin graft harvested from the groin or using the V-Y technique with a full-thickness skin graft. The skin graft is designed according to the dagger-shaped technique, as described by Giordano et al. [7] The graft is elevated and defatted. Multiple slits are created on the graft to prevent fluid collection beneath it. The dagger-shaped graft is transferred and sutured to close the defect on the forearm, after undermining of the surrounding skin and suturing the proximal portion of the incision (Fig. 2). The dagger-shaped skin graft technique allows sparing of 8.3% of the skin graft, less donor site complications and better long-term aesthetic outcomes (Fig. 3).

Surgical technique: UFFF

The harvesting of the UFFF was conducted according to Lovie et al. [3] and Hakim et al. [8] In this case, the course

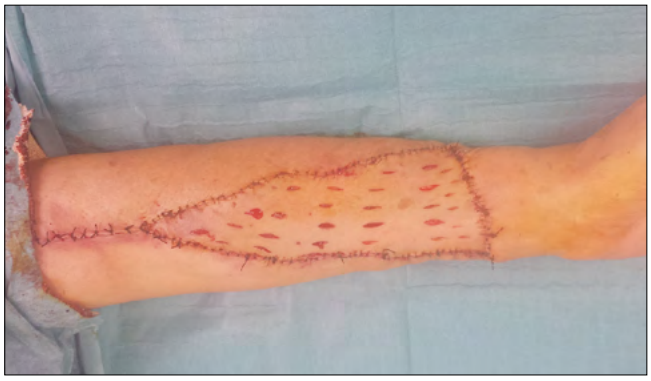

Fig. 2. Donor site reconstruction with the dagger-shaped skin graft.

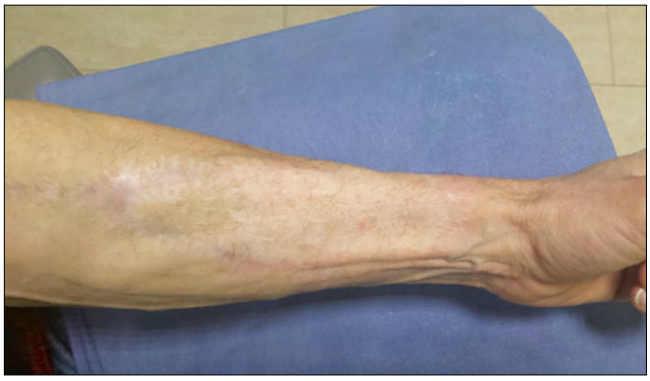

Fig. 3. Long-term aesthetic result of donor site after reconstruction with the dagger-shaped skin graft.

of the ulnar artery on the forearm is marked drawing a line connecting the medial epicondyle of the humerus and the pisiform bone, taking care to mark the perforators at 5, 7 and 12 cm from the pisiform bone (Fig. 4). The ulnar artery arises 1 cm distal to the antecubital fossa, more or less between the proximal third and middle third of the drawn line. Alternatively, it is possible to palpate the space between the belly of the flexor carpi ulnaris muscle and the superficial plexus of the fingers, at the level of the distal third of the forearm.

The cutaneous island is drawn at the middle third of the forearm, with the axis parallel to the course of the ulnar artery (Fig. 4) [9].

The ulnar artery may present important anatomical variations (1-10% of cases), as the superficial ulnar artery (SUA), so it is important to begin the flap elevation distally, re-centring the flap on the axis of the artery.

The upper limb is exsanguinated with a bandage and a tourniquet is applied at 250 mmHg.

The incision begins on the radial side at 5 cm from the pisiform bone, following the design of the flap, previously centred on the axis of the ulnar artery. The elevation of the flap proceeds from the radial edge to the ulnar one on a suprafascial plane, until the perforator arteries are identified. The next step is the isolation, at a subfascial level, of the best perforators for vascularisation of the cutaneous island, until their emergence from the ulnar vascular pedicle, which is dissected distal to proximal. During this manoeuvre, it is necessary to divide the vascular bundle from the ulnar nerve, taking care to retract and protect it [10].

By doing so and abstaining from an immediate circumferential incision, it is possible to preliminarily identify abnormal ulnar artery courses and avoid any compromise of the vascularisation and flap survival.

Cutaneous island dissection, once the vascular pedicle has been identified, is continued at a subfascial level, beginning

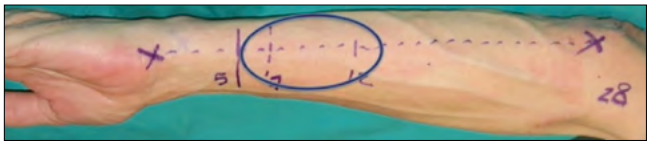

Fig. 4. Landmarks of the ulnar forearm flap and position of the cutaneous island.

from the ulnar flexor carpi. The elevation easily proceeds from below the belly of the superficial flexor digitorum muscle. It follows the vascular pedicle until the emergence of the interosseous artery is encountered and preserved. The forearm medial cutaneous nerve can be included in the harvest to give sensory innervation to the flap [11].

The deep venous system of the venae comitantes has usually a good calibre for venous anastomosis, and sometimes it is possible that the two satellites veins join to form a single vein [11].

Therefore, the basilic vein is dissected as well and included into the flap, so that another way of venous drainage of the flap is assured (Fig. 5).

Once the entire flap is elevated, the vascular pedicle is dissected, but not sectioned, until the surgical team is ready for the reconstruction (Fig. 5).

At this point, the vascular pedicle is tied up and dissected before the emergency of the interosseous artery, preserving the deep vascularisation of the forearm.

The ulnar artery is anastomosed usually with a branch of the external carotid artery (lingual, facial or superior thyroid arteries). The choice of the branch depends on a good size match between the ulnar artery and neck vessels and on the length of the vascular pedicle. For venous anastomosis, the basilic vein and/or one or both of the ulnar comitantes veins are used. The choice depends on the calibre of the veins and on the predominance of the venous drainage

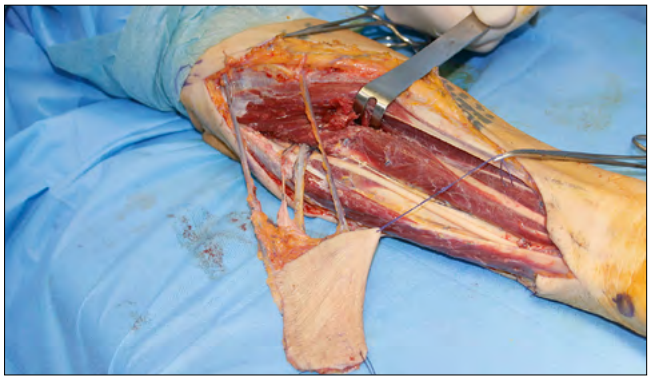

Fig. 5. Ulnar forearm flap harvested.

of the flap (comitantes veins vs basilic vein). The most frequently used veins for venous anastomosis are the thyro-lingual-facial trunk or the internal or external jugular vein. The second venous anastomosis is performed if the venous drainage of the first venous anastomosis is insufficient.
All the dissections were performed on the non-dominant arm and the skin defect was closed with a full-thickness skin graft harvested from the patient's groin.

Follow-up
In order to evaluate donor site outcomes, all patients were submitted, during the first follow-up visit, to the Italian version of the "Disabilities of Arm, Shoulder and Hand Questionnaire" (DASH) [12].
The DASH score [11] is a patient subjective score with 30 responses about symptoms and functional status during routine daily activities producing a score between 0 and 100 points. The questionnaire is divided into the following sections: symptoms, sport, music and work. The first section is composed of 30 items and evaluates symptoms and functional status, the second and third parts are two optional modules of 4 questions for sport and music and 4 questions for work. The parts regarding sport, music and work were not taken into consideration because of the low numbers of answers (10% of patients).
Each item is scored with a 5-point scale ranging from 1 = no difficulty from 5 = unable. The results are summed and transformed into the DASH score in the following way:

(absolute score -30)/1.2 = DASH total score

The DASH total score, as above calculated, ranges from 0 (no disability) to 100 (severe disability).

Statistical analysis
Quantitative variables (age, follow-up time, DASH scores) were not normally distributed (Shapiro-Wilk test) and so the results were expressed as median and interquartile range (IQR; 25th-75th percentile). The comparisons between the two groups were evaluated with Wilcoxon rank-sum test. Qualitative variables were summarised as counts and percentages.
In order to evaluate differences between the ability to practice daily activities and some symptoms of the arm, we separately analysed the first 23 questions regarding the ability to do certain activities and if and how the arm and hand problems interfered with normal social activities (DASH 1-23 score), from the 5 questions (DASH 24-28 score) regarding pain, tingling, weakness and stiffness of the arm and hand, and we then analysed the answers in percentages.
A $p < 0.05$ was considered statistically significant. All tests were two-sided. The data analysis was performed with the STATA statistical package (release 14.0, 2015, Stata Corporation, College Station, Texas, USA).

Results

Patient demography
The patients' demography is described in Table I.
One third of patients had an early stage cancer (I-II) and the oral cavity was the most represented site of the primary disease (63.3%). The two reconstructive options (RFFF and UFFF) were equally distributed. A selective neck dissection, homolateral to the donor site, was performed in 12 patients.
We observed no complications at the donor site in either group, with complete integration of the skin graft and no exposure of tendons in all patients. The mean healing time of the donor site was comparable in both groups: 29.7 days for UFFF and 31.1 for RFFF.

DASH score
The DASH score data are summarised in Tables II and III.
No significant difference was observed, except for the DASH 24-28 between patients undergoing neck dissection and those who did not.
The values were 17.5 (min. 0 - max. 40) and 3.76 (min. 0 - max. 65). These differences were near the level of statistical significance ($p = 0.08$) (Table III).

Discussion

The RFFF represents a widely known reconstructive option in head and neck oncological surgery. It is thin and pliable, making it ideal for the reconstruction of head and neck defects. While the use of the RFFF is well estab-

Table I. Patient demography.

	Total	RFFF (N = 15)	UFFF (N = 15)
Sex			
male	20 (66.7%)	9 (30%)	11 (36.7%)
female	10 (33.3%)	6 (20%)	4 (13.3%)
Age at the day of surgery			
median (IQR)	58.3 (50.4 - 64.8)	57.8 (50.2 - 67.5)	58.8 (51.1 - 63.8)
range	28.6 - 75.4	28.6 - 75.4	30.3 - 74.4
Stage			
I	3 (10%)	-	3 (10%)
II	7 (23.3%)	5 (16.6%)	2 (6.7%)
III	5 (16.7%)	3 (10%)	2 (6.7%)
IV	15 (50%)	7 (23.2%)	8 (26.8%)
Primary tumour site			
oral cavity	19 (63.4 %)	10 (33.7%)	9 (29.7%)
oropharynx	5 (16.7 %)	2 (6.7%)	3 (10%)
hypopharynx	4 (13.3 %)	3 (10%)	1 (3.3 %)
oral cavity/oropharynx	1 (3.3 %)	-	1 (3.3%)
hypopharynx/cervical oesophagus	1 (3.3 %)	-	1 (3.3%)
Demolitive surgery			
circular pharyngolaryngectomy	3 (9.9 %)	1 (3.3%)	2 (6.6%)
partial buccopharyngectomy	2 (6.6 %)	1 (3.3%)	1 (3.3%)
hemiglossectomy	17 (57.1%)	9 (30.2%)	8 (26.9%)
simple exeresis	2 (6.6 %)	1 (3.3%)	1 (3.3%)
partial pharyngectomy	2 (6.6 %)	2 (6.6%)	-
pelvectomy	2 (6.6 %)	1 (3.3%)	1 (3.3%)
pelviglossectomy	2 (6.6 %)	-	2 (6.6%)
Head and neck site			
Tongue + Floor of the mouth	19 (63.3%)	10 (33.3%)	9 (30.0%)
Oropharynx	6 (20%)	2 (6.7%)	4 (13.3%)
Hypopharynx	5 (16.7%)	3 (10.0%)	2 (6.7%)
Neck dissection ipsilateral to the donor site			
not performed	18 (60%)	11 (36.7%)	7 (23.3%)
selective	12 (40%)	4 (13.3%)	8 (26.7%)

lished in clinical practice, the UFFF is used occasionally, even though in recent years there has been an increase of its use as a reconstructive option, essentially due to the erroneous assumption that the ulnar artery provides the dominant vascular supply for the hand [4] and operator-dependent limits, as superficial knowledge of the anatomy of the forearm deep muscles and the risk to damage the ulnar nerve, which lies next the ulnar vessels and it is vascularised by the ulnar artery branches [11]. The surgical technique for UFFF harvesting, however, does not present greater difficulties than that of the radial flap, requiring about the same surgical time.

The artery and the venae comitantes of the ulnar pedicle are more reliable because they have calibres that are similar to those of the branches of the external carotid artery and internal jugular vein respectively [9]. This is not always

Table II. Median (IQR) DASH score for the whole group of patients and for the two types of flaps.

	OVERALL (N = 30)			RFFF (N = 15)			UFFF (N = 15)		
	Total	F (N = 10)	M (N = 20)	Total	F (N = 6)	M (N = 9)	Total	F (N = 4)	M (N = 11)
DASH total	9.17 (0.9-28.3)	13.3 (10-31.7)	5 (0.9-27.9)	7.14 (0-28.3)	12.7 (0.9-31.7)	3.33 (0-9.8)	10 (3.3-32.8)	13.3 (11.3-23.5)	5.83 (1.7-47.4)
DASH 1-23	6.67 (0-28.3)	12.2 (6.8-33)	5.1 (0-23.9)	4.76 (0-28.3)	9.67 (1.1-35.9)	3.26 (0-5.4)	9.78 (0-33)	12.5 (10.2-23)	6.52 (0-48.9)
DASH 24-28	10 (0-25)	8.76 (0-20)	10 (2.5-27.5)	5 (0-20)	8.76 (0-20)	5 (0-15)	10 (5-30)	15.4 (0.4-30)	10 (5-40)

Table III. Median (IQR) DASH score in patients submitted or not to neck dissection ipsilateral to the donor site.

	No neck dissection (N = 18)	Neck dissection (N = 12)
DASH total	7.5 (0.8-15)	11.7 (2.5-32.2)
DASH 1-23	5.98 (0-13)	10.9 (0-34.4)
DASH 24-28	3.76* (0-20)	17.5* (10-27.5)

* *p = 0.08*

true for the pedicle of the radial forearm flap: in fact, the diameter of the artery and, in particular of the venae comitantes, are usually smaller than the neck vessels, making anastomoses more difficult.

Despite its frequent use, the radial flap presents, compared to the ulnar one, some disadvantages: the cutaneous island site is more distal and involves exposure of flexor muscle tendons, while the UFFF involves exposure of muscles bellies, which constitutes a better bed for skin graft engraftment; the donor site is more visible, which leads to a lower cosmetic outcome (less accepted by women), and the skin is more hairy, representing an important disadvantage for reconstruction of the oral cavity and pharynx. Nevertheless, a possible advantage of RFFF is the possibility to prepare a full-thickness graft in the same donor area site: this graft has a similar coloured texture of the skin of the donor site and can be done without an additional surgical field, as described by Squadrelli-Saraceno et al. [13] and Giordano et al. [7]. The closure technique is comfortable, useful and provides a satisfactory cosmetic result. Instead, the UFFF donor site is closed with a full-thickness graft of a distant site.

The forearm fasciocutaneous flaps have, for both types, a certain degree of donor site morbidity.

The pre-operative assessment of the vascularisation of the hand with Allen's test is mandatory to reduce the incidence of the most feared complication for this surgery: hand ischaemia. In case of subjective anomalies, an objective Allen's test should be performed, since it offers greater specificity and sensibility [14]. Other complications include wound dehiscence, partial or total skin necrosis and sensory and motor hand disorders, such as cold intolerance [1].

In the literature, there are several studies that have evaluated donor site morbidity after RFFF or UFFF harvesting with objective or subjective methods, e.g. Sieg et al. [6] and Hekner et al. [8]. These authors have shown, evaluating the modality of donor site healing with pressure or heat measurements, that the morbidity is significantly lower for the ulnar flap than the radial one, because the skin graft used to cover the donor site lies on the muscle bellies and not on the tendons, like in the RFFF, resulting in a lower risk of retracting and ankylosing scars. Nevertheless, the subjective evaluation of donor site morbidity by patients showed no significant differences between the two groups, and the most widely used method to assess it is the DASH questionnaire. In the literature, it has been reported that the median values of DASH for ulnar flaps range from 3.4 to 13.3 [10 15]. In our study, we observed similar values for both the UFFF (10) and the RFFF (7.4); this is maybe dependent on the closure technique with a transposition flap or with a full thickness skin graft, which gives a more effective protection of the tendons in RFFF. Nevertheless, these results must be considered somewhat preliminary due to the small size of our cohort.

We observed no complications in terms of donor site healing in either study group, and thus we have no data about the possible effects of complications on the DASH score.

