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Contents

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Editorial

Editoriale

Acta Otorhinolaryngol Ital 2017;37:249

Dear readers, authors, and reviewers,

I would like to announce that on 1 June 2017, I became Editor-in-Chief of *Acta Otorhinolaryngologica Italica*, in accordance with the statutory provisions of the Italian Society of Otorhinolaryngology Head and Neck Surgery, which stipulate renewal of the editorial management of the journal every five years.

I am greatly honoured by this appointment, and firstly I should like to thank the President of the Society and the Governing Board for entrusting me with this prestigious duty. Secondly, I wish to pay tribute to the outstanding and efficient work carried out by my predecessor Professor Gaetano Paludetti, who gave a significant impetus to the journal, bringing its ranking to 21/43 among the ENT journals, and its impact factor to 1.53. Under his management, the contribution made by international authors increased, and today they represent some 25-30% of the submitted articles, coming from European, Asian, Latin American and African countries.

I am aware that the challenge I have taken up is a demanding one, and will call for great and unstinting commitment. Maintaining and improving today's standards is an arduous task. Globalisation, the burgeoning growth in novel ways of multimedia communication and the need to communicate the never-ending output of news in medicine with great rapidity, have led to a great deal of competitiveness between publishers, and have widened the range of possibilities for authors to choose from, when they are deciding where to publish the hard-won results of their work.

I and the incoming editorial staff will strive to continue on the road embarked upon by my predecessors to improve further promotion of the excellent research performed by the members of the Italian Society of Otorhinolaryngology Head and Neck Surgery. At the same time, we will encourage authors and researchers from abroad to submit their manuscripts and research.

Of course, for this we will streamline and enhance certain aspects of review process in order to speed up the time between submission and publication. Editorial staff will conduct evaluation of the submitted manuscripts within three working days; if the manuscript meets editorial criteria, it will be sent to the reviewers and the final decision will be communicated to the author within three months of submitting. We will endeavour to broaden the areas of interest of the journal, devoting space to those subjects which are of great interest (risk management, value medicine, etc.), but which are often less well-represented in the pages of other journals.

We will also renew and extend the members of scientific board in order to embrace the whole gamut of otorhinolaryngology and head and neck disease. We will benefit from an ongoing cross-fertilisation of ideas and suggestions thereby ensuring that *Acta Otorhinolaryngologica Italica* can keep pace with the stiff competition among scientific journals and make its own unique positive contribution, giving voice to the exciting innovations and original experiences generated in this challenging and stimulating field.

Sincerely,

Mohssen Ansarin
Editor-in-Chief Acta Otorhinolaryngologica Italica

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Review

The aetiopathologies of Ménière's disease: a contemporary review

L'eziopatogenesi della Sindrome di Ménière: stato dell'arte

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SUMMARY

Ménière's disease, a condition first described in the 1800's, has been an advancing area of clinical interest and scientific research in recent decades. Guidelines published by the American Academy of Otolaryngology – Head and Neck Surgery remained nearly static for almost 20 years, although we have certainly expanded our knowledge of the aetiology of the disease since that time. This review of the literature highlights the breadth and detail of the current theories in understanding the pathophysiology of this enigmatic disease. Histopathological specimens providing evidence of many of the aetiologies are presented as well. We aim to provide a centralised and updated resource regarding current and emerging theories for Ménière's disease.

KEY WORDS: Ménière's disease • Pathology • Aetiology • Update

RIASSUNTO

La Sindrome di Ménière, una condizione descritta nel 1800, è stata un'area di grande interesse clinico e di ricerca scientifica negli ultimi decenni. Le linee guida pubblicate dall' American Academy of Otolaryngology-Head and Neck Surgery sono rimaste pressoché invariate per quasi 20 anni, benché la ricerca scientifica sugli aspetti eziopatologici sia indubbiamente molto progredita nel frattempo. La presente revisione della letteratura evidenzia gli importanti progressi compiuti nella comprensione della fisiopatologia di questa malattia enigmatica. Le evidenze discusse sono inoltre accompagnate da una documentazione iconografica istopatologica. L'obiettivo della presente trattazione è fornire al lettore un quadro aggiornato ed accurato sulle teorie inerenti la Sindrome di Ménière.

PAROLE CHIAVE: *La Sindrome di Ménière • Patologia • Eziologia • Aggiornamento*

Acta Otorhinolaryngol Ital 2017;37:250-263

Introduction

Prosper Ménière brought the attention of vertigo and its possible relationship to the inner ear to light in his controversial paper presented in 1861 to the Imperial Academy of Medicine [1]. His series of articles challenged the existing theories of vertigo as a cerebral disease. The eventual development and acceptance of criteria used to describe the disease with Ménière's namesake has increased efforts in understanding the disease. The Committee on Hearing and Equilibrium of the American Academy of Otolaryngology – Head and Neck Surgery established diagnostic criteria and reporting guidelines for treatment. Their guidelines, published in 1995, define Ménière's disease (MD) as "an idiopathic syndrome of endolymphatic hydrops" [2]. This inner ear disorder is characterised by episodic vertigo with neurovegetative symptoms, sensorineural hearing loss, and tinnitus or aural fullness. Either tinnitus or aural fullness, or both, must be present in the affected ear. The Classification Committee of the Bárány Society (CCBS) has developed an international consensus for the diagnostic criteria for MD, released for publication in 2015. The new guidelines provide criteria for definite and probable MD, as seen in Table I [3].

As our knowledge regarding the aetiology of the disease expands, the controversy surrounding the pathophysiology of MD deepens. The debate is rooted in the histopathologic finding of endolymphatic hydrops (ELH). This significant step toward understanding the disease was based on the discovery of marked inflammation of the cochlear scala media in the temporal bones of patients with classic symptoms [4 5]. Although the certainty of ELH can only currently be identified post-mortem via temporal bone histopathology, our current guidelines provide the means to identify those who may suffer from the disease. The relapsing nature of the disease, and the sampling bias in prior studies, contributes to the varied rates of incidence and prevalence. Recognising these limitations, the incidence likely ranges between 10-150 per 100,000 persons. The most recent estimate of

Table I. Definitions of MD

Definition	Symptoms
Definite MD	• ≥ 2 definitive spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours • Audiometrically documented low- to medium-frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo • Fluctuating aural symptoms (hearing, tinnitus or aural fullness) in the affected ear • Not better accounted for by another vestibular diagnosis.
Probable MD	• Two or more episodes of vertigo or dizziness, each lasting 20 minutes to 24 hours • Fluctuating aural symptoms (hearing, tinnitus or aural fullness) in the affected ear • Not better accounted for by another vestibular diagnosis

prevalence in the United States is at 190 per 100,000. The prevalence increases markedly with increasing age [6-10].