The analysis of scores for the first 23 questions on evaluation of the ability to perform daily activities and in the 24-28 questions about the presence of pain, numbness, stiffness or weakness did not reveal significant differences between RFFF and UFFF patients, confirming that both groups showed no severe disability or sensory-motor deficits. This result is probably due to the choice of the non-dominant arm for surgery and the use of a full-thickness skin graft to close the skin defect, which reduces the possibility of retracting scars between the graft and muscles or tendons.

Evaluation of DASH scores based on sex showed lower median scores in male patients than those obtained in female patients, although the difference was not statistically significant. This is probably due to the fact that, even if in women aesthetic damage is an important factor, the scar is not considered particularly disfiguring to the forearm, although this aspect should be confirmed with additional studies with larger case series.

Neck dissection-related shoulder disability could possibly negatively influence the DASH scores, giving additional morbidities to those of the flap harvest. For this reason, we checked the presence of possible significantly different scores between the patients in whom neck dissection was performed on the ipsilateral site of the flap harvest and the ones in whom it was not. The comparison did not reveal significant differences, with the exception of the DASH 24-28 score, regarding pain, tingling, weakness, and stiffness of the arm, in which the difference was close to the level of statistical significance.

To the best of our knowledge, there are no papers in the literature that have evaluated this aspect; we believe that it

should be taken into consideration in the evaluation of the donor site morbidity in order to differentiate between the effects of the flap harvest and those of the neck dissection. Despite this possible bias, our results allowed us to consider the DASH questionnaire an appropriate and reliable method to assess donor site morbidity after dissection of a radial or ulnar forearm flap.

Conclusions

RFFF and UFFF are suitable choices for oncologic reconstruction of head and neck defects. Both have a long vascular pedicle of appropriate size; they are thin and pliable and guarantee good aesthetic and functional results.

Major advantages of the ulnar flap over the radial flap seem to be the better calibre of the ulnar artery and the venae comitantes, resulting in a better correspondence with the diameter of the neck vessels; more hairless skin, ideal quality for intraoral and pharyngeal reconstructions, and a less exposed donor site.

Nevertheless, additional studies with larger case series are necessary to compare long-term donor site morbidity between these two reconstructive options, and the DASH questionnaire may be considered a valid method of evaluation.

Conflict of interest statement

None declared.

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Rhinology

Olfactory dysfunction in patients with chronic rhinosinusitis with nasal polyps is associated with clinical-cytological grading severity

La disfunzione olfattoria è associata con la gravità del grading clinico-citologico nei pazienti con rinosinusite cronica con poliposi nasale

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SUMMARY

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common inflammatory disorder, affecting about 4% of the worldwide population and strongly impacting the quality of life. CRSwNP is still a challenge for ENT specialists in terms of its unknown pathogenesis, difficulty in management and frequent relapse. Olfactory impairment frequently affects CRSwNP patients. We tested the hypothesis that clinical-cytological grading (CCG) could be associated with olfactory dysfunction. The study was cross-sectional, enrolling 62 patients (37 males, 25 females, mean age 49 years, range 18-83) suffering from newly diagnosed CRSwNP. Olfactory dysfunction was very frequent (about 90%) and did not depend on nasal obstruction as assessed by both polyp size and nasal airflow limitation. A CCG > 4 was the best cut-off value to suspect olfactory dysfunction [area under the ROC curve of 0.831 (0.715 to 0.914)]; in addition, the statistical risk of having dysosmia was over 7-fold higher in subjects with CCG > 4 compared with subjects reporting a CCG < 4 (adjOR 7.46). The present study underlines that olfactory dysfunction is common in CRSwNP patients and demonstrates an association between olfactory dysfunction and inflammation, suggesting that CCG could be useful in the work-up of CRSwNP patients and in suspecting olfactory impairment.

KEY WORDS: Chronic rhinosinusitis with nasal polyps • Clinical grading • Cytological grading • Olfactory dysfunction

RIASSUNTO

La rinosinusite cronica con poliposi nasale (RSCPN) è una malattia infiammatoria abbastanza frequente, in quanto ne è affetto circa il 4% della popolazione generale ed ha un notevole impatto sulla qualità della vita dei pazienti. Peraltro la RSCPN rappresenta un problema per lo specialista ORL per quanto riguarda la patogenesi, il difficile controllo e le frequenti recidive. Un difetto olfattorio è comune nei pazienti con RSCPN. Lo scopo dello studio trasversale era la valutazione dell'algoritmo basato sul grading clinico-citologico (GCC) in funzione del disturbo olfattivo in un campione di 62 pazienti (37 maschi, 25 femmine, età media 49 anni, con intervallo di età tra 18 ed 83 anni) con nuova diagnosi di RSCPN. Il difetto olfattivo era molto frequente (circa nel 90% dei casi) e non dipendeva dall'ostruzione nasale ma dall'infiammazione. Un valore di GCC > 4 potrebbe essere una soglia in grado di indurre il sospetto di un'alterazione dell'olfatto (area sotto la curva 0,83, ORadj 7,46). In conclusione, questo studio sottolinea la frequente presenza di un'alterazione dell'olfatto nei pazienti con RSCCPN e dimostra che i disturbi dell'olfatto sono associati con i fenomeni infiammatori e la valutazione del GCC potrebbe essere utile nel sospettare un'alterazione dell'olfatto.

PAROLE CHIAVE: *Rinosinusite cronica con poliposi nasale • Grading clinic • Grading citologico • Disturbi dell'olfatto*

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterised by an inflammatory process involving the nasal mucosa. CRSwNP affects about 4% of the worldwide population and may strongly impair the quality of life [1]. CRSwNP represents an intriguing challenge for ENT specialists in terms of its unknown pathogenesis, difficulty in management and frequent relapse.

CRSwNP may be classified according to: comorbidity [2], endoscopic outcomes [3], X-ray features [4], and cytological pattern [5]. In particular, a clinical-cytological grading (CCG) has been proposed to better define the management strategy, individuate a prognostic index of relapse [6] and adopt a personalised medical approach [7].

Olfactory defects are common in the general population with a prevalence ranging between 9.5% and 15.3%,

which is higher in elderly subjects and males [8]. Olfactory defects may be classified as hyposmia (partial defect of smell) and anosmia (total loss of smell). Rhinosinusitis is a common cause of chronic olfactory impairment in patients with nasal disorders [9]. Indeed, patients with CRSwNP frequently suffer from olfactory defects [10]. A longitudinal study demonstrated that nasal eosinophilia is a negative predictive factor for olfactory recovery after surgery [11]. Moreover, it has been reported that improved olfaction significantly enhanced quality of life score [12].
Olfactory exploration is fundamental in patients with CRSwNP [13]. Olfactory assessment is based on history, clinical examination (mainly by fibreoptic endoscopy) and smell testing (e.g. psychophysical test Sniffin'Sticks). The "Sniffin'Sticks" olfactometric test has been validated and used in many studies [14]. The "Sniffin'Sticks" is a test of nasal chemosensory performance based on pen-like odour from a dispensing device [15]. The test evaluates three olfactory functions: odour threshold, odour discrimination and odour identification [16-18].
On the basis of this background, the present study evaluated which factors, including CCG, are associated with olfactory defects in patients with newly diagnosed CRSwNP.

Materials and methods

Study population
Sixty-two patients (37 males, 25 females, mean age 49 years, range 18-83 years) were consecutively visited at the Rhinology Unit of the ENT Clinic of the Bari University (Italy) and were enrolled in this cross-sectional study from June 2017 to June 2018.
The inclusion criteria were: 1) age > 18 years of age; 2) male or female; 3) suffering from newly diagnosed CRSwNP; 4) informed written consent.
The exclusion criteria were: 1) current or past treatment for NP; 2) previous functional endoscopic sinus surgery (FESS); 3) past surgery for NP, CRS and septal deviation; 4) severe anatomic defects; 5) secondary olfactory defects; 6) NP limited to the olfactory fissure; 7) severe anatomic defect of the nasal cavity and/or nasal pyramid; 8) workers at chemical industries or exposed to volatile toxic substances; 9) past head trauma or brain injury, recent severe hyperthermia, or neurodegenerative disorders documented by neurological examination.
The Review Board approved the procedures used in this study.

Study design
All patients were evaluated by: clinical history, objective examination, fibreoptic endoscopy, nasal cytology, skin prick test, rhinomanometry, pulmonology visit and olfactometric test.
A diagnosis of CRSwNP was made according to validated criteria according to European and International guidelines [1 19].

Outcome
The outcome of the current study was dysosmia as defined and scored below.

Variables
Nasal endoscopy was carried out by a 3.4 mm diameter flexible fibrescope (Vision-Sciences® ENT-2000). Nasal polyp endoscopic 4-grade classification proposed by Meltzer was adopted [3].
Nasal cytology includes: sampling, processing and microscope reading. Sampling requires the collection of cells from the surface of middle portion of the inferior turbinate using a sterile disposable curette. The procedure is performed under anterior rhinoscopy, with an appropriate light source, and is completely painless. The sample obtained is immediately smeared on a glass slide, air-dried and stained with May-Grünwald-Giemsa (MGG) for 30 min. The stained sample was examined by optical microscopy with a 1000x objective with oil immersion. Fifty fields are considered the minimum number to identify a sufficient number of cells. The count of each cell type was expressed by a semi-quantitative grading as previously described [20].
Skin prick test was performed as stated by the European Academy of Allergy and Clinical Immunology [21]. The allergen panel consisted of the following: house-dust mites (*Dermatophagoidesfarinae* and *Dermatophagoidespteronyssinus*), cats, dogs, grasses mix, *Compositae* mix, *P. judaica*, birch, hazel trees, olive trees, cypress, *Alternaria tenuis*, *Cladosporium* and Aspergilli mix. The concentration of allergen extracts was 100 immune reactivity/mL (Stallergenes-Greer Italia, Milan, Italy). A histamine solution in distilled water (10 mg/mL) was used as a positive control and the glycerol-buffer diluent of allergen preparations was used as a negative control. Each patient was skin tested on the volar surface of the forearm using 1-mm prick lancets. The skin reaction was recorded after 15 min by evaluating the skin response in comparison with the wheal given by the positive and the negative control. A wheal diameter of at least 3 mm was considered as a positive reaction.
Rhinomanometry measured nasal airflow resistance by active anterior electronic rhinomanometry. Patients wore a tight-fitting facemask and breathed through one nostril

with their mouth closed. A sensor, placed in the contralateral nostril, recorded data on pre- and postnasal pressures via airflow and pressure transducers. The instrument (Rhinomanometer Menfis, Amplifon, Italy) was connected to a personal computer. The signals of trans-nasal airflow and pressure were amplified, digitalised and saved for statistical analysis. Nasal resistance was measured in ml/sec as the sum of the recorded airflow through the right and left nostrils at a pressure difference of 150 Pa across the nasal passage. Four or more airflow measurements were performed for each patient, and the mean value was recorded when reproducible values were achieved. Normal values are 0.50 Pa/ml/sec.

Clinical-Cytological Grading has been previously described in detail elsewhere [6 7]. Briefly, CCG is a score based on both nasal cytology findings and comorbidities, including asthma, allergy and ASA sensitivity. For each variable, a score value was assigned: neutrophilic infiltrate was scored as 1, mast cell infiltrate was scored 1, eosinophilic infiltrate was scored 2, eosinophilic + mast cell was scored 4; similarly, ASA sensitivity scored 1, asthma 2, allergy 2 and ASA sensitivity + asthma 3. The CCG was composed as the sum of these individual scores. A global score between 1-3 is considered low grade, 4-6 moderate and > 7 severe, as reported in Figure 1 [6 7].

Sniffin' Sticks test was performed in all patients and TDI score was calculated according to a Position Paper on olfactory dysfunction [22]. The composite TDI score is the sum of each item, including olfactory functions, such as odour threshold, odour discrimination and odour identification. On the basis of the TDI score, patients can be classified as normoosmic (TDI > 30.5), hypoosmic (TDI < 30.5 and > 16.5) and anosmic (TDI < 16.5). In the current study, patients were divided into 2 groups based on normosmia, such as with TDI > 30.5 (n = 7), or dysosmia, such as with TDI < 30.5 (i.e. hyposmia or anosmia; n = 55).

Statistical analysis

Demographic and clinical characteristics were described using means with SDs for normally-distributed continuous data (i.e. age or CCG) or as absolute frequency and percentages for categorical data (i.e. male gender).

Any statistically significant difference in the mean values among patients with normal or impaired olfaction (i.e. hyposmia or anosmia) was evaluated by ANOVA followed by Bonferroni post hoc test.

Comparison of frequency distributions was made by chi-square test or Fisher's exact test in case of expected frequencies < 5.

A receiver operating characteristic (ROC) curve analysis was performed to determine a cut-off point for CCG to identify patients with dysosmia (i.e. patients with anosmia or hyposmia). The area under the curve (AUC) is graded as follows: AUC = 0.5, no discrimination (it corresponds to a level of performance of little more than that of chance); 0.7 < AUC < 0.8, acceptable discrimination; 0.8 < AUC < 0.9, excellent discrimination; AUC > 0.9, outstanding discrimination [21]. Sensitivity (i.e. the probability of the test being positive when performed on diseased patients), specificity (i.e. the probability of the test being negative when performed on healthy subjects), positive predictive value (PPV, i.e. the probability of the subject being diseased when the test result is positive, negative predictive value (NPV, i.e. the probability of not being diseased with a negative test result, Likelihood Ratio (LR) + (i.e. the ratio between sensitivity divided by 1 - specificity), LR− (i.e. the ratio between 1 - sensitivity divided by specificity), diagnostic Odds ratio (DOR, i.e. the ratio between LR+ and LR−) were reported.

To evaluate the role of different independent explanatory variables in association with dysosmia, multiple logistic regression analysis was performed. Variables that were considered important for the outcome *a priori* (i.e. age and gender) or that were statistically significant in univariate analysis (P < 0.05) were entered into the model. The effect is expressed as adjusted odds ratio (adjOR) with 95% confidence intervals (CIs). Statistical significance was tested using the likelihood ratio test.

Correlation between the rhinomanometry and olfactometry was evaluated with Spearman's rank-order correlation coefficient. We labelled the strength of the association as follows: for absolute values of r, 0 to 0.19 is regarded as very weak, 0.2 to 0.39 as weak, 0.40 to 0.59 as moderate, 0.6 to 0.79 as strong and 0.8 to 1 as very strong correlation [23].

Statistical significance was set at p < 0.05, and all analyses were performed using GraphPad Prism software (GraphPad Software Inc, CA, USA) and Epi-Info statistical software (Centers for Disease Control and Prevention, Atlanta, GA, USA).

Results

In CRSwNP patients, olfactory dysfunction was frequent and present in 55 patients with anosmia or hyposmia of 62 patients.

Table I reports demographic and clinical characteristics of the patients. Male gender, age, nasal polyposis severity grading and comorbidities such as allergy, asthma and/or ASA sensitivity were not different among the two groups of subjects. There was a different cytotype profile in the two

Table I. Demographic and clinical characteristics in subjects with CRSwNP and dysosmia (such as anosmia or hyposmia) or normosmia.

Variable	Dysosmia (n = 55)	Normosmia (n = 7)	P value
Male gender	22 (40.00%)	3 (42.86%)	1.00#
Age [years, mean (SD)]	50.25 (14.66)	47.43 (15.20)	0.63
Nasal polyposis			
Grade 1	15 (27.27%)	2 (28.57%)	0.76#
Grade 2	13 (23.64%)	3 (42.86%)	
Grade 3	20 (36.36%)	2 (28.57%)	
Grade 4	7 (12.73%)	0	
Allergy	38 (69.09%)	3 (42.86%)	0.21#
Asthma	22 (40.00%)	1 (14.29%)	0.24#
ASA sensitivity	7 (12.73%)	0	1.00#
Asthma + ASA sensitivity	5 (18.52%)	0	0.36#
Nasal neutrophils	4 (7.27%)	5 (71.43%)	**0.0004#**
Nasal eosinophils	50 (90.91%)	1 (14.29%)	**< 0.0001#**
Mast cells	25 (45.45%)	1 (14.29%)	0.22#
Cytotypes			
Neutrophils	4 (7.27%)	**5 (71.43%)**	**< 0.0001#**
Eosinophils	**26 (47.27%)**	1 (14.29%)	
Mast cells	1 (1.82%)	1 (14.29%)	
Eosinophils + mast cells	**24 (43.64%)**	0	
CCG [mean (SD)]	5.84 (2.20)	2.86 (2.48)	**0.0015**
CCG score			
Low (≤ 3)	5 (9.09%)	**4 (57.14%)**	**0.012#**
Medium (4-6)	**26 (47.27%)**	2 (28.57%)	
High (≥ 7)	**24 (43.64%)**	1 (14.29%)	

All variables are reported as absolute frequency and percentage in parentheses unless otherwise specified. #: Fisher exact test; ASA: Acetylsalicylic acid; CCG: clinical-cytological grading.