This review of the literature highlights the breadth and detail of the current theories in understanding the pathophysiology of this enigmatic disease. We aim to provide a centralised and updated resource regarding current and emerging theories behind MD.

Materials and methods

Using the PubMed MEDLINE NCBI database, a total of 291 results were retrieved on December 8, 2013 by utilising the search query "Ménière's Disease." Inclusion criteria include: articles published within the last 5 years, English, full-text, and a journal impact factor of 1 or greater. Two hundred and twenty-three of the 291 total articles which had no direct relation to either disease aetiopathogenesis or histopathology were excluded. Of the remaining 68 articles, there were: 2 case reports, 2 theoretical research articles, 42 original research articles, and 22 review articles. Each publication was meticulously analysed for this comprehensive review. A few choice articles were selected due to further elaboration of the aetiopathogenesis after the original query was performed.

Discussion

Normal physiology of endolymph

Understanding the endolymphatic system physiology will permit a clearer elaboration of the various pathologic alterations described in the literature. The cochlea is a coiled, bony tube approximately 35 mm long and composed of three chambers: scala vestibuli, scala media, and scala tympani. Together, the scala vestibuli and the scala tympani are part of a perilymph-filled periotic labyrinth encased in the bony labyrinth. The scala vestibuli and scala tympani are connected at the apex of the cochlea via the helicotrema. The scala tympani connects to the cerebrospinal fluid containing arachnoid space via the cochlear aqueduct.

The membranous labyrinth of the cochlea is the scala media, the endolymphatic containing chamber. It is connected to the saccule by the ductus reuniens. The remainder of the membranous labyrinth consists of the semicircular canals, saccule, utricle, endolymphatic duct and sac, and cochlear duct. The utricle is located in the posterosuperior portion of the vestibule. The saccule is located in the anteroinferior portion of the vestibule. The utricle connects posteriorly to the semicircular canals. Anteriorly it connects to the endolymphatic and saccular ducts via the utricular duct. The utricular valve likely serves to protect the superior part of the labyrinth against endolymph loss due to membrane rupture from the inferior part of the labyrinth (Fig. 1) [11].

The endolymphatic sac is one of the first structures of the membranous labyrinth to appear in embryonic development, and it is the last to stop growing [12]. It is closely associated with the layers of dura mater. The sac is connected to the endolymphatic duct, which lies within the bony vestibular aqueduct. The endolymphatic sac can be divided into portions based upon the cellular lining. The proximal, rugose portion is in a bony niche and has cells similar to the endolymphatic duct. The intermediate portion is between bone and dura and has light and dark cylindrical cells. The distal, smooth portion is within lay-

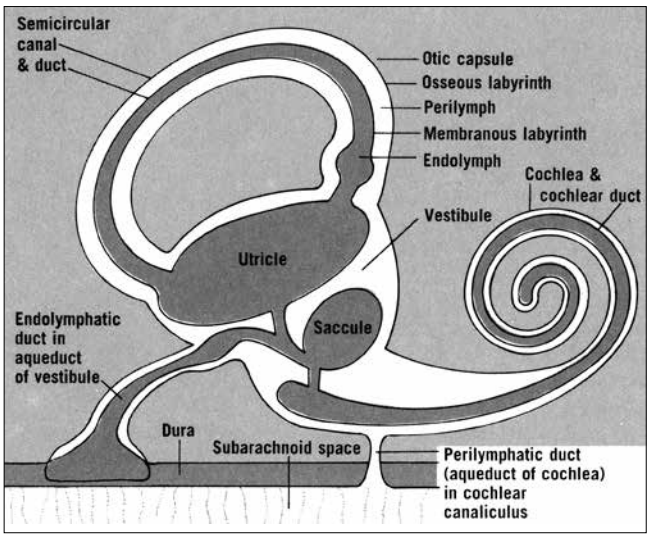

Fig. 1. Anatomy of the endolymph system. Used with permission from Rand S. Swenson. O'Rahilly R, Mueller F, Carpenter S, Swenson RS. Basic Human Anatomy: A Regional Study of Human Structure. 2009; http://www.dartmouth.edu/~humananatomy/figures/chapter_44/44-8.HTM. Accessed December, 24, 2014.

Table II. Functions of the endolymphatic sac.

- Resorption of the water content of endolymph
- Participate in some ionic exchanges with endolymph
- Remove metabolic and cellular debris, including otoconia
- Immunodefense
- Inactivation and removal of viruses
- Secretion of glycoproteins to attract extra fluid
- Secretion of saccin to increase production of endolymph

ers of dura mater and consists of cuboidal cells [13]. In 1997, Gibson and Arenberg described the likely functions of the endolymphatic sac (Table II) [13].

The endolymphatic sac's role in endolymph homeostasis is well recognised, but the control mechanisms are still being established. The composition of the fluid is maintained by ion transport systems [14]. It is unclear as of yet where the sensor might be for maintaining the volume of the scala media, and if it is even in the cochlea. Endolymph is unique to other extracellular fluids in that it has a high potassium, low sodium and low calcium concentrations (Table III) [15 16]. The high potassium concentration and low calcium concentration are critical for sensory conduction in the cochlea [15].

The ion transport system is mostly well established, with a few remaining concepts under debate. In general, potassium in endolymph is driven by the endocochlear potential into sensory hair cells via apical transduction channels. Basolateral potassium channels carry it out into the perilymph. From there, potassium is taken up by fibrocytes of the spiral ligament where it diffuses into strial intermediate cells. These cells, and potentially other potassium channels, release potassium into the intrastrial space where it is taken up by strial marginal cells and secreted out of the stria vascularis and into endolymph [15].

Interestingly, in a euvolemic state the endolymph is maintained without significantly detectable volume flow. However, in abnormal volume states the direction of volume flow may contribute to endolymph homeostasis. Salt has shown that an enlarged endolymphatic space will result in endolymph flow toward the base of the cochlea, contributing to the removal of volume and electrolytes. Contrary to this, in hypovolemic states, the flow is apically oriented in the cochlea, leading to increased volume and electrolytes in the endolymph [17].

Aetiopathologies

A variety of pathologic findings have been identified during the course of MD. Perhaps the most established is the finding of endolymphatic hydrops. This histologic finding was first reported by Hallpike and Cairns in 1938 as well as Yamakawa who demonstrated this pathologic finding in the same time period [4]. Since then, many reports have been described about the histopathologic findings in MD. We present the most updated comprehensive list in at least the past 10 years. Figure 2 provides a concise look at the relationships between the most recent pathologic mechanisms for MD.

Endolymphatic hydrops (ELH)

The mechanism for clinical manifestation of MD secondary to endolymphatic hydrops was led by Schuknecht's theory of Reissner membrane rupture secondary to endolymphatic duct distention. This would have allowed for potassium rich endolymph to bathe the basal surface of hair cells as well as the eighth cranial nerve. Repeated hair cell and nerve exposure to potentially toxic levels of potassium-infused perilymph could cause episodic vertigo as well as long-term decline in auditory and vestibular function (Fig. 3a) [18]. The rupture theory eventually stimulated new ideas about endolymphatic flow and blocka-

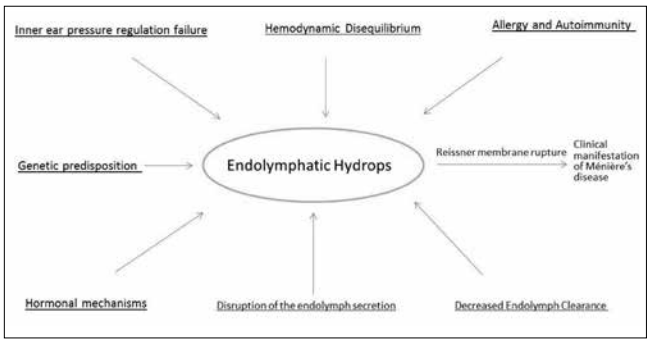

Fig. 2. Aetiologies of endolymphatic hydrops.

Table III. Composition of cochlear fluids.

Component	Unit	Endolymph scala media	Intrastrial fluid	Perilymph scala vestibuli	Perilymph scala tympani	Plasma
Na^+	mM	1.3	85	141	148	145
K^+	mM	157	2	6.0	4.2	5.0
Ca^{2+}	mM	0.023	0.8	0.6	1.3	2.6
Cl^-	mM	132	55	121	119	106
HCO_3^-	mM	31	n/a	18	21	18
Glucose	mM	0.6	n/a	3.8	3.6	8.3
pH	pH units	7.4	n/a	7.3	7.3	7.3
Protein	mg dl	38	n/a	242	178	4238

ge along the endolymphatic duct pathway as a potential cause for hydrops. Prevalence of endolymphatic hydrops in MD is reported as 100% in the cochlea, 86.3% in the saccule, 50% in the utricle and 36.4% in the semicircular canals (Fig. 3b) [19]. However, one of our histopathologic exams interestingly showed spared cochlear involvement in a patient with MD (Fig. 3c). Earlier studies showed that in the late stages of MD, there might be severe dilatation or collapse of the ampullary walls, which could be restricted with the cupular movement, resulting in a poor caloric response [20]; caloric response is reduced in about 65% of patients with MD (Fig. 3d) [21].

Saccular hydrops may be dependent upon the degree of membrane distention toward the stapes footplate; cochlear hydrops is seen as bowing of Reissner's membrane into the scala vestibuli (Fig. 4 a, b) [18]. The saccule is the second most common site of hydrops; severe hydrops is most frequently in the saccule.

Reports have also been made regarding displacement of the basilar membrane in the apical segments of the cochlea, to the degree that the basilar membrane contacts the bony wall of the scala tympani. This too may further explain the variable degree to which hydrops is seen in different areas of the same temporal bone specimen [22].

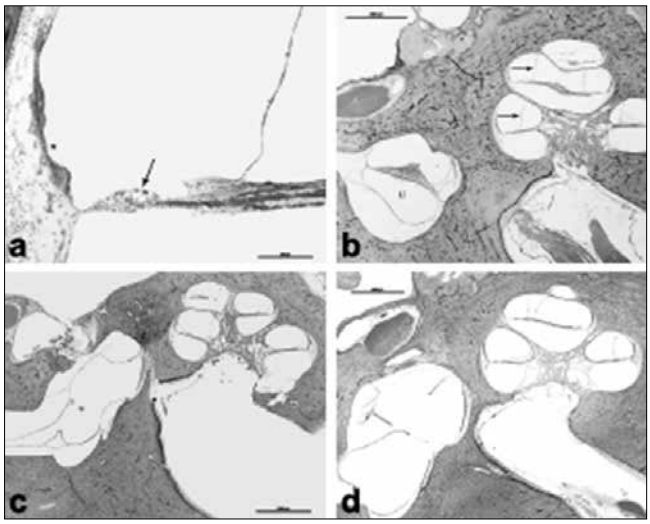

Fig. 3. **a)** HB 655 Lt 130 10x: A higher magnification of the cochlea showed outer hair cell loss (arrow) and stria vascularis atrophy (*), **b)** HB 655 Lt 100 1x: 72-year-old male patient diagnosed with Ménière's disease. He had a history of bilateral fluctuating hearing loss, tinnitus and vertigo episodes. Histopathologic exam of the left ear showed profound cochlear hydrops (arrow). Utricle (U), **c)** HB650Lt110. This 79-year-old patient had a history of bilateral profound mixed type hearing loss and left stapedectomy. She was extremely vertiginous right after the surgery for months. Histopathologic exam showed bilateral otosclerosis, which is located anterior to the oval window. This slide shows the surgery site, otosclerosis and hydropic saccular membrane that showed healed perforation. Interestingly, cochlea did not show any hydropic changes, **d)** HB593Lt 470. This was an 86-year-old patient who had a history of Ménière's disease and 8th nerve resection. Histopathologic exam showed profound hydropic changes in the cochlea, utricle and saccule. Note the outpouching, and hydropic saccular membrane.

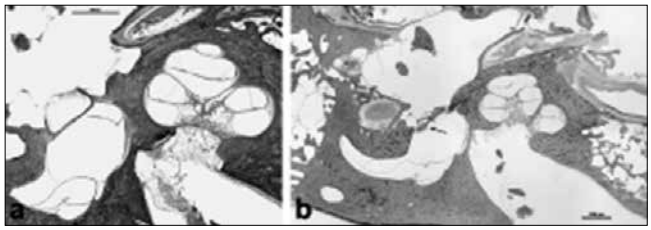

Fig. 4. a) HB333Lt 142. This was a 79-year-old patient who had a history of bilateral Ménière's disease. Histopathologic exam shows profound cochlea-saccular hydrops. Note that saccular membrane shows fistulae and touches to the footplate of stapes, **b)** HB839 Lt 260 1x: This 86-year-old male patient was diagnosed with left Ménière's disease. Histopathologic exam of his left ear showed profound hydrops in every turns of the cochlea as well saccule. Arrow shows that saccular membrane touches the footplate of stapes.