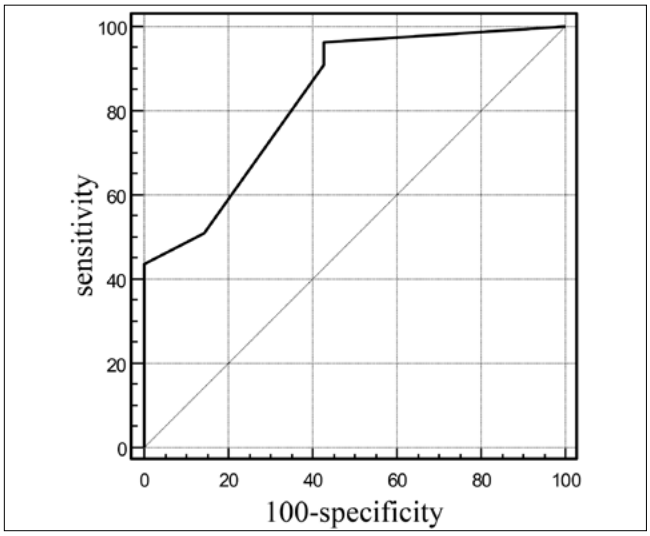

Fig. 1. Receiver operating characteristic (ROC) curve to determine the best cut-off point for CCG to identify patients with dysosmia (i.e. patients with anosmia or hyposmia).

Table II. Performance measures for CCG as test for discriminating between patients with dysosmia and subjects with normosmia (cut-off: > 4).

Parameter	Value
Sensitivity	70.9 (57.1- 82.4)
Specificity	71.4 (29.3- 95.5)
Positive predictive value (PPV)	95.1
Negative predictive value (NPV)	23.8
Youden index	0.423
Likelihood ratio (LR)+	2.48
Likelihood ratio (LR)-	0.41
Diagnostic odds ratio (DOR)	6.09

subgroups: compared to dysosmic patients, in normosmic subjects neutrophils were the most frequently found cells, whereas in dysosmic patients, eosinophils or eosinophils + mast cells were the most frequently found cells.

Mean CCG was significantly higher in dysosmic patients than in normosmic subjects. A low CCG score was detected in over a half of normosmic subjects, whereas there was a medium or a high CCG score in over a half of dysosmic patients.

Since the CCG score was significantly different between normosmic and dysosmic patients, we calculated the best cut-off point for CCG that was able to discriminate between patients with or without dysosmia (i.e. those with ano- or hyposmia or those with normosmia). For this purpose, a ROC curve analysis was performed (Fig. 1). The optimal cut-off value was > 4. Performance measures for CCG as a test for discriminating between patients with dysosmia and with normosmia are reported in Table II. The area under the ROC curve was 0.831 (0.715 to 0.914), corresponding to excellent statistical discrimination. LR+ and LR- were 2.48 and 0.41, respectively, with a significant diagnostic odds ratio of 6.09 (1.07-34.73). This means that the risk of having dysosmia was over 6-fold higher in subjects with CCG > 4 compared with subjects with a CCG < 4.

We also evaluated whether age or gender could have an effect on the association between CCG and dysosmia: a logistic regression model of positive CCG (> 4), male gender and age as predictors of the study outcome demonstrated that positive CCG should be considered an independent prognostic factor of olfactory dysfunction in patients with nasal polyps, giving a more than 7-fold higher risk of having dysosmia in subjects with CCG > 4 compared to subjects with a CCG < 4 (adjOR 7.46) (Table III). Figure 2 reports the distribution of normosmia

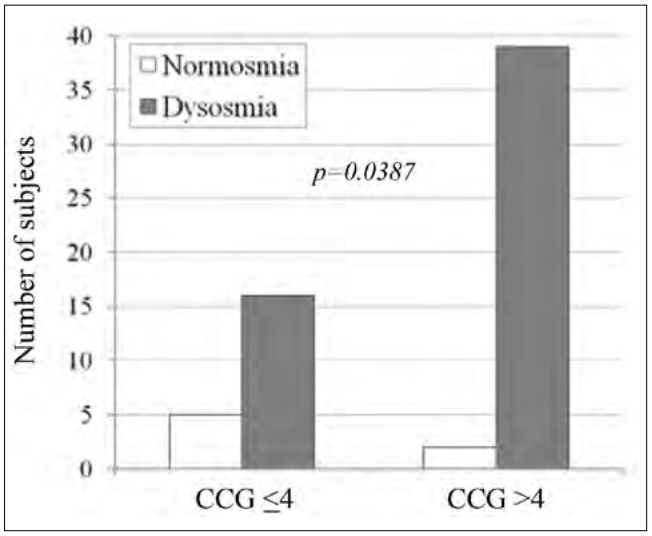

Fig. 2. Distribution of normosmia and dysosmia in patients with CCG > 4 or CCG < 4 score.

and dysosmia in patients with a CCG > 4 or a CCG < 4. In the group with positive CCG, the proportion of dysosmic patients was significantly higher as to normosmic subjects (Fisher exact test, p = 0.0387).

No correlation was found between olfactometry and rhinomanometry (r = – 0.1978, p = 0.12) (Fig. 3A). There was a moderate and significant inverse relationship between CCG and olfactometry (r = – 0.42; p < 0.0007), as reported in Figure 3B.

Discussion

The current study demonstrated that olfactory dysfunction is frequent in CRSwNP patients and that there is an association between olfactory impairment and inflammation. In addition, a CCG score > 4 is significantly associated with dysosmia. Actually, CCG could be useful in clinical practice to phenotype CRSwNP patients, identify the best treatment, and avoid under or overtreatment [7 24]. Moreover, olfactory dysfunction in patients with CRSwNP is an intriguing topic that is argument of research and clinical debate [25-27].

On the basis of this background, we explored the potential factors associated with olfactory dysfunction in patients with CRSwNP in real-world experience. Notably, about 90% of our CRSwNP patients had olfactory dysfunction that was not associated with nasal obstruction, as evaluated by endoscopy grading and rhinomanometry.

Table III. Logistic regression model of positive CCG, male gender and age as predictors of the study outcome.

Outcome	Explanatory variables	Adjusted odds ratio	95% CI	P value
Dysosmia (yes vs. no)	CCG (> 4)	7.46	1.18-47.19	0.0328
	Male gender	1.59	0.28-9.03	0.6000
	Age (yr)	1.02	0.96-1.08	0.4759

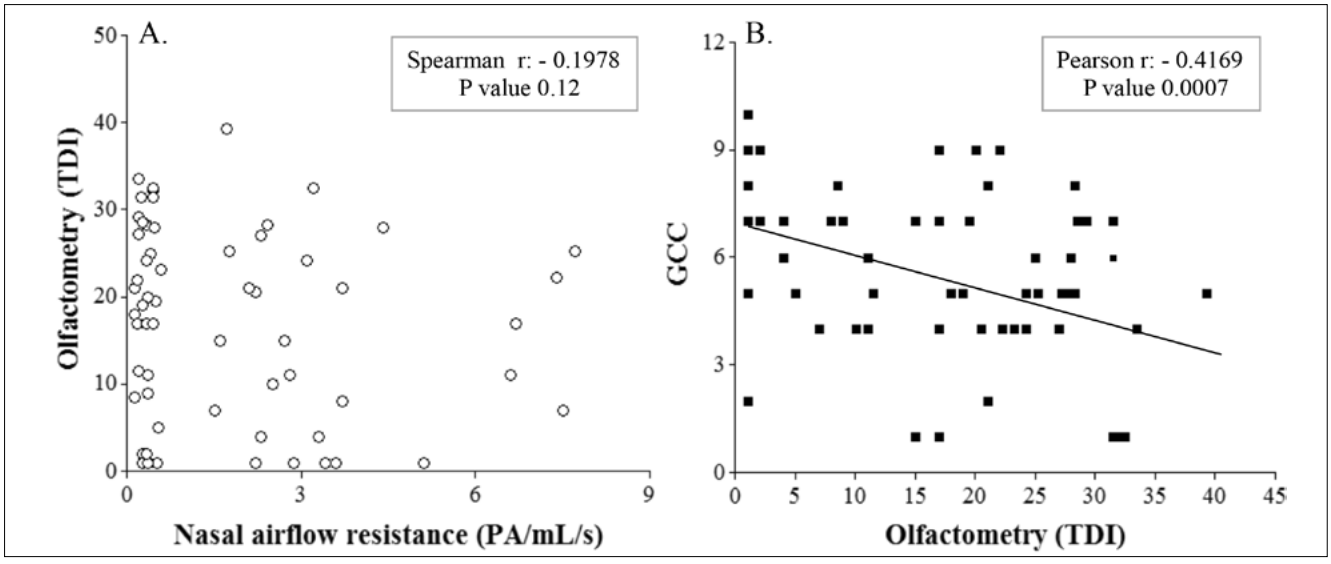

Fig. 3. Correlation between olfactometry and rhinomanometry (A) or CCG (B).

On the contrary, olfactory impairment was associated with inflammation, mainly concerning the eosinophilic and mast cell infiltrate.

From a clinical point of view, the assessment of the CCG could also be useful to suspect olfactory impairment in patients with a score > 4. Obviously, a diagnosis of impaired sense of smell should be based on specific olfactory testing.

However, the current study has some limitations, including the small number of patients (overall there was also a relevant imbalance between subgroups: 55 patients with dysosmia and only 7 with normosmia), the common presence of allergic rhinitis and its cross-sectional design. However, the study design was real-world to mirror daily clinical practice and newly diagnosed CRSwNP was a specific inclusion criterion. Therefore, a limited number of patients can be enrolled over a one year period. In addition, as the study was performed in a real-world setting, the percentage of normosmic patients was very low, as expected. Allergic patients were included as this comorbidity is very common and their exclusion drastically diminished the sample size. regarding the third issue, a follow-up longitudinal study is ongoing to evaluate whether CCG can predict persistent olfactory dysfunction over time after surgical treatment.

Nasal cytology has some limitations, including the limited reproducibility due to several factors, such as the area of the scaping, quantity of recovered cells, variations over time and training of the operator. Consequently, these limitations could influence the current findings and their interpretation.

In conclusion, the present study underlines that olfactory dysfunction is common in CRSwNP patients and demonstrates an association between olfactory dysfunction and inflammation and is consistent with findings obtained in the model of obstructive sleep apnoea [28]. Moreover, CCG may be useful in the work-up of CRSwNP patients and a CCG score > 4 could lead the clinician to suspect of olfactory impairment.

Conflict of interest statement

None declared.

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Rhinology

Chronic rhinosinusitis with polyposis and serum vitamin D levels

Rinosinusite cronica con poliposi e livelli sierici di vitamina D

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SUMMARY

The pathogenesis of chronic rhinosinusitis (CRS) is still unknown, but it is accepted that various inflammatory factors are responsible for the different CRS subtypes. Vitamin D3 has been shown to alter inflammatory mediators in some diseases and its deficiency might also be associated with CRS with nasal polyposis (CRSwNP). Herein, we investigated serum vitamin D3 levels in patients with CRSwNP and its association with disease severity. In a cross-sectional study, 166 cases with CRSwNP and 172 healthy subjects were enrolled. Serum vitamin D3 levels were measured and compared in both groups. Furthermore, the relationship between serum vitamin-D3 level and the patient's allergic status and severity of disease (clinically and based on computed tomographic imaging and nasal endoscopy) among patients with CRSwNP was assessed. Serum vitamin D3 level in the CRSwNP group was significantly lower than in the control group ($P < 0.0001$). After controlling for possible confounding factors, an increase in vitamin D level showed a protective effect in CRSwNP (OR = 0.69 95% CI:0.62-0.76). A negative correlation was found between serum vitamin-D3 level and the Lund-Mackay score (LMS) ($P < 0.0001$, $R = -0.66$), the Lund-Kennedy score (LKS) ($P < 0.0001$, $R = -0.71$) and the Sino-Nasal Outcome Test-22 ($P < 0.001$, $R = -0.49$). Serum vitamin D level in the CRSwNP group was significantly lower than the control group. Disease severity, based on imaging, endoscopic and clinical criteria, was inversely associated with serum vitamin D levels.

KEY WORDS: Chronic rhinosinusitis • Vitamin D3 • Nasal polyposis • CRSwNP • Deficiency

RIASSUNTO

La patogenesi della rinosinusite cronica (CRS) è ancora oggetto di discussione, ma è già noto che vari fattori infiammatori siano responsabili dei diversi sottotipi di CRS. È stato dimostrato che la carenza di vitamin D3 potrebbe essere associata a CRS con poliposi nasosinusale (CRSwNP). In questo lavoro abbiamo studiato i livelli sierici di vitamina D3 nei pazienti con CRSwNP e la sua associazione con la gravità della malattia. In questo studio cross-sectional sono stati arruolati 166 casi con CRSwNP e 172 soggetti sani. I livelli sierici di vitamina D3 sono stati misurati e confrontati in entrambi i gruppi. Inoltre è stata valutata la relazione tra livello di vitamina-D3 sierica e stato allergico del paziente e gravità della malattia (clinicamente e sulla base di imaging tomografico computerizzato e endoscopia nasale) tra i pazienti con CRSwNP. Il livello sierico di vitamina D3 nel gruppo CRSwNP era significativamente inferiore rispetto al gruppo di controllo ($P < 0,0001$). Dopo aver controllato i possibili fattori confondenti, l'aumento del livello di vitamina D ha mostrato un effetto protettivo nei pazienti CRSwNP (OR = 0,69 95% CI: 0,62-0,76). Una correlazione negativa è stata trovata tra il livello sierico di vitamina D3 e il punteggio di Lund-Mackay (LMS) ($P < 0,0001$, $R = -0,66$), il punteggio di Lund-Kennedy (LKS) ($P < 0,0001$, $R = -0,71$) e il test dell'outcome sino-nasale-22 ($P < 0,001$, $R = -0,49$). Il livello sierico di vitamina D nel gruppo CRSwNP era significativamente inferiore rispetto al gruppo di controllo. La gravità della malattia, basata su imaging, criteri endoscopici e clinici, era inversamente associata al livello sierico di vitamina D.

PAROLE CHIAVE: *Rinosinusite cronica • Vitamina D3 • Poliposi nasale • CRSwNP • Carenza*

Introduction

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the paranasal sinuses. The underlying etiology of the disease is not yet fully understood. It seems that many factors including cilliary impairment, allergy, asthma, aspirin sensitivity and genetic factors are involved in the development of CRS [1]. Clinical symptoms consist of congestion, facial pain and pressure, anosmia, headaches, excessive mucus production and increased susceptibility to acute bacterial infection of the sinuses, which may impair the quality of life. To confirm a diagnosis of CRS, symptoms must persist continuously for over 12 weeks and also include an objective sign of mucosal inflammation in computed tomography (CT) to provide a comprehensive view of the opacification within the paranasal sinuses and the nasal cavity or via the nasal endoscopy (NE) to directly visualise the nasal cavities and paranasal sinus ostia [1 2].
According to EPOS guidelines [1], CRS may be divided in-

to two subtypes, with (CRSwNP) and without (CRSsNP) nasal polyposis. Previous authors have tried to distinguish nasal polyp (NP) patients based on predominant inflammatory cell type/cytokine expression; the most common classification differentiates them into eosinophilic and non-eosinophilic CRSwNP. Increased activity of T-helper type 2 (Th2) cells leads to eosinophils recruitment and is mostly associated with CRSwNP, whereas Th1 increased activity leads to neutrophil recruitment and is more frequently associated with CRSsNP [3-6].

Several studies suggest that vitamin D3 acts as a steroid hormone that has anti-inflammatory effects [7-9] and plays an important role in regulating dendritic cells (DC) [10]. The mechanism of immune system modification by vitamin D3 is similar to other corticosteroids [7 10-12]. Various studies have shown that vitamin D3 is able to stop the production of cytokines and inhibit differentiation of immune cells. It prevents maturation and differentiation of monocytes to DCs, increases interleukin-10 production by CCs and thereby decreases DC stimulation of Th1/Th2 differentiation, resulting in higher tolerance [13 15]. Active (1,25) OH-vitamin-D3 also recruits interleukin-10, producing T-regulatory cells which could help reduce inflammation. In previous studies, an inverse relationship was found between serum vitamin D levels and the level of dendritic cells in CRSwNP patients [11]. A similar correlation was revealed between serum vitamin D levels and the granulocyte monocyte colony-stimulating factor (GMCSF) [16].

Some studies suggest that local regulation of vitamin D in the sinonasal tissue during CRS may be independent of serum 25(OH)-D levels and that local calcitriol and tacalcitol inhibit the synthesis of pro-inflammatory cytokines (IL-6 and IL-8) in fibroblast cultures [17]. A significant dose-dependent decrease in fibroblast proliferation was also observed when tissue samples were treated with calcitriol and tacalcitol [18-20].

In this study we aimed to compare serum vitamin D3 levels in patients with CRSwNP and healthy controls. The innovative aspect of the current study was to reveal the association between disease severity based on "imaging and endoscopic evaluations" and vitamin D3 levels, which to our knowledge has not been addressed in previous studies.

Materials and methods

This cross-sectional study was conducted in the Rhinology Clinic of Qaem and Imam Reza educational hospitals as a tertiary institute with accredited residency and fellowship program, Mashhad, Iran; from Oct 2015 to Aug 2017. The study protocol was approved by the local Ethics Committee of Mashhad University of Medical Sciences. Mashhad is a large city located in northeastern Iran that is almost always sunny albeit with polluted weather. The latitude longitude coordinates for Mashhad are 36°18'56.12"N, 59°34'4.66"E.