Salt applies the theory that abnormal volume states in ELH are detected by small changes in volume when pressure changes are minimal. The endolymphatic sinus, located between the saccule and the utriculoendolymphatic valve at the entrance to the endolymphatic duct, may be able to detect small mechanical pressure changes. For example, as pressure is applied to perilymph, the endolymphatic duct is occluded; this is presumably secondary to displacement of endolymph from the sinus to the endolymphatic sac, thereby allowing the sinus membrane to occlude endolymphatic duct opening [22 23]. As of yet, there is no definitive theory for what is causing the pressure fluctuations.

Decreased endolymph clearance

a. Endolymphatic sac (ES)

Just as there are multiple theories regarding the pathogenesis for ELH, many other potential aetiopathologies have been introduced for MD. Observations of changes and dysfunction in the ES may contribute to this disease process. Theories for this dysfunction developed around the ES's role in endolymph regulation, embryologic abnormalities, immune mediator effects on the ES, and hormonal mechanisms.

Hornibrook et al. favour that in states of endolymph excess, such as MD, the ES removes endolymph by longitudinal flow. They note that the ES contains absorptive and secretory cells, suggesting that hydrophilic glycoproteins produced by the secretory cells are stimulated in this state of excess [24]. Paparella et al. suggested that patients may have an underlying predisposition to MD in the setting of developmental anomalies of the ES, such as hypoplasia [25]. However, the leading theory at that time was the endolymphatic flow concept which newer research has brought into question, as aforementioned. A 2009 study showed that the ES may play a role in endolymph

pressure regulation. The use of systemic isoproterenol, a β-adrenergic agonist, increased endolymph pressure and decreased the ES lumen potential. The CSF pressure was not affected by the systemic agent. When ablating the ES, the effects of isoproterenol on endolymph pressure and ES lumen potential were suppressed. This suggests that the ES plays a role in pressure regulation [22]. As we identify which components of the ear play a role in endolymph homeostasis, particularly those under hormonal control, we will also need to clarify how these systems are interrelated. The ES is generally accepted to play a role in endolymph volume regulation, although the exact sensor location is not clear. Given the location of the sac, near the pulsations of the sigmoid sinus, Salt proposes that it may not be as well suited to monitor pressure changes [22]. He supports this by pointing out that the ES is not bounded by perilymph, the endolymphatic duct restricts access of perilymph to the periphery of the sac, and the detection of hydrops likely requires the detection of small changes in endolymph pressure with respect to perilymph. Instead, the endolymphatic sinus, discussed later, may be the more likely candidate [22].

The role of the ES as an immune mediator for the middle ear presents another fashion by which MD could be provoked. Details of the immunologic factors involving the ES will be discussed later, but a brief background is warranted. Immunoglobulins (Ig) G, IgM, and IgA, as well as secretory components of the immune system have been found in the ES. Additionally, macrophages and plasma cells reside in the perisaccular connective tissue [26 27]. The ES can process antigen and produce its own antibody response, but the overall role of this in inner ear immune response is not fully elucidated. Surgical destruction of the ES has been shown to result in locally decreased antigen and antibody responses [26 27]. Currently, one proposed mechanism is access of immune complexes, mast cells, and viral antigens into the highly vascular subepithelial space via the fenestrated vasculature [26 27]. Immune complex access to this otherwise barrier protected region is thought to be via the many fenestrated branches of the posterior meningeal artery which help supply the ES and the endolymphatic duct [26 27]. This will be discussed later along with a review of mast cell degranulation in the perisaccular connective tissue and viral antigen-allergic reaction with T-cell homing to the ES.

Investigations of immune-mediated dysfunction of the ES started in 1979 when McCabe described patients with sensorineural hearing loss (SNHL) who benefited from corticosteroids and cyclophosphamide. By the 1990's, Bloch et al. had purified an antibody seen in 35% of patients with progressive SNHL; this antibody targeted heat shock protein 70 (HSP70) [24]. The question arose as to whether there was any overlap in subjects with progressive SNHL and MD. After multiple follow-up studies, there has been no correlation between HSP70 antibodies and MD. The question remains about an autoimmune component for the disease, but certainly HSP70 antibodies are not causative agents in MD.

In the setting of ELH, models studied by surgical ablation of the endolymphatic duct and sac were performed in guinea pigs. The most obvious limitation to this study is that the ES is completely non-functional, which does not seem to be reflective of the ES in MD [22]. One study circumvented this limitation while examining the effect of aldosterone on hydrops. The distal portion of the ES was detached from the sigmoid sinus while leaving the intraosseous portion alone. This study was able to demonstrate that even partial sac ablation can cause hydrops. Aldosterone and its effect on sodium-potassium adenosine triphosphatase (Na-K ATPase) levels in stria vascularis as well as the potential enhanced secretion of potassium into endolymph are discussed in the *Hormone* section [22].

b. Endolymphatic duct (ED)

The ED lies within the bony vestibular aqueduct. A recent histologic study of the otic capsule evaluated the cellular appearances of the normal vestibular arch, and with that, a theory of how the canals in the otic capsule may contribute to the homeostasis of the ED. It appears that lamellar bone contributes to the foundation of the otic capsule. Many Volkmann's canals and micro-Volkmann's canals are present as channels throughout the bone in the vestibular arch. Osteoblasts likely line the mature vestibular arches, as the arch is derived from osteogenic cells of the external layer of the otic capsule [28]. The development of the otic capsule skeleton is activated by signalling molecules from the nearby epithelium, including that of the ED [28]. Michaels et al. suggest this close relationship may result in osteoblast proliferation and consequent microcanalisation throughout life. They propose that the slow breakdown of

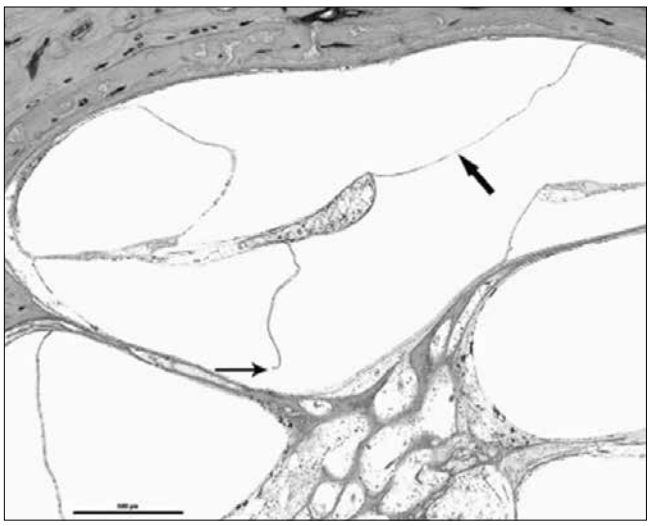

Fig. 5. HB839 Lt 260 4x: A higher magnification of the cochlear hydrops is seen. Thick arrow shows profound hydrops; thin arrow indicates the rupture of Reissner's membrane.

proliferated osteoblasts, via apoptotic mechanisms, may nourish the nearby endolymph with potassium ions [28].
The ED has also been implicated in theories of endolymph obstruction as aforementioned, and in particular, Schuknecht's theory of Reissner membrane rupture secondary to ED distention, allowing for potassium rich endolymph to bathe the basal surface of hair cells as well as the eighth cranial nerve (Fig. 5) [18].
Additionally, the ED may play a role in the effect of spiral ligament fibrocytes on ELH. ED obstruction is thought to alter the cytochemistry of the perilymph, by a yet unknown mechanism, leading to cellular stress of the spiral ligament fibrocytes. These fibrocytes, in turn, disrupt the potassium recycling mechanism within the scala media, resulting in an osmotic imbalance and expansion of endolymphatic compartment [29].

c. Endolymphatic sinus
The potential role of the endolymphatic sinus was briefly discussed during our review of ELH. The endolymphatic sinus may assist in endolymph volume regulation by detecting minute changes in endolymph pressure with respect to perilymph. The walls of the sinus are distensible, and given the position of the sinus at the entrance to the ED, it would be ideally placed to monitor pressure changes. Prior studies showing ED occlusion with increased pressure in the perilymph suggests the endolymph is displacing the sinus walls into the ES, thereby occluding the duct opening [22]. Additionally, the amount of endolymph being displaced into the ES may depend upon the degree of distention of the sinus, adding yet another means of volume control for the endolymphatic sinus [22].
The projected role of the sinus may be compatible within the controversial theories of longitudinal flow and ion transport regulation of endolymph. Further research will need to be done to elucidate such details. One prominent theory is that under exceptional circumstances, in situations with large volume increase, endolymph will move longitudinally toward to the ES to be resorbed. In such situations, the rate of longitudinal flow would be limited by the narrow isthmus of the ED, and the endolymphatic sinus may act as a reservoir [30]. In situations where the sinus has an overflow state, or blocks the entrance to the ED, the utriculoendolymphatic valve may be affected.

d. Utriculoendolymphatic valve (UEV)
The exact purpose of the UEV, or Bast's valve, remains unclear. One theory is that it anatomically acts as a shutter, allowing for excessive volumes of endolymph to be processed in the ES, in a fashion regulated by unknown means as of yet. It would simultaneously prevent an excessive loss of endolymph, consequently leading to membrane distortions and interference of vestibular sense organs [30 31]. It is uncertain if the UEV is open or closed in normal situations, or situations without volume excess of endolymph. Additionally, the mechanisms which open and close the valve are not yet elucidated [31]. The UEV has been observed to be open for a few days once ELH develops, then closes due to compression from increasing hydrops [32]. A more recent evaluation of the UEV in a temporal bone series did not show significance between closure of the valve in MD patients and normal ears [33]. Shimizu et al. suggested that the position of the UEV in temporal bones does not directly reflect the pathologic condition of MD [33].

e. Ductus reuniens (DR)
The DR (reuniting duct) is a membranous path between the saccule and cochlea. Blockage of this usually patent pathway can be caused by ELH. The longitudinal flow of endolymph was shown to be blocked most frequently, between 59-67%, at the DR as determined by two case series [34 35]. These series evaluated the bony saccular orifice to the bony groove of the DR utilising computed tomography. The mechanism of obstruction at the DR needs further elucidation, but one report from Gussen et al. shows that otoconia traveled from the saccule, fell into the DR, and then migrated further to the cochlea [36]. If the cochlear endolymphatic pressure builds to a critical point, the material blocking the DR can be washed into the sacculus, resulting in a classic vertiginous attack characteristic of MD. Given the relative reported frequency of DR obstruction, pathology at the level of the DR likely contributes to the aetiology of MD.

f. Vestibular arch
Within the inner layer of the bony vestibular aqueduct lies the vestibular arch, a cylindrical lining of thin, osseous cells extending into the posteromedial aspect of the vestibule. It closely envelops the ED in an arch-like fashion and surrounds it throughout most of its length. A striking loss of these cells was previously observed in 20 cases of MD, together with the apparent new formation of large intraskeletal channels [37]. Additional studies have revealed associated degenerative changes with apoptotic bodies and denudation of osteoblasts throughout both the microcanals and Volkmann's canals in the vestibular arch. Dislocation of dead microcanals into blood vessels of Volkmann's canals has also been described in some MD patients. Collectively, these findings suggest that the origin of ELH could potentially be localised to a pathologic lesion located at the vestibular arch [28].

g. Semicircular canals
Recently, a proposed theory by Phillips and Prinsley described the presence of free floating particle (FFP) deposits distal to the semicircular canals at five different sites within the labyrinth as a potential source of aberrations in vestibular function seen in Ménière's patients. These changes would result in disturbances of balance and he-

aring, depending on the quantity and size of the floating particulate matter. Progressive damage would initially be reversible but would ultimately result in irreversible harm to the auditory and vestibular apparatus. The role of mineral intake may have an effect on the composition of these FFPs; it may be that the mineral composition of endolymphatic fluid is critical with respect to thresholds for crystallisation. Becvarovski coined the term "ductolithiasis" to describe these phenomena, and the associated histopathological findings of ELH in the temporal bones of Ménière's patients may simply be the consequence of FFP matter [38]. This theory is certainly reasonable, but unable to be verified at this time.

The clinical setting of MD can be clouded when patients have associated disorders such as benign paroxysmal positional vertigo (BPPV). Recent literature suggests a possible correlation between the two disorders, and it has been hypothesised that the pathophysiology of one disease may lead to the other. Although many authors support the idea that BPPV can be secondary to MD, some suggest that MD secondary to BPPV is also a possibility. The mechanism by which this may occur is thought to be due to loose otoconia decreasing endolymphatic absorption, resulting in endolymphatic hydrops [39].

Disruption of the endolymph secretion

Another model which attempted to explain ELH by means of disruption of the endolymph secretion in the cochlea and resorption of endolymph in the ES has been disproven. This theory was introduced as a result of iatrogenically introducing the effect of endolymphatic flow when a large volume of marker was injected into endolymphatic space. The homeostasis of endolymph seems more dependent upon ion transport and osmotic gradients than volume secretion. These ion transport systems have been shown to be under the regulation of hormonal mechanisms, which will be discussed later [22].

Hormonal mechanisms

Various hormones have been associated with effects on endolymph homeostasis. Based upon our recent literature review, a few key hormonal influences have associations with the pathophysiology of MD. Specifically, we review antidiuretic hormone, the aquaporin system, ion channels, epinephrine and aldosterone.