All patients with signs and symptoms of CRS referred to the Rhinology clinic were evaluated and those with CRSwNP 2 were enrolled in the study. CRS was defined according to the American Academy of Otolaryngology [2]. All cases with these criteria who had sinonasal polyposis confirmed by CT and endoscopic evaluation were entered into the study as the study group (CRSwNP). In total, 166 patients with eosinophilic polyps were enrolled; all patients underwent history, physical examination, nasal endoscopy and sinus CT scan. Lund-Mackay [20] and Lund-Kennedy [21] scores were calculated based on CT and endoscopic findings, respectively.

Skin prick testing with common local allergens as a gold standard was also done to clarify allergic status of subjects. Exclusion criteria were: history of vitamin D supplementation, anticonvulsant use, 1 or more cycle of low or high oestrogen OCP usage in last 3 months or corticosteroid use in the last 3 months. History of any chronic disease associated with low vitamin D3 serum levels such as chronic renal, cardiac, and liver diseases and malnutrition. Patients who did not consent to participation.

The control group consisted of 172 healthy subjects who did not have any symptoms suggesting chronic sinusitis or allergy and were matched with the study group in term of age, gender, ethnicity and approximate latitude and geographical location. The control group was selected from regional normal population in different lab office with check up panel without history of vitamin D medication or any related condition such as chronic diseases, asthma and allergy who were matched for sex and age.

Serum level of vitamin D3 was measured in both groups by HPLC [33].

Data were analysed using the Statistical Package for Social Sciences (SPSS, version 16). Descriptive statistics were used to describe the quantitative (mean and standard deviation and mean and 95% confidence interval, CI) and qualitative variables (frequencies). The Kolmogorov-Smirnov test was used to assess normality. Baseline demographics and clinical characteristics were compared among groups using the Mann-Whitney U test and the chi-square test as appropriate. For assessing the relation between quantitative variables with normal and non-normal distribution, Pearson and Spearman correlation coefficient were used respectively.

To study the effect of vitamin D deficiency on sinonasal polyposis, independent of the role of allergy, we compared vitamin D levels in non-allergic CRSwNP patients and the control group with an independent t-test.

Multivariate analysis was performed with an Enter meth-

od of logistic regression analysis. Confounding variables were entered into the binary logistic regression model and OR (odds ratio) with 95% CI. A P-value < 0.05 was considered statistically significant.

Results

The mean age in the study and control groups was 41.04 ± 13.0 yrs and 41.00 ± 14.8 yrs, respectively, indicating no significant difference (P = 0.98).The male-to-female ratio was 98/68 and 93/79 in the study and control group respectively, with no significant difference in terms of gender (P = 0.35). Table I shows the demographic characteristics of the case and control groups.

The mean vitamin D level in patients with CRSwNP was 12.11 ± 6.27 ng/ml and 90 ± 17.18 ng/ml in the control group. The difference of 23.79 (95% CI: 21.01-26.58) was statistically significant (P < 0.0001) (Fig. 1).

The correlation between Lund-Mackay score, Lund-Kennedy grading score and mean serum vitamin D level was assessed using Spearman's correlation test; it showed a significant negative correlation (P < 0.0001; rho = – 0.66, P < 0.0001; rho = – 0.71, respectively). The correlation between SNOT 22 and mean serum vitamin D level was assessed using Pearson's correlation test (P < 0.0001; R = – 0.49) (Table II).

In CRSwNP patients (study group), 55 (33%) had allergy and 52 (31%) had asthma. Accordingly, there was no significant difference between vitamin D levels in non-asthmatic (12.61) and asthmatic (11.00) CRSwNP patients [– 1.61 (– 3.68-0.45) P = 0.13], but a significant difference was observed in vitamin D levels between non-allergic (12.87 ± 6.17) and allergic (10.5 ± 6.26) CRSwNP patients [– 2.29 (– 4.31 - – 0.28) P = 0.026]. Since the control group was composed of healthy people with a negative history of allergy and asthma, for controlling the possible confounding effect of allergy, again the vitamin D level among non-allergic CRSwNP (12.87 ± 6.17) individuals in comparison to healthy controls (35.90 ± 17.19) showed a significant difference [– 23.03 (– 26.38 - – 19.69) P = 0.026]. Thus, the patients with allergy were excluded from further analysis.

After potential risk factors (education and smoking) were entered into the model, the odds ratio for vitamin D level was (OR = 23.64, 95% CI: 11.63-48.04). The results of the multivariate analysis are shown in Table III.

Table I. Demographic data of the patient (CRSwNP) and control groups.

	CRSwNP patients N = 166	Controls N = 172	P value
Sex (N%)			
Male	98 (59%)	93 (54%)	P = 0.35
Age (mean 95% CI)	41.04 (39.05-43.05)	41.01 (38.77-43.24)	P = 0.98
Smoking (N%)	82 (49.4%)	17 (9.9%)	P < 0.001
Education (N%)			
Primary education	89	55	P < 0.001
Academic education	76	111	
Vitamin D (ng/ml)	12.11 (11.15-13.07)	35.90 (33.32-38.50)	P < 0.001

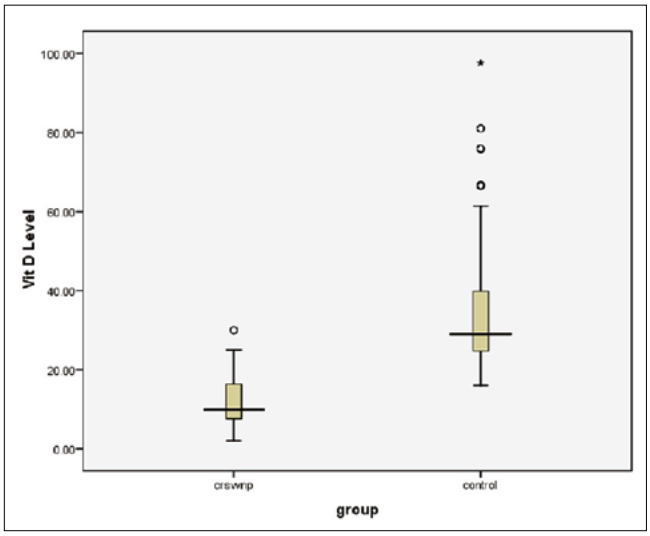

Fig. 1. Box- and -whisker display vitamin D level in the two groups.

Table II. Relationship between serum vitamin D level and Lund-Mackay (LM) score, Lund-Kennedy score, SNOT22 score.

	Mean	95% confidence interval	R	P value
Lund-Mackay score	19.4	18.99-19.85	– 0.66	< 0.001
Lund-Kennedy score	9.2	8.86-9.7	– 0.71	< 0.001
SNOT22 score	89	87.74-91.21	– 0.49	< 0.001

Discussion

Nowadays ethnicity is believed to play an important role in vitamin D level. Based on epidemiological studies, the prevalence of vitamin D deficiency is higher in Middle Eastern countries compared to Western nations [23 24]. Accordingly, we decided to design a study with a larger sample size than previous studies to investigate the relationship between serum vitamin D levels, CRSwNP and disease severity in Mashhad, Iran (L = 36°N).

To the best of our knowledge, this study is the first to investigate the correlation between serum vitamin D levels and polyposis severity in CRSwNP patients, based on "endoscopic evaluation", in addition to CT-scan grading. In addition, as far as we know, this study has the largest sample size among similar surveys having investigated the asso-

Table III. Independent risk factors for CRSwNP in multivariate analysis.

Variable	OR	CI 95%	P value
Smoking positive	1.02	0.36-2.88	0.79
Vitamin D level	0.69	0.62-0.76	> 0.001
Education level	1.79	0.46-2.79	0.78

ciation between vitamin D3 level and CRS. Our findings revealed a significantly lower vitamin D level in patients with CRSwNP in comparison to healthy controls; severity of disease also correlated inversely with serum vitamin D levels. In addition, multivariate analysis controlled for confounding factors such as allergy, education and smoking; the effect of vitamin D3 deficiency on CRSwNP is supposedly independent of these confounding factors on CRS. Vitamin D3 has currently been shown to have many immunologic effects, especially on dendritic cells, T cells and macrophages [25 26]. Vitamin D receptors have been found in many cells. Rostkowska and colleagues [20] found a significant dose-dependent decrease in fibroblast proliferation when tissue samples from nasal polyps were treated with various doses of vitamin D analogs. In another study by the same author [19], calcitriol and tacalcitol were demonstrated to inhibit the synthesis of pro-inflammatory cytokines such as IL-6 and Il-8 in fibroblast cultures. A significant inverse correlation was also found between serum vitamin D levels and the level of dendritic cells, prostaglandin E2 and granulocyte monocyte colony-stimulating factor in CRSwNP patients by Mulligan et al. [11].

These and several recent studies suggest an anti-inflammatory and immune-modulatory role for vitamin D3 in patients with CRSwNP. In the current study, this relationship in CRSwNP cases was statistically significant. Previous studies have also mostly reported this correlation as significant [10 11 13 27-29], although exceptions exist [8].

In the present study, only CRSwNP patients were investigated and not CRSsNP cases. Most studies found that vitamin D3 level in CRSwNP is lower than in CRSsNP patients [10 11 13 27-29], although one study reported different results [8].

Furthermore, similar to three other studies [11 27 29] we used CT imaging as a diagnostic factor to evaluate disease severity and found somehow similar results, showing a significant inverse correlation between disease severity and serum vitamin D3 levels ($P < 0.0001$).

Additionally, we endoscopically assessed polyps using the LKS system, and a significant relationship was achieved between serum vitamin D3 levels and endoscopic grade of disease ($P < 0.0001$).

Although the exact pathogenesis of CRSwNP is yet unknown, the available evidence suggests the same inflammatory process seen in allergic rhinitis and asthma. Some studies support the role of vitamin D3 in these two diseases. Given the fact that vitamin D3 has the ability to modulate the innate and adaptive immune system, its role in the pathophysiology of allergy has been the field of interest for many years. Vitamin D3 plays an important role in maintaining skin integrity and reducing pathogenic colonization in atopic dermatitis [31]. Yenigun et al. [32] found that vitamin D3 levels in patients with allergic rhinoconjunctivitis are significantly lower compared to healthy controls. Nevertheless, 55 of our 166 (33%) CRSwNP cases had simultaneously suffered from allergy. Therefore, we aimed to determine whether allergy may play a role in lowering the vitamin D level in this group. It could be postulated that patients with allergy avoid outdoor environments to reduce their symptoms and consequently, have lower vitamin D levels. This study shows that allergic patients have significantly lower vitamin D levels compared to non-allergic CRS individuals ($P < 0.026$), confirming the proposed hypothesis. Moreover, even in non-allergic CRS individuals the level of vitamin D is significantly lower than healthy subjects ($P < 0.0001$). Therefore, the role of vitamin D3 deficiency in CRS seems to be independent of the allergic basis.

This study had certain limitations. Many conditions play a role in the level of serum vitamin D such as skin colour, race, socioeconomic status, lifestyle, nutritional status, sun exposure during the day, use of sunscreen agents, chronic kidney and liver diseases, body mass index and others [33]. We matched the two studied groups in terms of race, sex, age and lack of chronic diseases, whereas other factors were not evaluated and matched between the two groups. Therefore, in order to prevent bias, it is highly recommended to assess all these conditions in future studies. Also to further approve the results of similar studies, the role of vitamin D supplementation in the treatment of CRSwNP should be considered.

Conclusions

In conclusion, a significantly lower vitamin D level was found in Iranian CRSwNP patients, indicating a positive correlation with disease severity. Serum vitamin D levels may be used as a workup in these patients and such data could be applied to further determine disease severity.

Conflict of interest statement

None declared.

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Vestibology

Analysis of the nystagmus evoked by cross-coupled acceleration (Coriolis phenomenon)

Analisi del nistagmo evocato da accelerazione "cross-coupled" (fenomeno di Coriolis)

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SUMMARY

Motion sickness and spatial disorientation represent two outstanding challenges in aviation medicine. In both cases, the vestibular system plays a fundamental role in their genesis. One of the most common ground-based simulations utilised in aero-physiological training is the sense of vertigo and tilt generated by the cross-coupled stimulation of the semicircular canals, while exposed to rotation in the yaw axis (Coriolis' Phenomenon: CP). However, the complex stimulus induced on the two labyrinths by this manoeuvre still deserves investigation. Nine male subjects sitting on a rotatory chair were asked to tilt their head back and forth during a yaw – axis clock – (CW) or counter-clock-wise (CCW) rotation at a constant speed of 70°/sec, generating the CP. Eye movements were recorded via Video-Oculo-Scopy and qualitatively analysed. A second camera simultaneously recorded the subject's and chair's movements. The observed nystagmus (Ny) was then analysed and related to the actual head/chair position and motion. A clear relationship was detected between Ny, head movements and direction of chair rotation. During CW rotation, backward head tilts systematically induced a CW-Ny, while a CCW-Ny was observed while returning to the upright position, or during forward head tilt. Opposite patterns were detected during CCW chair rotation. Minor lateral eye movements were also observed, due to the activity of horizontal semicircular canals, but no vertical ones. Due to the neural connections between extra-ocular muscles and each labyrinth sensor, the semicircular canals involved in the genesis of the Ny during this form of stimulation could be identified. In agreement with the third Ewald's law, our results indicated a dominant left labyrinth during backward tilt and CW motion, or forward tilt and CCW rotation. On the contrary, during forward tilt and CW rotation, or backward tilt and CCW rotation, the right vertical canals produced the main contribution to ocular response.

KEY WORDS: Motion sickness • Spatial disorientation • Vestibular system • Nausea and vomiting • Eye movements

RIASSUNTO

Le chinetosi e il disorientamento spaziale costituiscono due sfide di particolare rilievo in medicina aeronautica. In entrambi i casi, il sistema vestibolare svolge un ruolo determinante nella loro genesi. Una delle forme più comuni di simulazione a terra, impiegata nel corso dell'addestramento aerofisiologico degli equipaggi di volo, consiste nel senso di vertigine e inclinazione generato dalla stimolazione incrociata dei canali semicircolari durante una rotazione sull'asse verticale (yaw) con simultaneo movimento attivo della testa in pitch o in roll (cosiddetto fenomeno di Coriolis). Nonostante l'esistenza di pregressi studi, la complessità dello stimolo indotto da tale manovra sui due labirinti richiede ancora alcuni approfondimenti, come nel caso della stimolazione specifica dei singoli recettori labirintici e della seguente risposta oculomotoria. Nove soggetti di sesso maschile hanno partecipato allo studio, sottoponendosi a sedute su sedia rotatoria, durante le quali hanno inclinato attivamente il capo in avanti e indietro (i.e. solamente in pitch) nel corso di rotazioni della sedia in yaw sia in senso orario che antioratio, ad una velocità costante di 70°/sec, generando il fenomeno di Coriolis. I movimenti oculari sono stati registrati attraverso Video-Oculo-Scopia e quindi analizzati. Una seconda videocamera registrava contemporaneamente i movimenti del soggetto e della sedia. Durante ogni manovra in pitch della testa, il soggetto riferiva inoltre la propria percezione soggettiva di movimento. Il nistagmo (Ny) registrato era poi messo in relazione al movimento del capo e della sedia. Un'evidente relazione è stata osservata tra direzione del Ny, movimenti del capo e senso di rotazione della sedia. Durante la rotazione della sedia in senso orario, l'inclinazione indietro del capo induceva sistematicamente un Ny rotatorio orario, mentre uno antiorario veniva osservato al ritorno in posizione verticale del capo, o nel caso di una sua flessione in avanti. Parametri opposti sono stati osservati durante la rotazione della sedia in senso antiorario. Minimi movimenti laterali degli occhi, legati all'attività dei canali semicircolari laterali, sono stati anche registrati, unitamente a una sostanziale assenza di movimenti verticali. Più eterogenee sono invece risultate le risposte riferite alla percezione soggettiva di movimento. A causa delle connessioni neurologiche tra sensori labirintici e muscolatura extraoculare, è stato possibile identificare i canali semicircolari coinvolti nella genesi del Ny durante questo particolare tipo di stimolazione. In armonia con la terza legge di Ewald, i nostri risultati indicano un labirinto sinistro dominante durante la retroflessione del capo e la rotazione della sedia in senso orario, oppure durante l'anteroflessione del capo in corso di rotazione antioraria della sedia. Al contrario, durante l'anteroflessione del capo in corso di rotazione oraria della sedia, oppure durante la sua retroflessione durante una rotazione antioraria, sono i canali verticali del lato destro a fornire il maggiore contributo alla risposta oculomotoria. I nostri dati indicano inoltre un'elevata variabilità interindividuale nella percezione soggettiva di movimento durante tale tipologia di manovre.

PAROLE CHIAVE: *Chinetosi • Cinetosi • Disorientamento spaziale • Sistema vestibolare • Nausea e vomito • Movimenti oculari*

Introduction

Motion sickness (MS) and spatial disorientation (SD) represent two outstanding challenges in aviation medicine. In both cases, the vestibular system plays a fundamental role in the genesis of these phenomena [1-5].