A correlation between antidiuretic hormone (ADH, vasopressin) and the exacerbation of MD has often been proposed. ADH works on the vasopressin-2 receptors (V2R) to activate aquaporin-2 channels, which in turn moves water from the tubular lumen of the renal collecting duct into the cell, regulating body fluid homeostasis and maintaining systemic osmotic pressure. Endolymphatic homeostasis appears to be related to ADH although the exact mechanism remains unclear; when there is no change in plasma osmolality, the predominant theory is that inner ear pressure plays a role in controlling plasma ADH release. ADH may suppress water reabsorption in the ES, leading to ELH [40 41]. However, recent follow-up studies investigating serum concentrations of ADH in MD patients have been inconclusive. Lim and colleagues found no significant correlation of serum ADH levels with unilateral disease [42]. One proposed reason for this contrasting evidence is the variable accuracy of measuring plasma versus serum ADH. Aoki and colleagues showed that during a Ménière's attack there was a significant increase in ADH concentration [40]. Interestingly, both nausea and emesis are stimuli for ADH and often accompany an attack [40].

In conjunction with ADH, the aquaporin system presents a feasible means for the development and manifestation of MD from the vantage point of a hormonal fluid balance disorder. These ubiquitous transmembrane channels that actively move water and other solutes through cell membranes within the kidneys, brain and lungs could be involved in the ES as well. Within the inner ear, aquaporin-2 receptors, the only humorally controlled aquaporin, have been found with high concentrations in human ESs [43]. Kitahara and colleagues have also shown that V2R mRNA expression in the ES is up-regulated in MD and clearly distributed together with aquaporin-2 in the luminal epithelium of the human ES. This V2R overexpression in the ES could attenuate the membrane turnover and cause the endolymphatic fluid overflow into the endolymphatic space after even a small increase in plasma vasopressin. V2R and subsequent cyclic AMP-linked signalling could suppress the endolymphatic fluid absorption in the ES, resulting in the inner ear hydrops [44]. Other aquaporin channels have been identified in the ear, including aquaporin-1 in most of the inner ear, aquaporin-3 in the epithelium of the ELS, aquaporin-4 in the supporting cells of the cochlea and vestibular end organs, aquaporin-5 in the organ of Corti and Reissner membrane and aquaporin-6 in the epithelium of the ELS [45].

In addition to the ADH-aquaporin system, voltage and non-voltage dependent ion channels play a crucial role in the regulation of the endolymphatic fluid composition, and more importantly, in the regulation of the endocochlear potential. Potassium plays an integral role in the generation and maintenance of the endocochlear potential. Its recirculation through the supporting cells of the organ of corti, the fibrocytes of the spiral ligament and the marginal cells of the stria vascularis, known as the potassium cycle, maintains the endocochlear potential [46]. This cycle involves an active and passive transport of potassium via ionic channels, gap junction (connexins) and tight junctions.

Animal model studies using systemic dosing of aldosterone have shown an elevation of Na-K ATPase levels in the stria vascularis [47]. Speculation suggested an enhanced secretion of potassium into endolymph would increase the rate of endolymph production, thereby creating volume

excess in the partially impaired endolymphatic sac. Additional investigations into the genes KCNE1 and KCNE3, two voltage-gated potassium channels expressed in the inner ear, have been studied in MD patients. Doi et al. found that single nucleotide polymorphisms (SNPs) in KCNE1 and KCNE3 are associated with MD in the Japanese population, whereas Campbell et al. found no association in the Caucasian population and could not duplicate the Doi et al. results [48] [49]. A subsequent study evaluating the influence of epinephrine, a known modulator of potassium secretion by marginal cells, on endolymph in the cochlea and sac revealed an increase in the dilation of the intraosseous portion of the sac in the hydrops model [50] [51]. A disturbance in the function of any of these channels or associated electrolytes may result in alterations of the endocochlear potential and subsequent auditory dysfunction. Calcium channel blockers have been explored in the treatment for MD by Teggi et al. Use of cinnarizine improved cochlear and vestibular symptoms, likely due to its inhibition of potassium currents rather than blocking voltage-gated calcium currents [52].

Treatment with intratympanic lipopolysaccharide (LPS) combined with systemic aldosterone in mice has been shown to induce ELH. This study left the ES undisturbed, unlike prior models. LPS causes a non-infectious immune response in the ear. The degree of hydrops in the cochlea was shown to be similar for an LPS alone group and an LPS plus systemic aldosterone group. However, the ES was more dilated in the LPS plus aldosterone group and the sac lumen was partially collapsed [53]. Using the same model, the effect of epinephrine on endolymph in the cochlea and sac has been evaluated. Epinephrine increased the dilation of the intraosseous portion of the sac in the hydropic model [22] [50]. Since potassium secretion in strial marginal cells can be modulated by epinephrine, ongoing investigation with this mouse model is being used to evaluate the influence of different transport processes [22] [51].

Hemodynamic disequilibrium

a. Dysfunctional cochlear blood flow

Evidence from research on animal models suggests the pathophysiology in MD is closely associated with dysfunctional cochlear blood flow (CoBF). Miller demonstrated that the magnitude of an evoked CoBF response was reduced by approximately one-third in hydropic ears compared to normal ears [54]. Brechtelsbauer reported reduced autoregulation of CoBF in guinea pigs with ELH [55]. Andrews revealed that that increased blood viscosity can result in inner ear dysfunction with symptoms of hearing loss, tinnitus and vertigo [56]. Radiological MR imaging has also confirmed the presence of an intense contrast effect in ears with hydrops, indicating that the blood–labyrinth barrier is impaired in ears with MD [57]. However, the evidence is not consistent. For example, Larsen found no change in regional or total cochlear blood flow in hydropic ears [58]. CoBF measurement in patients with MD and control groups has shown no statistically significant difference with respect to CoBF amplitudes [59]. Resolving the issue of whether microcirculation and ear hydrops are correlated rests on the development and advancement of means to measure blood flow in the cochlea.

An emerging area of research for endolymphatic hydrops is at the level of the venous drainage of the inner ear. Filipo et al. evaluated patients to determine if cerebrospinal venous abnormalities were associated with MD patients. If there is an increase in arterial pressure at the inner ear microcirculation, theory suggests an increase in endolymph pressure would occur if the venous outflow were impaired [60]. Filipo's study assumes that radial resorption of endolymph drains into cochlear and vestibular aqueduct veins and that impaired outflow would not permit physiologic endolymphatic drainage. This recent study suggests MD patients have a significantly higher rate of chronic venous insufficiency in the head and neck compared to controls [60].