One of the most common ground-based simulations utilised in aviation medicine, reproducing within a laboratory setting some of the potential effects of an in-flight vestibular illusion along with a nauseogenic environment, is the artificial sense of vertigo and tilt generated by the so-called cross-coupled stimulation of the semicircular canals from the two labyrinths, during the exposure to an on-axis yaw rotation on a standard rotatory chair [6].

During these exercises, the subject tilts his/her head back or forth (pitch), or on one side (roll), while passively rotating, and this movement generates a sudden change in the direction of the rotatory acceleration acting on the cupulae, along with a variation in the direction of the gravito-inertial force acting on the otoliths. In unadapted individuals, this particular type of vestibular stimulation, if performed during a sufficiently high speed of chair rotation (i.e. ≥ 50-60°/sec), easily provokes a strong sense of vertigo with nystagmus (Ny), and if the manoeuvre is repeated several times, an evident neurovegetative response, when sweating, pallor, nausea, or even vomiting, occurs.

In aviation medicine, these effects are usually identified as Coriolis' phenomenon (CP), although the acceleration forces involved in labyrinth fluid displacement are different from those reported by Gustave Gaspar de Coriolis in the early nineteenth century [7]. As a matter of fact, the genuine Coriolis' acceleration a is that experienced by a body which linearly moves at a velocity v while exposed to rotation at a speed ω about an orthogonal axis with respect to the body linear movement, so that $a=2v\omega$.

In the animal model, the ocular response to this acceleration was investigated by Maruta et al. [8], who observed different vestibulo-ocular reflexes secondary to translation while rotating, depending on the direction of the acceleration with respect to the head, and to the frequency of the linear component.

Therefore, in this experimental setting, no additional rotational forces are experienced except for the rotating platform, which is not the case for the CP normally evoked in humans during SD training or MS evaluation and treatment, where pitch and/or roll head movements are also made [5 9 10].

Although the clinical findings related to the genesis of the CP are well documented in the literature [3 5 6 9 10], only a few studies tried to focus attention on the human vestibular physiology underlying such a very particular form of stimulation, during [11 12], or immediately after rotation (so-called Purkinje effect) [11 13]. More in detail, some authors analysed the impact of CP on body sway, ocular movements, and subjective perception [12], although they limited their analysis to the sole recording of eye movements, without examining its probable source at the vestibular end organs [14]. Therefore, the analysis of the peripheral genesis of ocular motion in the CP-related head movements (i.e. during passive clock- and anti-clock-wise body rotation in the yaw axis) may still require some further contribution. Such head movements induce a bilateral stimulus on the two labyrinths, in its turn producing specific eye movements, due to the strict interrelation existing between vestibular sensors stimulation and oculomotor response, and to the dominant vestibular input, as reported in Ewald's laws [15]. The rotatory component of the CP-induced nystagmus might be a useful contributing factor in detecting the dominant labyrinth, due to its neurophysiological links with each crista ampullaris. In many cases, such analysis could not be performed in the past with the use of electrophysiological recordings of eye movements as they are not able to report ocular rolling [16].

More recently, the use of the video-oculo-scopic techniques (VOS) has significantly improved the capability of detecting those torsional components of eye movements that represent part of the final output of a stimulus involving the cupolae of the two vertical canals connected to the superior and the inferior oblique muscles, and so produce as a primary action the intorsion or the extorsion of the eyeball [14 17]. Therefore, the VOS significantly increases the capability of analysing these details of eye movements during the execution of CP related head tilts. Thus, the aim of this study was the VOS analysis of normal subjects during both forward and backward head tilts while undergoing an on-vertical axis rotation on a rotatory chair, identifying those semicircular canals mainly contributing to the genesis of the CP, and to the related perception.

Materials and methods

Our data were collected at the Aerospace Medicine Department of the Italian Air Force Flight Experimental Centre. The research was approved by the local Ethics Committee, and was in agreement with the Helsinki Declaration.

Our sample consisted of nine male volunteers (mean age 26 ± 4 years), forming part of the aircrew members undergoing standard aerophysiological training, according to the current NATO STANAG 3114 [18]. Each subject re-

sulted normal in past medical checks, and certified as fit for flying duties at one of the Italian Air Force Institutes of Aerospace Medicine, where screening for vestibular disorders is also conducted.

All individuals were seated on a rotatory chair, wearing VOS devices with monocular recording of the right eye (Synapsys infrared videocamera, with a sample rate of 48 Hz), connected to a wireless camera battery pack, which was secured on the subject's right arm via an elastic band (Fig. 1). All subjects were asked to keep their eyes open during each test session, in order to easily record eye movements (monitored by the operator via a video-recording system). Visual fixation was inhibited by the dark visual environment generated by the VOS mask (Fig. 1). The VOS signal was then transferred to a wireless receiver, and then to a multichannel digital video recorder. All data was stored and analysed in an off-line mode by a computerised system. During the test session, eye movements could be observed on a screen connected to the VOS videocamera. A second camera (IR digital CCD videocamera) simultaneously recorded the chair and the subject's movements and was connected to the same video-recorder so that the subject's head position and movement could be easily coupled with the corresponding eye movement.

Fig. 1. Subject sitting in upright position on the rotatory chair, wearing the VOS mask and wireless camera battery pack on his right arm.

Each subject randomly underwent both a clockwise (CW) and a counter-clockwise (CCW) session of rotations at a constant speed of 70°/sec, lasting for a total of roughly 10 minutes. After rotation began, once the target speed was reached, each individual maintained an upright position for a few tens of seconds so as to obtain a complete fading of the subjective perception of rotation and of the rotation-induced eye movements (detected via the VOS recording). The individual was then asked to actively rotate his head back or forth (pitch rotation), according to a random sequence that systematically included:

1. a pitch-up movement (i.e. backward tilt), followed by a return to the upright position;
2. a pitch-down movement (i.e. forward tilt), with subsequent return to the upright position.

Therefore, in this experiment, only data from pitch-head movements during passive body rotation in the yaw axis were considered (i.e. no responses from roll-head movements were obtained). Each movement started exclusively after the complete fading of symptoms (sense of rotation and/or movement) and Ny evoked by the previous manoeuvre (observed via the on-line VOS recording).

Throughout each test session, the Ny evoked by each manoeuvre was recorded, along with the chair and subject's movements, and with the perception and/or symptoms reported by each individual (these were related to the perceived sense of rotation and/or tilt, along with the onset of MS related symptoms).

Due to the aim of this research, the following parameters were analysed for each subject:

1. direction of chair rotation (i.e. CW or CCW);
2. type of head movement performed (i.e. backward tilt, back to upright from backward tilt, forward tilt, back to upright from forward tilt);
3. presence/absence of a Ny evoked by these manoeuvres;
4. direction of the evoked Ny;
5. presence/absence of a concurrent change in the subjective sense of orientation (as reported by the subject).

A calculus of the peripheral sensors (i.e. the cristae ampullarum of the semicircular canals) generating those specific eye movements was then performed. As usual, the direction of the Ny was diagnosed according to its fast phase, which means that the vestibular component was in the opposite direction (i.e. slow phase). Fast torsional components were denoted as a CW or CCW Ny, as observed by the investigator's side (i.e. not by the subject's one).

Results

All subjects were able to perform the entire experimental session, consisting in the VOS recording under eight different test conditions (i.e. backward tilt, back to upright from backward tilt, forward tilt, back to upright from forward tilt; all of these repeated for both CW and CCW chair rotation), without the need to interrupt the test session due to the onset of nauseogenic vertigo. During all these test conditions, a clear oculomotor response was detected in all subjects.

In every case, the VOS showed small and irregular horizontal components of eye motion, while an evident CW or CCW Ny was also detected. No evident vertical ocular movements were detected during the majority of test sessions.

Results for CW chair rotation

The backward head tilt systematically produced a torsional CW Ny, indicating a left vestibular dominance of the two vertical canals (i.e. anterior and posterior). On the contrary, during the return to the upright position, a CCW nystagmus was observed (i.e. dominance of right vertical canals). During these manoeuvres, a sense of pitch up during backward tilt and of pitch down on return to upright was usually experienced, although not in all cases (i.e. 5 of 9 individuals: 56%).

During forward head tilt, opposite VOS findings were observed in all cases (i.e. a CCW Ny indicating dominant right vertical canals), and a CW Ny at the return to the upright position (i.e. dominance of left vertical canals). Even in this case, symptoms were not uniform among individuals, with the most represented consisting of a perception of pitch down during the tilt (67% of cases), and of right roll at the return to upright (7 out of 9 individuals: 78%). These results are summarised in Table Ia.

Results for CCW chair rotation

In CCW chair rotation a constant type of oculomotor responses was observed, resulting in being of opposite direction with respect to those recorded during CW chair rotation, with a CCW Ny during backward tilt (i.e. right dominant labyrinth), a CW Ny at the return to upright (i.e. left dominant labyrinth), a CW Ny at the forward tilt (i.e. left dominant labyrinth), and a CCW Ny at the return to upright from forward tilt (i.e. right dominant labyrinth). As to the sensation during such manoeuvres, this was mainly represented by a sense of pitch up during backward tilt (56% of cases) vs a sense of pitch down at the return to upright (44% of cases). For forward tilts, in 4 subjects (44% of total sample) a sensation of pitch down was usually experienced, with a sense of rolling to the right at the return to upright. The results from CCW chair rotation are summarised in Table Ib.

Discussion

The main finding of this study is represented by the constant and uniform type of oculomotor response observed in the entire sample, contrasting with a high interindividual variation in the sense of orientation. This is not a new finding, since a discrepancy between stimulus profile, oculomotor response and movement perception has already been reported in several publications focusing on this particular behaviour of the vestibular system, especially in the presence of complex motion [19-21].

In our case, the total response observed from the two labyrinths during for- and/or back-ward tilt is in agreement with Ewald's third law, asserting that the ampullofugal (i.e. excitatory) endolymph flow in the vertical canals causes a greater response than the ampullopetal (i.e. inhibitory) one [15], with an opposite direction of the Ny recorded during these two different stimuli. In both cases, a reverse of Ny direction was observed on return to upright, which indicates that the return movement, rather than the final position itself, mainly conditioned the vestibulo-ocular reflexes. In fact, for CW chair rotation, both a CCW and a CW Ny were observed in the same upright position, on return from backward and forward tilt respectively. Accordingly, opposite findings were detected during CCW chair rotation.

In our sample, the lateral canal contribution was not so

Table I. Direction of nystagmus and subjective sensation during CW (a) and CCW (b) chair rotation. The first column indicates the head movement evoking both the oculomotor response and the subjective illusion in the same row. While the oculomotor response resulted extremely constant within our sample (100% of cases), the subjective sensation varied among individuals and only the most represented one is reported (prevalence in brackets).

a. CW chair rotation		
	Ny direction	**Subjective sensation**
Backward head tilt	CW	Pitch up (56%)
Upright from backward	CCW	Pitch down (56%)
Forward head tilt	CCW	Pitch down (67%)
Upright from forward	CW	Right roll (78%)
b. CCW chair rotation		
	Ny direction	**Subjective sensation**
Backward head tilt	CCW	Pitch up (56%)
Upright from backward	CW	Pitch down (44%)
Forward head tilt	CW	Pitch down (44%)
Upright from forward	CCW	Right roll (44%)

evident, with the exception of per- and post-rotatory Ny with an upright subject at the beginning and end of each experimental session. During head tilt, this was possibly due either to a relatively mild stimulus involving the lateral canal and/or to a masking effect on the part of those eye roll movements induced by activation of the two vertical canals.

The lack of evident vertical components of eye movements is probably due to the simultaneous activation of both vertical canals from the same labyrinth (i.e. anterior and posterior). In this case, while a synergic roll movement is evoked on the eyeball from the two cupolae, a simultaneous input producing eye movements having opposite direction is generated by the same two sensors, acting on the extraocular muscles dedicated to up- and downward rotation of the eyeball (i.e. the superior and inferior rectus respectively), inhibiting each other [14].

Our VOS findings are substantially identical to those observed in two subsequent studies by Takahashi et al. [22] and by Watanuki et al. [12], although in their case a constant subjective sensation was reported, with a sense of lateral sway that we did not observe except in a few cases (cfr. Table I). These data further confirm how, especially for complex and/or atypical stimulations, the cognitive response to vestibular input might result in a high intersubject variability.

Besides the absolute single subject's sensitivity to the CP, which is very variable, a careful and highly specific description of the subjective perception of such a brief illusory motion might be difficult to obtain and standardise in individuals who are not trained for this specific purpose, as in our sample. However, if past findings indicating the generation of illusory motion (or no-motion) during particular and complex vestibular stimulations are also considered [19-21 23], this might be an interesting topic for further research.

As to the vestibular side involved in the genesis of CP, our data clearly indicate that during backward head tilt the left labyrinth plays the major role for CW rotation, while the right labyrinth is dominant for CCW rotation. Opposite findings can be observed in the case of forward head tilt, with a dominant right labyrinth if a CW rotation is performed, vs the left labyrinth under CCW chair rotation. In all cases, a rebound Ny having similar parameters, but opposite direction is detected at the return to the upright position.

Due to the high prevalence of vestibular related misperception in aircrew members, as well as in other categories of individuals exposed to moving environments, both in the case of MS as in that of SD events [6 24-26], our findings might contribute to a better understanding of those sensory phenomena underlying the correct evaluation of different sensory cues, especially when particularly demanding tasks are required.

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Conflict of interest statement

None declared.

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Vestibology

Observational study on risk factors determining residual dizziness after successful benign paroxysmal positional vertigo treatment: the role of subclinical BPPV

Studio osservazionale sui fattori di rischio che causano residual dizziness dopo il trattamento della vertigine parossistica posizionale benigna: il ruolo della VPPB subclinica

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SUMMARY

After successful treatment for benign paroxysmal positional vertigo, many patients may complain of residual dizziness. Possible explanations may be the persistence of otolith into canal insufficient to provoke noticeable nystagmus, utricular dysfunction and undiagnosed coexisting vestibular disorder. We conducted a prospective observational case-control study, focusing on the role of risk factors in determining residual dizziness after BPPV treatment. In the present study, 148 patients were recruited and residual dizziness was documented in the 57.5% of the cohort. Among patients with residual dizziness 36 had subclinical BPPV and after retreatment, although nystagmus was not clinically evident, there was resolution of dizziness. We conclude that residual otoliths may play a role in determining post-maneuver residual dizziness that is often linked to subclinical BPPV; this conclusion is also supported by the high prevalence of BPPV recurrence in patients with residual dizziness, as confirmed by our analysis. The main cause appears to be linked with dispersed otolith in semicircular canals.

KEY WORDS: Residual dizziness • Benign paroxysmal positional vertigo • Subjective BPPV • Dizziness • Nystagmus

RIASSUNTO

Alcuni pazienti, dopo il trattamento della vertigine parossistica posizionale benigna concluso con successo, possono lamentare un disequilibrio residuo. La possibile spiegazione potrebbe essere: la persistenza di otoliti canalari insufficienti a provocare un nistagmo clinicamente evidente, una disfunzione utriculare, coesistenza di altri disordini del sistema vestibolare. Abbiamo condotto uno studio osservazionale prospettico caso-controllo, focalizzando l'attenzione sul ruolo di fattori di rischio che possono causare un disequilibrio residuo dopo il trattamento della VPPB. Abbiamo reclutato 148 pazienti e un disequilibrio residuo è stato documentato nel 57,5% dei casi. Tra i pazienti con disequilibrio residuo in 36 è stata diagnosticata una VPPB subclinica, che dopo il ritrattamento, sebbene senza evidenza clinica di nistagmo, hanno avuto una risoluzione dei sintomi. Possiamo concludere che gli otoliti residui possono avere un ruolo nel determinare il disequilibrio residuo post-manovra, poiché legato a una VPPB subclinica. Questa conclusione è testimoniata anche dall'alta prevalenza di recidive nei pazienti con disequilibrio residuo. La causa principale sembra legata alla persistenza di otoliti dispersi nei canali semicircolari.

PAROLE CHIAVE: *Disequilibrio residuo • Vertigine parossistica posizionale benigna • VPPB soggettiva • Disequilibrio • Nistagmo*

Introduction

Benign paroxysmal positional vertigo (BPPV) accounts for about 20% of vestibular complaints [1]. Being a mechanical disorder of the semicircular canals, management consists of "mechanical" repositioning of the otoconial debris, also called otolith or canalith, detached from vestibular sensorineural epithelia. Posterior semicircular canal (PSC) is the most involved by BPPV with approxi-

mately 90% of cases, while horizontal semicircular canal (HSC) is the next most common [2]; superior semicircular canal (SSC) involvement is rare. The canalithiasis consists of dispersed fragments of otoliths into semicircular canals, which are able to cause vertigo when, by gravity, move into canals. The repositioning maneuvers to treat canalithiasis are well established and used widespread, with some variations recently reported in literature [3].