Allergy and autoimmunity

a. Allergy mechanisms

Since 1923, inhalant and food allergies have been linked with MD symptoms, and many studies have addressed the difficulties in confirming a relationship between allergy and MD [27]. Studies by Derebery and Berliner have shown that 59.2 and 40.3% of patients with MD, respectively, have confirmed or suspected airborne and food allergies [61]. Three mechanisms have been described which explore the role of allergic reactions in MD. First, the ES itself could be a target organ of the allergic reaction. The sac's peripheral and fenestrated blood vessels could allow antigen entry, stimulating mast cell degranulation in the perisaccular connective tissue. The resulting inflammatory mediator release could affect the sac's filtering capability, resulting in a toxic accumulation of metabolic products, and interfering with hair cell function. Also, the fenestrated blood vessels to the ES could be pharmacologically vulnerable to the effects of vasoactive mediators such as histamine, which are released in a distal allergic reaction [26]. A second possible mechanism involves the production of a circulating immune complex, such as a food antigen, which is then deposited through the fenestrated blood vessels of the ES, producing inflammation. A third possible mechanism is a viral antigen-allergic interaction. A predisposing viral upper respiratory infection in childhood (e.g., mumps, herpes) antigenically stimulates Waldeyer's ring, with subsequent T-cell homing to the ES, resulting in a chronic low-grade inflammation [61].

In clinical practice, it is well known that MD patients frequently complain of gastrointestinal tract symptoms such as diarrhoea, abdominal pain, dyspepsia, and weight fluctuation; however, this observation is hidden by the

importance of otological manifestations (hypacusis and vertigo). Multiple studies have reported that wheat is the most common food allergen found in patients with MD, up to 68.2% of patients, and the presence of late skin reactions to gliadin in MD suggests a potential relationship between the immune response to wheat proteins and MD symptoms [62].

b. Autoimmune mechanisms

The concept of an autoimmune aetiology of inner ear disease was first introduced more than 30 years ago, and it still remains an active area of research today. Many of MD's clinical characteristics suggest an underlying inflammatory or autoimmune aetiology, such as its propensity to wax and wane [26]. The finding of lymphocytes, macrophages, and a rich network of lymphatics and capillaries, venules and fenestrated blood vessels in the guinea pig and human ES raised the possibility that the sac may have an immune function. Subsequent experiments demonstrated antibody production in the inner ear and showed that the ES can generate an immune response [24]. It is assumed that autoimmunity occurs via one of three basic pathways to cause tissue damage in MD, which may or may not be organ-specific: (1) autoantibodies directed against antigens found upon or within tissue cells, (2) circulation and deposition of antigen-antibody complexes with activation of the complement system and resultant inflammatory tissue destruction, or (3) an inflammatory reaction mediated by sensitised T lymphocytes. This hypothesis is supported by the fact that hydrops can be induced experimentally by injection of antigens or monoclonal antibodies and the deposition of circulating immune complexes may produce inflammation and interfere with the ES's filtering capability. Several studies demonstrated raised levels of circulating immune complexes (CIC) in a percentage varying from 21 to 96% of MD patients [63]. These abnormalities include immune responses to homogenous or heterogeneous inner ear proteins (28–30 kDa, 40 kDa, 42 kDa, 50 kDa, 68–70 kDa, 220 kDa), S-100 beta protein and type II or type IV collagen antigens [64]. Yoo et al. suggested a possible role for type II collagen autoimmunity in the aetiology of otosclerosis as well [65]. Our experience and histopathological studies suggest that certain combinations of otologic diseases, such as otosclerosis and MD, can occur and may have causative links, although other associations (e.g. otitis media) are commonly only coincidental (Fig. 6 a, b) [66 67]. Otosclerosis may result in endolymphatic hydrops by abutting the spiral ligament, resulting in a chemical disruption of ion-fluid recycling, obstruction of the ED and sac, and biochemical changes [68-70].

Certain D-related loci may be associated with MD. The elevated CIC induces endothelial injury and leads to an increase in the permeability of the 'leaky capillaries' that surrounds the ES. This sudden efflux of fluid results in acute ELH and rupture of Reissner's membrane. The mixture of potassium-rich endolymph with perilymph hyperpolarises the neural afferents and causes the acute Ménière's attack [71].

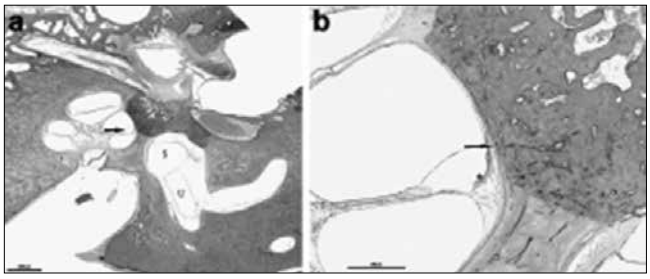

Fig. 6. a) HB 856 Rt 560 1x: This is an 80-year-old man who had bilateral mixed hearing loss and vertigo episodes. Histopathologic exam of his right ear showed otosclerosis that involves the otic capsule and endolymhatic hydrops in the basal turn of the cochlea (arrow), saccule (S) and utricle (U), **b)** HB 856 Rt 560 4x: A higher magnification of the basal turn of the cochlea showed clearly otosclerotic involvement of the otic capsule (arrow) and stria vascularis atrophy (*).

Finally, an association of thyroid dysfunction in patients with MD has also been suggested. Brenner and colleagues showed that 32% of patients with MD were being concomitantly treated with supplemental thyroid hormone, and those older than 60 years of age were taking a supplement at a higher rate than the general population [72]. Of the Ménière's patients Fattori et al. studied, 38% showed the presence of thyroid autoantibodies, which was significantly higher than the two control groups [73]. These studies suggest a predisposition of MD patients for autoimmune disease, given the significant association MD patients have with thyroid dysfunction.

c. Viral infection

As previously mentioned, ELH is a well-known and clinically appreciable finding in many patients with MD. Recently, a temporal bone study has suggested that ELH is a marker for disordered homeostasis of the labyrinth in which an unknown factor produces both the clinical symptoms of MD and ELH [29]. A possible chemical injury to the labyrinth could be the release of infectious nucleic acids from vestibular nerve terminals following virus reactivation in the vestibular ganglion (VG) [74]. The presence of Herpes simplex virus (HSV-1) antibodies in the perilymph and HSV-1 DNA in the VG excised from MD patients have shown promise, although the ubiquitous nature of these viruses in the worldwide population raise questions with respect to the direct correlation between these findings [75 76]. However, electron microscopy by Gacek has shown that virion particles were noted to be present in transport vesicles of vestibular ganglion cells excised from a patient with MD. The virions reportedly led to focal vestibular nerve axonal degeneration and subsequent inflammatory changes associated with ELH [77]. Since reactivation of latent neurotropic viruses like herpesvi-

ridae is dependent on viral load in a sensory ganglion, VG loss in the contralateral nerve may also represent the development of bilateral MD, which has been reported to occur in 15-50% of patients with MD [78].