In clinical practice, among patients admitted to emergency for vertigo, 8-9% are diagnosed with BPPV [4]. The treatment of BPPV is often simple and immediate, giving the patient a prompt resolution of the symptoms. Some patients with resistant BPPV require several maneuvers to reach adequate results, while other patients, after initial resolution of symptoms, show delayed positional nystagmus due to canal reentry of otoliths [5].

Furthermore, patients without noticeable nystagmus during diagnostic assessment for BPPV, although experiencing vertigo and autonomic symptoms while the diagnostic test are performed, are diagnosed as subjective (subclinical) BPPV, since dispersed otolith are unable to give a clinical manifestation of nystagmus, and is manageable in the same manner of traditional BPPV [6].

Despite successful BPPV treatments, many patients complain of residual dizziness (RD) that is described variously by patients and can be classified as non-vestibular dizziness, based on the characteristics of the disequilibrium and absence of nausea and vomiting [7].

We conducted a prospective case-control study on BPPV treated by canalith repositioning maneuvers, focusing on the role of residual debris in determining subclinical BPPV as a cause of RD.

Materials and methods

All consecutive patients admitted for BPPV to our ENT divisions in the period 2012-2014 were included in the study, according to the approval of the institutional review board. Recent vertigo other than BPPV, head trauma and lifetime history of previous episodes of vertigo other than BPPV were considered as exclusion criteria. Residual dizziness was expressed as sensation of unsteadiness or lightheadedness without rotational vertigo [8]. Data of included patients were prospectively collected in an electronic database. The following variables were recorded: age (< 40; 40-65; > 65), gender (male/female), side (left/right), tinnitus (yes/not), hearing loss (yes/not), previous BPPV episodes (yes/not), affected semicircular canal (PSC, LSC, SSC), recurrence (yes/not), liberatory nystagmus (yes/not), number of maneuvers done, success of maneuvers (yes/not) and residual dizziness (yes/not). All patients underwent otolaryngologic examination, pure tone audiometry, evaluation of nystagmus with infrared video-Frenzel lens, diagnostic test for positional nystagmus with Dix-Hallpike manoeuvre for PSC, supine roll-test for HSC, head-hanging manoeuvre for SSC, video Head Impulse Test (vHIT) done with Interacoustics Eyseecam® and Vestibular Evoked Myogenic Potentials (VEMPs) with Hedera Biomedics Socrates®. Ocular and Cervical VEMPs were done by Air-conducted stimulus examining both ears separately by tone burst 130 dB at 500 Hz. Normative values considered in all patients for VEMPs were: latency values, inter-amplitude and inter-latency asymmetry between range 0-45%, and absent or not reproducible wave; for vHIT symmetric gain and absence of overt and/or covert saccades was considered as normal, the gain value was not considered because several issue about to assess normative [9]. The PSC diagnostic test was considered positive when nystagmus was appropriate with head position as torsional type with up-beating component. The HSC was considered positive when during supine head roll-test a direction changing horizontal nystagmus was detected, and for SSC when during head-hanging test a down-beating nystagmus with latency, crescendo and transience was observed with or without torsional component [10]. The treatment included the same manoeuvre in all patients related to canal involved to avoid bias due to type of manoeuvre: Gans manoeuvre for PSC BPPV [3], Gufoni and Yacovino manoeuvre respectively for HSC and SSC involvement [2 11]. The success of treatment was defined as disappearance of both symptoms and nystagmus at diagnostic tests performed 45 minutes after treatment. The clinical features of BPPV were recorded: side involved, canal involved, number of manoeuvres done to treat the BPPV, presence of liberatory nystagmus, canal re-entry or canal switch [5] and recurrence of BPPV after successful treatment. Follow-up was done with clinical control at one and two weeks after treatment and with control visits at 6 months and 12 months even if symptoms were absent. The presence of dizziness even without nystagmus at clinical control was recorded, and the vertigo elicited during the diagnostic manoeuvre for BPPV without clinical evidence of nystagmus was considered as subclinical (subjective) BPPV [6]. The recurrence was defined as further BPPV episodes with noticeable nystagmus at otoneurologic examination in the follow-up period. All patients with persistence of untreatable dizziness underwent to imaging to exclude pathologies of the central nervous system. Distributions of continuous variables in different groups were analysed by T-student test parametric method. For categorical variables, comparisons were performed using Chi-square test with Yates correc-

tion and Fisher's exact Test. Univariate and multivariate logistic regression analysis were performed. Odds ratios and 95% confidence intervals were calculated. Statistical significance was set at $p < 0.05$. Data were analysed using the R statistical software package, version 2.2.0. Informed consent was obtained from all participants.

Results

During the study period, 165 patients were treated for BPPV at our institutions, but 17 patients were lost during follow-up. We conducted our analysis on 148 patients, 92 (62.2%) females and 56 (37.8%) males, average age 53 (s.d. = 13.9) and median age 53, who were recruited according to the inclusion criteria. 63.5% of cases were in the 40-64 age category. No spontaneous nystagmus was recorded. Residual dizziness was documented in 57.5% of the sample. Most of the cases (76.4%) had PSC involvement at clinical examination. Tinnitus was present in 23 subjects (15.5%). The audiometric test revealed a sensorineural hearing loss (SNHL) in 65 patients: 22 mild SNHL and 43 severe SNHL. Imaging performed in 25 patients with persistence of dizziness after retreatment excluded a central nervous system pathology. VEMPs were presents in all subjects complaining of residual dizziness or recurrent BPPV; the mean P1/N1 latency for c-VEMPs was 15.9/23.6 msec (SD 1.9/2.4); no latency or amplitude asymmetry was recorded with interaural difference under 30% (SD 5%). vHIT was also normal (absence of covert and/or overt saccades) in all patients with no asymmetric gain value recorded.

At least one episode of recurrence was documented during follow-up in 18 patients (12.2%), which statistically differed between the comparison group by age, canal reentry and absence of liberatory nystagmus during the first session of treatment (Table I). In 65 patients, more than one manoeuvre was needed to obtain BPPV resolution.

The logistic regression model documented significant risk excess for recurrence of BPVV associated with age (OR = 1.063; C.I. = 1.014-1.12), while a significant high reduction associated with success of therapeutic manoeuvre (OR = 0.028; C.I. = 0.001-0.33).

In Table II, comparison between patients complaining residual dizziness (57.4%) and the ones without residual dizziness (42.6%) is shown. Female gender ($p = 0.00$), advanced age ($p = 0.00$), previous episodes of BPPV ($p = 0.01$), more than one manoeuvre for treatment ($p = 0.00$) and recurrence of BPPV ($p = 0.00$) explained the statistical difference between the two groups.

Table I. Comparison between patients with and without recurrence. Age, canal reentry and presence of liberatory nystagmus were significant predictor of recurrence.

		No recurrence	Recurrence	P-value
		N 130 (%) 87.8%	N 18 (%) 12.2%	
Gender	Male	48 (85.7%)	8 (14.3%)	0.7
	Female	82 (89.1%)	10 (10.9%)	
Age	Average	52.7 S.d. (13,94)	67.3 s.d. (13,79)	0.006
Previous BPPV	None	60 (93.7%)	4 (6.3%)	0.1
	> 1	70 (83.3%)	14 (16.7%)	
Number of CRM	1	76 (91.6%)	7 (8.4%)	0.2
	> 1	54 (83.1%)	11 (16.9%)	
Canal reentry	No	126 (89.4%)	15 (10.6%)	0.04
	Yes	4 (57.1%)	3 (42.9%)	
Liberatory Ny	No	1 (25%)	3 (75%)	0.006
	Yes	129 (89.6%)	15 (10.4%)	

Table II. Comparison between patients with and without persistence of dizzy symptoms after treatment; numbers of manoeuvres and recurrence were predictive of persistent dizziness.

		Residual dizziness Yes	Residual dizziness No	P-value
		85 (%) 57.4%	63 (%) 42.6%	
Gender	Male	24 (42.9%)	32 (57.1%)	0.005
	Female	61 (66.3%)	31 (33.7%)	
Age	Average	57 S.d. (14,41)	47 s.d. (10,78)	0.000001
Previous BPPV	None	29 (45.3%)	35 (54.7%)	0.01
	More than one	56 (66.7%)	28 (33.3%)	
Numbers of manoeuvres	One	34 (41%)	49 (59%)	0.000004
	More than one	51 (78.5%)	14 (21.5%)	
Liberatory Ny	No	26 (68.4%)	12 (52.6%)	0,1
	Yes	59 (28.2%)	51 (71.8%)	
Canal reentry	No	80 (56.7%)	61 (43.7%)	0.7
	Yes	5 (71.4%)	2 (28.6%)	
Success of manoeuvres	No	4 (100%)	0 (0%)	0.1
	Yes	81 (56.3%)	63 (43.7%)	
Recurrence	No	68 (52.3%)	62 (47.7%)	0.0005
	Yes	17 (94.4%)	1 (5.6%)	

Among patients readmitted for residual dizziness following clinical vestibular examination, 36 were diagnosed with a subclinical BPPV, while only 2 patients had subclinical BPPV at follow-up in the group without RD ($p = 0.00$). No recurrence was detected in patients with subclinical BPPV who underwent retreatment of the same canal.

Discussion

Residual dizziness is a frequent complaint of patients after treatment for BPPV, even if therapeutic success was achieved, which might be present in two-thirds of cases. Four theories have been hypothesised to explain the RD: 1) remaining otoconial debris due to incomplete repositioning that can produce soft positional vertigo, because the remaining debris are insufficient to deflect the cupula to a degree able to provoke overt nystagmus [12 13]; 2) BPPV is not only a disorder of the semicircular canals, but also of otolith organs that sense orientation in the space, and otolith dysfunction might account for transient mild dizziness [14 15]; 3) another vestibular lesion that is difficult to identify from history alone might coexist with BPPV, and the prevalence of less-specific dizziness was significantly higher in BPPV patients with additional peripheral or central vestibular dysfunction [16]; 4) delayed recovery might be due to the longer time needed for central adaptation after particle repositioning.

The English literature also reports that patients with residual dizziness have higher anxiety scores than patients with no residual dizziness [8]. Anxiety has been demonstrat-

ed to play a role in dizziness, and anxiety and dizziness are comorbid in a larger percentage of patients than would be expected from chance alone [17 18].

The vestibular system participates in autonomic regulation adjusting cardiovascular control during body movement and change in posture [19 20]. Patients with BPPV occasionally experience postural light-headedness when righting from a sitting position, despite successful repositioning procedures [21]; it is similar to orthostatic dizziness reported by patients with orthostatic hypotension [22].

One-third of patients with BPPV have some abnormality of autonomic system response as shown by orthostatic hypotension tilting test or blood pressure response during Valsalva manoeuvre; the rate of autonomic dysfunction is higher in patient with residual dizziness than in those without [23].

Residual dizziness was found to be related to duration of vertigo before repositioning manoeuvre. A longer duration of BPPV was associated with the presence of residual dizziness after the particle repositioning maneuver [7]. In our observation, patients with more than one episode of BPPV in their history had a significantly increased risk to develop a RD, which is increased if the patient is more than 65 years of age. Our dataset showed that the elderly population has a generically high risk of BPPV recurrence, effectively confirming our previous results, where we described some risk factors (hypertension, diabetes, osteoporosis) that influence the high rate of recidivism in patients over 65 years [24]. The increased prevalence in the elderly population is considered to be caused by changes in otoconia morphology, possibly related to vascular damage in the inner ear [25], although signs of inner ear aging such as tinnitus and hearing loss have showed no relationship with RD in our patients. Elderly patients affected by BPPV also complain of dizziness and unsteadiness instead of typical positional vertigo; this may be due to unconscious avoidance of positions provoking vertigo rather than decreased perception of vestibular stimuli related to otolith organ damage [26]. Furthermore, in the elderly we found a reduced success rate of repositioning manoeuvres that may be linked to that chronic vascular damage of the inner ear and modification of otoconia. This reduced success rate of treatment was parallel to a significantly increased rate of RD in those patients, which leads to the consideration that some dispersed otolith into semicircular canals may play the main role in RD.

The responsibility of dispersed fragments of otolith could also be hypothesised by our observation that patients who underwent more than one repositioning manoeuvre in the same session had an increased risk to have RD in the post-manoeuvre period, as shown by logistic regression where the success of the manoeuvre reduced the recurrence rate.

In a previous report, we described the linkage of canal re-entry BPPV risk with number of manoeuvres, thinking that the otolith may be dispersed into canals [5]. Although patients do not complain a true positional vertigo after treatment, they may have dizziness due to otolith fragment, the mass of which is not enough to elicit a true positional vertigo. Effectively, we noted a high percentage of subclinical BPPV in patients with RD, which after re-treatment, even if nystagmus was not clinically evident, had resolution of dizziness [27 28]. However, the RD may be linked not only with dispersed otolith (main cause of subclinical BPPV), but also with age, BPPV recurrence and absence of liberatory nystagmus that could predict the chance of RD as shown in our analysis. In our opinion, following the reported dataset, residual otoliths play a main role in determining post-manoeuvre RD that is often linked to subclinical BPPV; this conclusion is also supported by the high prevalence of BPPV recurrence in patients with RD, as confirmed in our analysis.

Conclusions

RD may be a long lasting complaint in patients treated for BPPV. The pathophysiology may be related with several diseases and comorbidities. Our study focused on dispersed otolith into semicircular canals as a risk factor for RD. The high prevalence of subclinical BPPV among patients readmitted for RD is one of the possible explanations. Advanced age and recurrence of BPPV may be predictive of post-treatment RD. However, more than half of patients with RD remain without an explanation of the likely cause, and warranting further studies.

Conflict of interest statement

None declared.

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Otology

The endoscopic anatomy of the cochlear hook region and fustis: surgical implications

Anatomia endoscopica della "cochlear hook region" e del fustis: importanza per la chirurgia

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SUMMARY

The cochlear hook region can be considered as the interface between the middle and inner ear. The identification of surgically-relevant endoscopic landmarks of this anatomical entity and assessment of their clinical value is still lacking in the literature. Procedures like cholesteatoma surgery and minimal invasive endoscopic approaches to the lateral skull base may particularly benefit from these considerations. We hypothesize that the spatial orientation of anatomical landmarks in the cochlear hook can be expressed in angles and are reproducibly identifiable by transcanal otoendoscopy. Therefore, endoscopic dissection of the cochlear hook region was performed in 32 temporal bone specimens. Topographic anatomy was documented and analysed. We performed computed tomography of 28 specimens to assess the region in three-dimensional reconstructions. The mean angle between the round window and the basal scala tympani was assessed 25.9° in endoscopic and 28.2° in three-dimensionally reconstructed models. The fustis was recognised as a reliable landmark for the basal turn. A mean angle of 155.4° to the basal scala tympani was assessed. A slight bulging without obstruction of the basal turn was observed in 5 cases. The utility of the revealed anatomical details was assessed in minimal invasive endoscopic lateral skull base approaches. In conclusion, we described the angles between anatomical landmarks of the cochlear hook region. Moreover, the angle as recorded through an endoscope was found to be reliable compared to three-dimensional reconstructions from computed tomography.

KEY WORDS: Cochlear hook region • Endoscopic ear surgery • Cochlear implant • Lateral skull base surgery • Fustis • Cholesteatoma • Vestibular schwannoma

RIASSUNTO

La "cochlear hook region" (CHR) può essere considerata come una interfaccia tra l'orecchio medio e l'orecchio interno. L'identificazione endoscopica dei reperi chirurgici della CHR e la valutazione della loro rilevanza clinica non sono ancora state descritte in letteratura. Specialmente la chirurgia del colesteatoma e gli approcci mini-invasivi al basicranio laterale possono beneficiare di queste considerazioni. Ipotizziamo in questo lavoro che l'orientamento spaziale dei reperi chirurgici nella CHR possono essere espressi in forma di angoli e risultano essere riproducibili in approcci otoendoscopici. 32 dissezioni di ossa temporali sono state condotte in questo lavoro. L'anatomia topografica è stata documentata e analizzata. Una TC è stata eseguita in 28 temporali per valutare l'anatomia attraverso ricostruzioni 3D. L'angolo medio tra la finestra rotonda e il giro basale della chiocciola (scala tympani) è risultato essere di 25,9° in endoscopia, e di 28,2° nelle ricostruzioni 3D. Il fustis ha rappresentato un repere affidabile per il giro basale della chiocciola, con un angolo medio di 155,4° con il giro basale della scala tympani. Una lieve prominenza senza ostruzione del giro basale della chiocciola è stata osservata in 5 casi. L'utilità di questi rilievi anatomici è stata confermata negli approcci mini-invasivi al basicranio laterale. In conclusione gli angoli tra i reperi anatomici della CHR così come descritti attraverso gli approcci endoscopici forniscono un orientamento utile per procedure come impianti cocleari, approcci mini-invasivi all'apice petroso o accessi transpromontoriali al condotto uditivo interno.

PAROLE CHIAVE: *Cochlear hook region • Chirurgia endoscopica dell'orecchio • Impianto cochleare • Chirurgia endoscopica basicranio laterale • Fustis • Cholesteatoma • Schwannoma vestibulare*

Introduction

The cochlear hook region represents an important interface between the middle ear and lateral skull base including the inner ear. It represents the most basal part of the cochlea and contains structures such as the round window membrane (RWM), the stapes footplate, the vestibule connected to the scala vestibuli (SV), the ductus reuniens and the scala tympani (ST) [1 2]. The position of the basal turn (BT) and its relationships to middle ear structures are of special surgical interest, especially in cochlear implant (CI) surgery [3].

With the emergence of minimally-invasive, transcanal en-

doscopic techniques in ear and lateral skull base surgery, there is a growing interest in describing the topographical anatomy of the cochlear hook region from an endoscopic perspective. It is particularly important in the infracochlear approach [4], where access to the inferior petrous apex is performed between the BT, jugular bulb (JB) and internal carotid artery (ICA). The transcanal transpromontorial approach to the internal auditory canal (IAC) requires exposure and dissection of the hook region before accessing the IAC. The anatomy of the cochlear hook region and the vestibule allows prediction of the position of the labyrinthine portion of the facial nerve (FN). This is important in order to safely remove the pathology from the IAC whilst preserving the FN [5-7].

However, an endoscopic description of the cochlear hook region is still lacking in the literature. We hypothesise that the angles measured between anatomical landmarks are reproducibly identifiable using the endoscope when compared to high resolution computed tomography (HRCT). Therefore, we compared endoscopically assessed angles to three-dimensional reconstructions of HRCT scans of the temporal bone. This work aims to provide the surgeon with anatomical details, which are directly applicable during surgery.

Materials and methods

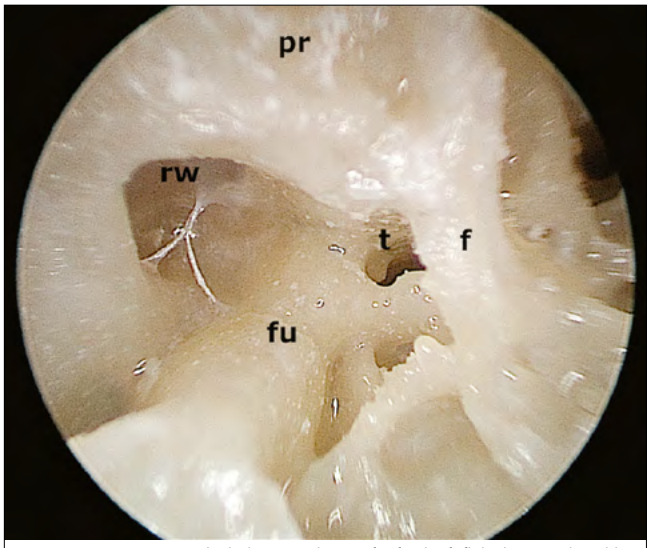
Endoscopic dissection

The local institutional review board granted approval to perform the present study (KEK-BE 2016-00887). We conducted cadaveric dissection on human whole head and temporal bone specimens. We used a 0°, 3 mm diameter and 14 cm length endoscope connected to a high-resolution camera system and monitor (Karl Storz, Tuttlingen, Germany).

The endoscopic access to the middle ear was obtained through the external auditory canal (EAC) performing a routine tympanomeatal flap. First, we performed a thorough exploration of the middle ear and documentation of the round window niche. To this end, we identified the subiculum, finiculus, subcochlear canaliculus, anterior and posterior pillars, tegmen and RWM. The fustis, a small bony plate, was identified on the floor of the subtympanic sinus running from the styloid prominence to the round window niche as shown in Figure 1 [8 9].

As the next step, we uncovered the cochlear hook region. The promontory bone was gently removed using small diamond burrs to expose the RMW, vestibule, SV ST, spiral lamina and spiral ligament. Figure 2 gives an illustrative overview on the endoscopic landmarks of the cochlear hook region.

To answer the study questions, we assessed following anatomical relationships:



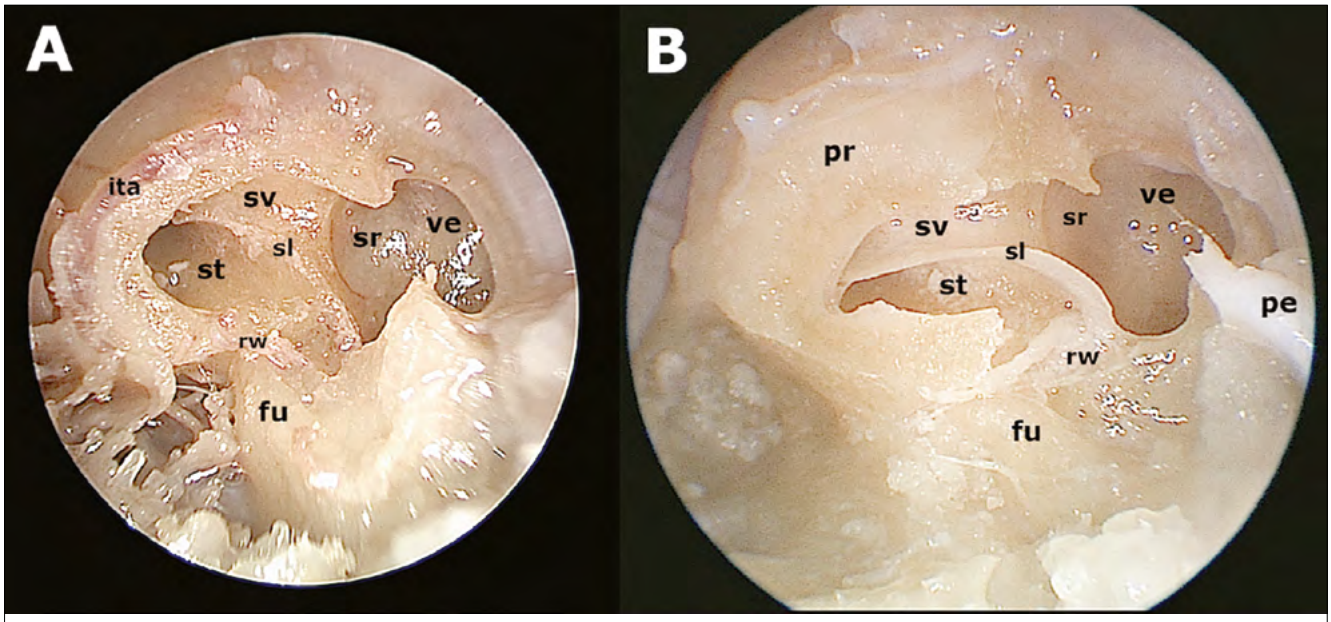
pr: promontory; rw: round window membrane; fu: fustis; f: finiculus; t: subcochlear tunnel

Fig. 1. *Round window niche.* Right ear: Details of important middle ear landmarks for the surgical treatment of the cochlear hook region. Note the direction of the fustis pointing towards the basal turn and representing the superior limit of the subcochlear tunnel.

- *The fenestro-basal angle (FBA):* the angle between a line approximated through the RWM center and the center of the basal ST was defined and measured from endoscopic photography.
- *Morphology of the fustis*: the orientation of the fustis and its configuration in relation to the RWM and the BT were assessed. Based on photographs taken with the endoscope, we measured the angle between the fustis and the BT.
- *Inside the ST*, an eventual bulging of the lateral cochlear wall into the hook region was assessed.

Three-dimensional assessment of the fenestro-basal angle

To investigate the suitability of an endoscopic view to determine the above-mentioned angles, 28 sides were imaged with HRCT scans (SOMATOM Definition Edge, Siemens, Erlangen, Germany) with a voxel size of 0.156 x 0.156 x 0.2 mm^3 before dissection. In the images, the cochlea, round window and promontorial bone were segmented, and three-dimensional surface models were created. A semi-automatic algorithm based on the selection of anatomical landmarks including the centre of the RWM [10] was used to approximate the centerline of the scala tympani in the cochlear basal turn. The tangent of the ST centre line was computed at the RW centre. The orientation of the RW membrane (which has a curved shape) was approximated by fitting a plane through the coordinates of the 20 closest RW membrane vertices in the vicinity of the RW center. The FBA was assessed as the angle between the fitted round window plane and tangential vector of the ST centerline (Fig. 3).



ita: inferior tympanic artery; sv: scala vestibuli; st: scala tympani; sl: spiral lamina; sr: spherical recess; rw: round window membrane; ve: vestibule; fu: fustis; pe: pyramidal eminence; pr: promontory.

Fig. 2. *Hook region anatomy.* Left ear: The endoscopic anatomy of the cochlear hook region in overview (A) and in detail; (B) after removal of the promontory bone and the stapes.

Statistical analysis

A two-tailed Wilcoxon matched-pairs signed rank test was performed to evaluate the association between the angles measured in endoscopic dissection with the angles measured in the three-dimensional model. All analyses were conducted using GraphPad Prism 7®. Alpha for statistical significance was set at 0.05.

Results

We analysed a total of 32 sides. The landmarks were well identifiable in all cases using the transcanal endoscopic approach. Figure 1 gives an overview over the important endoscopic landmarks of the round window niche and Figure 2 on the cochlear hook region.

The mean FBA was assessed endoscopically 25.9° (± 5.6°) and radiologically 28.2 ° (± 10.9°). The main difference of 2.3° between the endoscopic and radiologic assessment was not statistically significant (p = 0.23).

A small bulging of bone into the basal ST at the level of the anterior pillar of the RWM was identified in 5 cases (15.6%). However, we observed only minor narrowing of the ST width.

The fustis bone was identifiable in all specimens and was pneumatised inferiorly in 14 cases (43.8%). Concerning

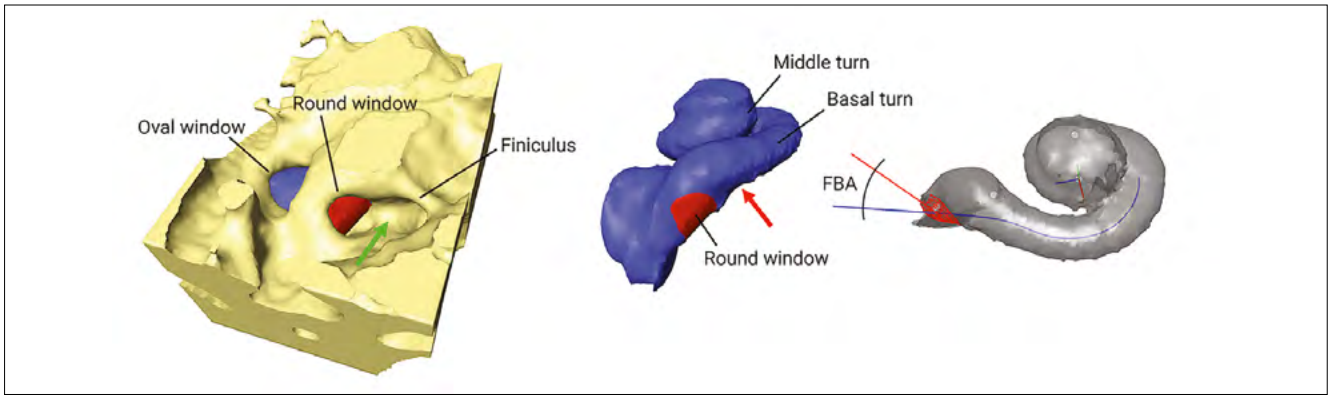


Fig. 3. *Three-dimensional model.* Three-dimensional model of a right cochlear hook region and the finestro-basal angle (FBA) measured as a normal vector to the round window membrane and the center of the basal scala tympani. The green arrows indicate the fustis, and the red arrow indicates a bony bulging into the scala tympani.

the direction of the fustis, we observed three kinds of configurations:

1. Horizontal: the fustis runs from the styloid prominence posteriorly to the anterior part of the RWM, directly pointing to the basal ST (n = 14; 43.8%).
2. Inferior: the fustis points inferior to the basal ST just anterior to the RWM (n = 12; 37.5%).
3. Fused: the fustis is fused to the bone of the area concamerata (n = 6; 18.7%).

The mean angle between the tangential vector of the fustis and the centre line of the ST was measured 155.4° (± 16.2°).

Discussion

This study describes refined surgical landmarks and relationships of the cochlear hook region from an endoscopic view. Previous descriptions of the round window niche and the cochlear hook anatomy showed abundant inter-individual anatomical variability. Su et al. dissected 549 temporal bones, measuring the transverse diameter of the round window membrane with a mean of 1.65 mm (range: 0.96-2.28) and the depth of the round window niche had a mean of 1.34 mm (range: 0.69-2.28), thus representing a large variability especially in terms of size of the analysed structures [11]. Tóth et al. investigated 783 temporal bones endoscopically and described the anatomical variability of the round window niche [12]. In the same line, abundant anatomical variability was recently published on a series of 23 temporal bones. The authors provide interesting measures such as the distance between the center of the oval window (OW) and the RW rim (1.50 mm, range: 1.11-2.24) or the distance between the anterior rim of the OW and the anterior rim of the RW (3.26 mm, range: 2.31-3.94) [1]. Another interesting publication observed 7.5% cases with basal turn constrictions [13]. Actually, in our dissection we also observed 15.6% of cases with minimal bulging of the hook region into the basal turn. However, we did not observe any obstruction of the ST.

In contrast to previous descriptions of the cochlear hook regions, where topographical relationships were expressed by measuring distances between landmarks, we aimed to add the angulation of the structures to the topographical description. Due to the panoramic views offered by the endoscope, the surgeon is able to understand the angles between middle ear landmarks (RWM or fustis) and the inner ear (BT). Knowledge about these relationships allows the surgeon to draw conclusions about the spatial orientation of the cochlear hook region. Therefore, the FBA was defined as the angle between the RWM and the basal ST. When comparing these values to a three-dimensional reconstruction of the cochlea from HRCT scans, a similar angle of 28° was observed, which indicates good reliability of endoscopically perceived angles. The same considerations apply for the angle between the fustis and the basal ST.

These topographical descriptions are particularly interesting in the context of minimally-invasive endoscopic skull base surgery. The first example to mention is the subcochlear approach [4]. This transcanal route is used to treat pathologies of the inferior petrous apex (e.g. cholesteatoma, cholesterol granuloma) conserving the ossicular chain and the cochlea, and therefore hearing. The cochlear hook region represents in this case the superior limit of the approach that is important for surgical access (14). The second application of the FBA in endoscopic lateral skull base surgery is the exclusive endoscopic transcanal transpromontorial approach to the IAC. This approach is used to remove small vestibular schwannomas in patients with unserviceable hearing [5]. The fustis and the BT are important landmarks as they indicate the inferior and posterior limit of the IAC fundus.

Marchioni et al. presented in 2015 an endoscopic classification of the round window niche and highlighted its anatomical aspects in 65 surgical cases [8]. In that study, the authors emphasised the utility of the endoscope to assess the round window niche. We could reproduce these results in all specimens. In 2016 Marchioni et al. described the anatomy of the fustis bone in greater detail [15]. They proposed a classification for the fustis as type A: pointing to the RWM and type B pointing anterior and inferior to the RWM in direction of the BT. This classification is equivalent to our investigations (type A = horizontal and type B = inferior). However, according to our observations, we suggest to add a third type of fustis configuration to the classification: namely, the fusion of the fustis to the area concamerata (type C = fused, compare Fig. 2A). Another interesting observation was the pneumatisation of the fustis bone in 44% of cases. This suggests that a cholesteatoma could spread inside and below the fustis bone. In these cases, an infracochlear approach should be adopted to completely remove the pathology. It would be interesting to know whether the fustis pneumatisation is related to the pneumatisation of the subtympanic sinus, which would have additional considerations in cholesteatoma surgery [15].

In our experience, the knowledge of the FBA also facilitates correct positioning of the CI array into the ST. This consideration may be the key clinical utility of the present investigation, as we would expect less injury to the basal spiral lamina and spiral ligament when inserting the array in a smooth way by respecting the natural direction of the ST. Steeper insertion angles may result in perforation of the spiral lamina and insertion of the array into the SV [1]. Lo et al. demonstrated in a guinea pig model the importance of the cochlear hook

region in minimising trauma during CI. They found either the RW or the cochleostomy approach to be suitable to avoid insertion trauma [17]. This consideration gains clinical importance if the visibility of the round window niche through a facial recess approach is limited [18 19]. Thus, knowledge of the FBA and direction of the fustis may serve as reliable landmarks for successful array implantation.

Conclusions

The fenestro-basal angle was 26° and the angle between the fustis and the basal ST was 155°. These measurements represent reliably identifiable topographical relationships during the endoscopic approach to the lateral skull base.

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Conflict of interest statement

None declared.

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CASE SERIES AND REPORTS

A case of external auditory canal osteoma complicated with cholesteatoma, mastoiditis, labyrinthitis and internal auditory canal pachymeningitis

Un caso di osteoma del condotto uditivo esterno complicato da colesteatoma, mastoidite, labirintite e pachimeningite del condotto uditivo interno

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SUMMARY

The association between external auditory canal osteoma and external auditory canal cholesteatoma is rare, with only a few reports in the current literature. Intracranial complications are very rare in the external auditory canal cholesteatoma, especially with direct propagation through the internal auditory canal. A case of 27-year-old male presenting with external auditory canal osteoma with secondary external auditory canal cholesteatoma is described. Progression of the disease created in turn a mastoiditis, labyrinthitis and pachymeningitis confined to the internal auditory canal. The patient was treated by a subtotal petrosectomy, without entering the internal auditory canal. A control MRI after 3 months showed reduction of the internal auditory canal enhancement.

KEY WORDS: Cholesteatoma • Osteoma • External auditory canal • Labyrinthitis • Pachymeningitis

RIASSUNTO

L'associazione tra osteoma del condotto uditivo esterno e colesteatoma del condotto uditivo esterno è rara, con soli pochi casi descritti in letteratura. Le complicanze intracraniche del colesteatoma del condotto uditivo esterno sono molto rare, specialmente con diretta propagazione attraverso il condotto uditivo interno. Descriviamo il caso di un uomo di 27 anni con colesteatoma del condotto uditivo esterno, secondario ad osteoma del condotto uditivo esterno. La patologia si è complicata con mastoidite, labirintite e pachimeningite confinata al condotto uditivo interno. Il paziente è stato trattato con petrosectomia subtotale, senza aprire il condotto uditivo interno. La RMN di controllo, 3 mesi dopo, mostrava una riduzione dell'enhancement del condotto uditivo interno.

PAROLE CHIAVE: *Colesteatoma • Osteoma • Condotto uditivo esterno • Labirintite • Pachimeningite*

Introduction

An osteoma involving the external auditory canal (EAC) has been estimated in 0.05% of patients requiring ear surgery [1]. The association between EAC osteoma and external auditory canal cholesteatoma (EACC) is rare, with only a few reports in the current literature [1]. EACC is the most common complication of EAC osteoma [2]. The most common complications of EACC, due to extension to the mastoid or middle ear, are facial palsy, ossicles erosion and labyrinthine fistula [3].

Otogenic brain abscess and meningitis may represent the intracranial complications of standard middle ear cholesteatoma [1], but they occur exceptionally in EACC, with only one case reported in the literature [1].

We describe the case of 27-year-old male presenting with EAC osteoma and secondary EACC, complicated with mastoiditis, labyrinthitis and internal auditory canal (IAC) pachymeningitis.

Clinical case

A 27-year-old male patient with a history of obstruction of the right EAC reported since he was 10 years old and progressive ipsilateral hearing loss, presented to another centre during summer 2015 with right sided otalgia,

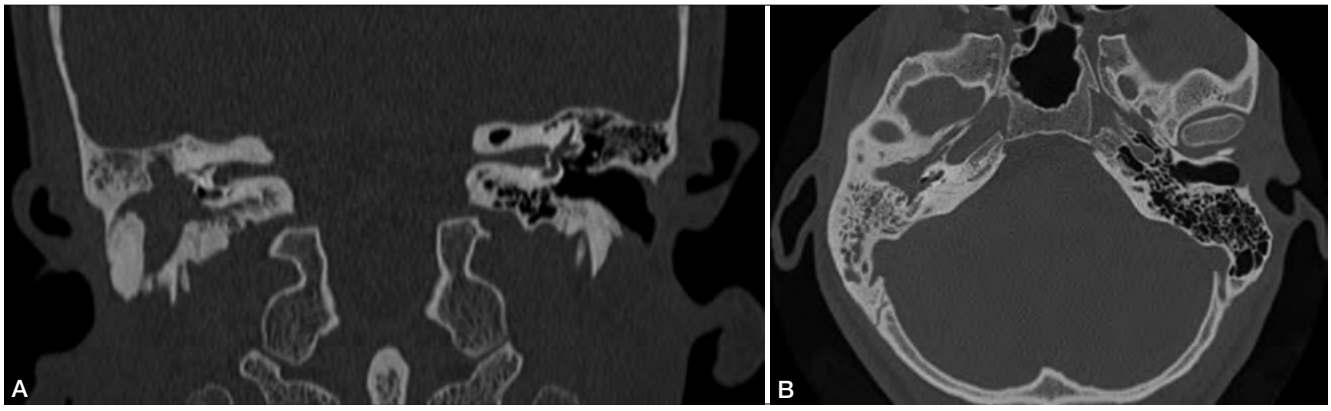

Fig. 1. CT scan with bone window; A) coronal view: a large bony mass obstructs the right external auditory canal. This latter and the middle ear are occupied by material with a soft tissue density. The floor of the external auditory canal is eroded as well as the promontorium, with a cochlear fistula confirmed by the presence of air bubbles into the cochlear lumen. B) axial view: the cochlear fistula is best visualised on axial scans.

post-auricolar pain and swelling. Clinical examination revealed complete obstruction of the right EAC by a solid mass. Tonal threshold audiometry showed right anacusis. He had neither facial paralysis nor neurological symptoms. A clinical diagnosis of acute mastoiditis was made.

CT imaging (Fig. 1A and B) showed a bony mass with a large base and obstructing the right EAC. EAC and middle ear were completely occupied by material with a soft tissue density as well as the mastoid cells. The floor of the EAC was eroded as well as the promontorium, with a cochlear fistula confirmed by the presence of air bubbles into the cochlear lumen. An initial ossification of the lateral semicircular canal was also visible. MRI showed enhancement of the vestibule and lateral semicircular canal extending to the all length of the IAC (Fig. 2). High resolution T2 images did not allow any visualisation of ipsilateral perilymphatic fluid, cerebrospinal fluid into the IAC, as well as the 7th and 8th nerve bundle.

The patient underwent a mastoidectomy to treat the emergency and then was referred to our centre. For unknown reasons, he came to our attention only after 1 year and 3 further episodes of mastoiditis, which were treated with antibiotics and external puncture. After the 3rd recurrence of mastoiditis in May 2016, he finally presented to the authors' department.

At that time, clinical examination confirmed complete obstruction of the EAC by a solid mass, combined with a retro-auricolar fistula in the area of the evacuation of the last mastoiditis. Facial nerve function was normal. Tonal threshold audiometry showed right anacusis.

A new radiological examination (CT and MRI) was planned.

Bone window CT showed the standard mastoidectomy outcomes. The other findings coincided with the previous examination with the addition of a complete ossification of the inner ear. (Fig. 3A and B).

MRI showed a significant reduction of the enhancement of the internal ear and IAC and the 7th and 8th nerve bundle was now partially visualised (Fig. 4A). Coronal and axial diffusion-weighted imaging (TSE DWI b1000 non-EPI) highlighted a focus with restricted diffusion (high signal) within the mass, a ra-

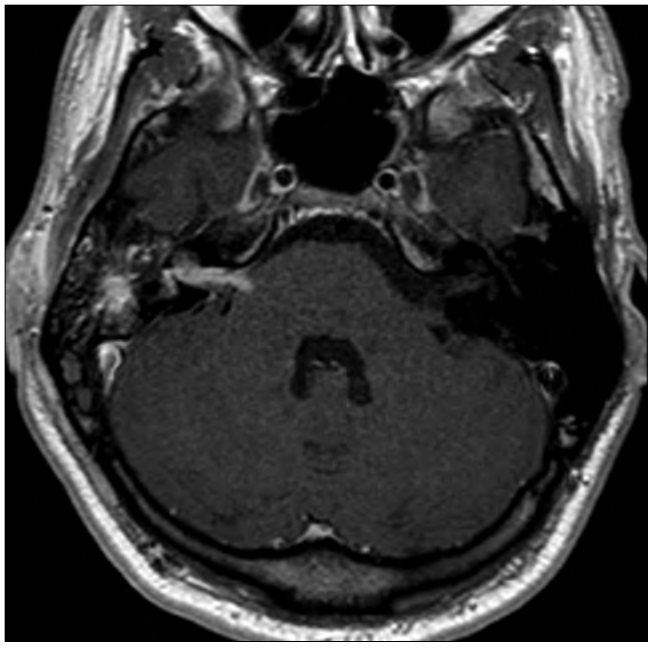

Fig. 2. MRI imaging, T1 sequence after gadolinium infusion, axial view: gadolinium enhancement of the antrum, vestibule and internal auditory canal.

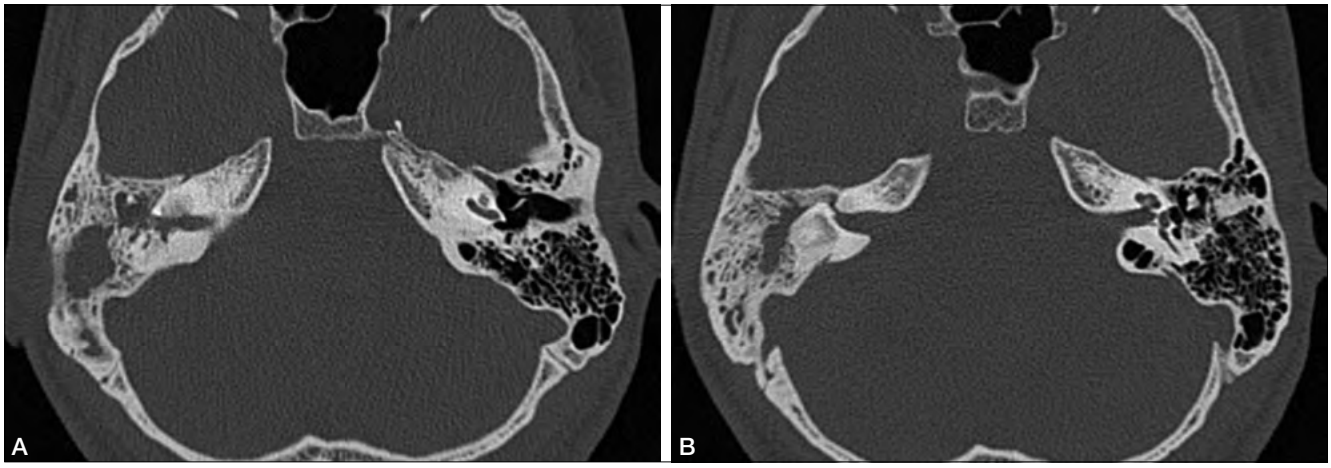

Fig. 3. CT scan with bone window after the first mastoidectomy; A) axial view: regular outcomes of the standard mastoidectomy; complete ossification of the cochlea; B) complete ossification of the vestibule and lateral semicircular canal.

diological finding strongly indicative for presence of cholesteatoma.

Due to the reduction of the IAC enhancement and the normal facial nerve function, it was decided to remove only the infection into the temporal bone by subtotal petrosectomy, leaving the IAC undisturbed. The surgical findings confirmed the presence of cholesteatoma in the EAC and middle ear, with inflammatory tissue in the site of previous mastoidectomy. Fibrous tissue was found to fill the cochlear fistula as well as the vestibule (after removal of the footplate). The resulting surgical cavity was filled with abdominal fat. The patient was placed under intravenous antibiotics and was discharged 3 days after surgery without complications. Three months later, a control MRI showed further reduction of the IAC enhancement (Fig. 4B). A new MRI has been scheduled in 6 months.

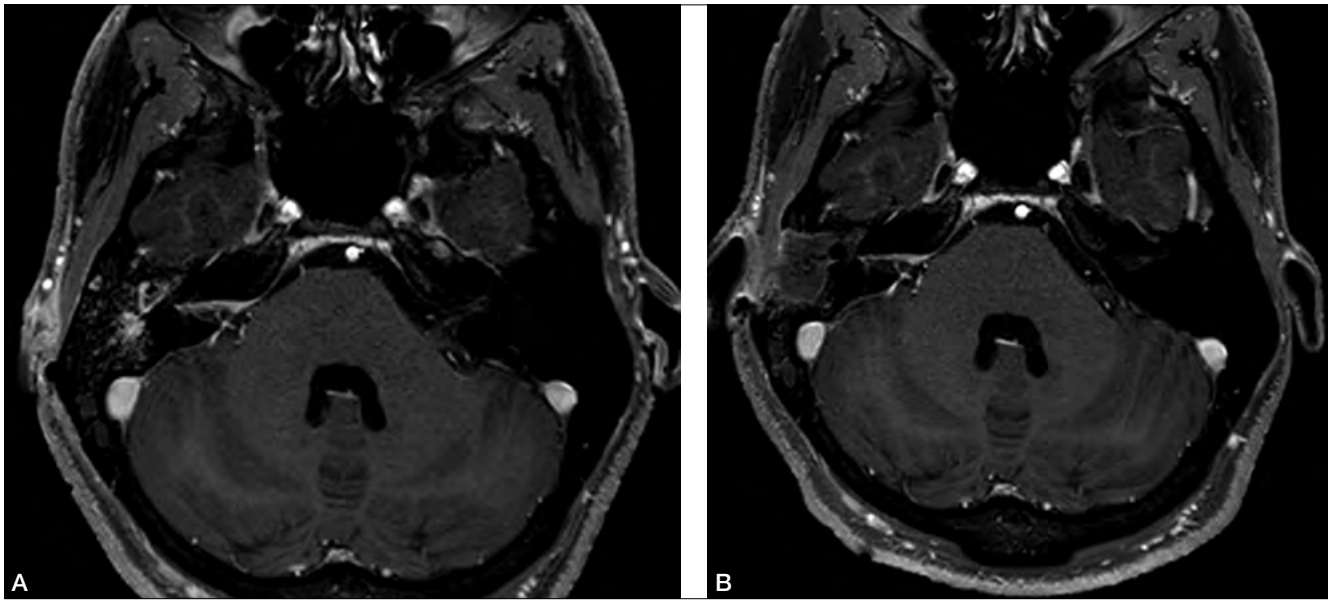

Fig. 4. MRI, T1 sequence after gadolinium infusion, axial view, before surgery: clear reduction of the enhancement of the internal auditory canal; no more enhancement is visible at the level of the inner ear; B) control MRI, T1 sequence after gadolinium infusion, axial view, 3 months after the surgery: external and middle ear are packed with fat tissue; further reduction of the enhancement of the internal auditory canal.

Discussion

Osteoma is a benign bony tumour that can be asymptomatic for many years. In the temporal bone, EAC is the most common site of osteoma, usually originating along the tympano-mastoid or tympano-squamous suture lines [3-5].

The main complication of EAC osteoma, even if rare, is secondary cholesteatoma [2], which is produced by lateral obstruction of EAC [6] with medial collection of squamous debris [7]. The bony erosion produced by the EACC may be accelerated by the concomitant chronic infection.

If left untreated, the cholesteatoma may grow medially, involving the middle ear and mastoid, even if in the literature, there are only 3 cases of EACC secondary to osteoma with mastoid invasion [1].

Progression of the disease may give rise to additional complications such as facial nerve involvement, labyrinthine fistula [3] and neck abscess [8].

Cochlear fistula and/or dead ear have not been reported as complications of EACC. Intracranial complications due to EACC secondary to osteoma are exceptional, with only one case in the English literature, namely a cerebellar abscess described in 2007 by Viswanatha [1] in a 12-year-old female.

Nowadays, at least in the western world, intracranial complications secondary to every type of cholesteatomas are relatively rare. Abscesses are usually located in the temporal lobe and/or cerebellum because the infection progresses through the osseous limits of temporal bone via osteitis and /or bone erosion [9]. Direct infective extension through the IAC is exceptionally rare, with only one case reported in the literature by Martinez et al. in 1999 [10]. The authors described the case of a 21-year-old man with congenital left sided deafness related to inner ear malformation, and a recent history of headache, left facial weakness and numbness. MRI showed a 1.5 cm ring enhancing mass involving the pons and the left middle cerebellar peduncle with enhancement also involving the left 7th and 8th nerve bundle, cochlea and vestibule. During surgical exploration through a retrosigmoid approach, biopsy of the 8th cranial nerve confirmed a bacterial neuritis in continuity with a posterior fossa abscess.

The present case showed a sequential occurrence of many rare complications in a case of EAC osteoma. The EAC occlusion produced an EACC (complicated by a mastoiditis) that in turn eroded the cochlea originating a labyrinthitis with direct extension of the inflammation to the IAC for what was diagnosed as a confined pachymeningitis.

The reduction of the IAC enhancement, shown in the 2nd MRI, reinforced the hypothesis of the inflammatory nature of the IAC process. Due to normal facial nerve function and prolonged absence of neurological symptoms, the possibility to limit the surgical intervention to the petrous bone was taken into consideration.

In fact, regression of the IAC enhancement was considered as a sign of an already "cold phase" of the inflammation in the IAC. The final phase of the inflammatory reaction was also confirmed by the progression of the ossification of the inner ear. In this situation, opening of the intradural spaces and connecting them with the main infection in the temporal bone should be discouraged, because it increases the risk of a new infective contamination. In addition, opening the IAC in presence of post-inflammatory scar tissue would put the facial nerve at high risk.

Removal of the main source of infection and periodical radiological control to monitor the progressive regression of the IAC pachymeningitis was considered the best treatment option. The first radiological control performed 3 months after the surgery corroborated the correctness of the surgical option, even if further evaluations will be required before considering the patient completely healed. In case of further increase of the IAC enhancement, exploration of the IAC could be performed through a now sterile route.

Conflict of interest statement

None declared.

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