Genetic predisposition

Multiple hereditary mechanisms have been proposed over the years as means to explain the events that occur in MD. Genetic predisposition has been reported in 2.6–12% of patients with MD [79]. Familial MD appears to follow an autosomal dominant inheritance pattern with 60% penetrance and evidence of anticipation, or a more severe phenotype, in offspring [80]. Early investigations into the causes of MD focused on autoimmunity and sought to identify human leukocyte antigen (HLA) associations; although many have been proposed, none have been proven [81 82]. Linkage analysis in a large Swedish family defined an interval on chromosome 12p12.3 and screened two candidate genes (RERGL and PIK3C2G), although a precise MD gene on chromosome 12 has yet to be found [83 84]. Furthermore, two studies have shown associations with MD and SNPs: one variation in heat shock protein HSP70-1, which is thought to be involved in the cellular stress response [85]; the other being a variation in adducin (Gly460Trp), previously known for its association in hypertension, where heterozygous individuals manifest changes in sodium excretion and blood pressure. The adducin variation mechanism is theorised to act via increased Na-K ATPase activity, inducing hyperosmolarity in endolymph which may lead to pathologic hydrops [86].

Additionally, the genetics of immune signalling pathways has been studied in MD. Many protein tyrosine phosphatases (PTPs) play a negative role in T cell receptor signalling. In particular, PTPN22 1858C/T genotype, primarily expressed in T cells, B cells, monocytes, neutrophils, dendritic cells, and natural killer cells, has been associated with autoimmune disease and may confer differential susceptibility to bilateral MD [87]. Conversely, longer alleles of $(CA)_{17\text{-}20}$ poly (ADP-ribose)-polymerase 1, a nuclear enzyme that contributes to both neuronal death and survival under stress conditions, has been shown to be protective against bilateral MD [87]. Host cell factor C1on the X chromosome haplotype block, known for its role in herpes virus replication within neurons, has been shown to be protective against MD, suggesting a potential trigger between an external source and activation of a molecular pathway that leads to the development of cochleovestibular symptoms.

Inner ear pressure regulation failure

a. Cochlear aqueduct

The cochlear aqueduct plays a key role in the regulation and transmission of pressure equalisation between the middle and inner ear. In particular, the flow resistance of the cochlear aqueduct is crucial for pressure release. The anatomic complex of the round window, connected to the cochlear aqueduct over a pouch-like extension of the round window, allows its position to influence the patency of the cochlear aqueduct and inner ear pressure [88]. Multiple studies have reported pathological middle ear pressures and alterations of cochlear aqueduct patency in patients with MD. In 1966, Tumarkin postulated that middle ear ventilation changes influenced vertigo [89]. Lall reported that 30.9% of patients with MD had pathological middle ear pressure changes [89]. Furthermore, Morinaka and Nakamura found an increased difference of middle ear pressure between bilateral ears in MD patients [90]. Finally, patients with MD showed on average a significant negative middle ear pressure, - 43 decapascals, compared with healthy subjects and patients with sudden hearing loss [91]. Given these findings, due to the previously described importance of the cochlear aqueduct and its functional anatomic proximity to the round window, inner ear disorders such as ELH present conditions in which abnormal middle ear pressures might trigger or worsen vertigo attacks.

b. Vestibular aqueduct

The vestibular aqueduct is also involved in inner ear pressure regulation and plays a role in MD by causing changes in hydrostatic pressure equilibration during states of dysfunction. Hypoplasia of the vestibular aqueduct already appears in the development of the labyrinth before childhood and might have an impact on the aetiology of MD [92]. Numerous radiographic studies by Sennaroglu et al. have demonstrated that the vestibular aqueduct is significantly narrower in the affected ear in patients with MD than the unaffected ear [93]. Any condition that causes narrowing of the vestibular aqueduct and the production of excess endolymph could result in the same symptom complex as patients with MD [30]. In Figure 7, we present a histopathologic slide of a 78-year-old woman diagnosed with Ménière's disease. Histopathologic evaluation of her right ear indicated endolymphatic hydrops associated with extensive otosclerosis that involves the otic capsule and blocked the vestibular aqueduct (Fig. 7, arrow). Please note cochlear, saccular and utricular hydrops. Secondary causes, such as treponemal disease blocking the aqueduct and viral labyrinthitis narrowing the aqueduct, have added further support to pathological changes in the vestibular aqueduct and subsequent ELH.

c. Middle ear muscles (MEM)

The MEM have a long history of being implicated in many inner ear disorders such as tinnitus, otalgia, MD, and SNHL. In particular, spasm of the tensor tympani (TT) has been implicated in a range of conditions including tinnitus, myofascial pain-dysfunction syndrome, and MD. Sectioning of the TT has been a suggested treatment

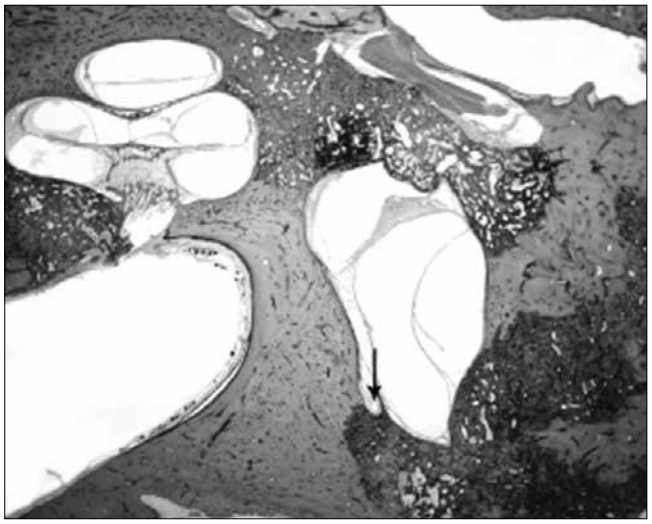

Fig. 7. HB 693 Rt 570 1x: 78-year-old woman diagnosed with Ménière's disease. Histopathologic evaluation of her right ear indicated endolymphatic hydrops associated with extensive otosclerosis that involves the otic capsule and block the vestibular aqueduct (arrow). Note cochlear, saccular and utricular hydrops.

for MD. Embryologically, the TT, derived from the 1st pharyngeal arch mesenchyme, develops into a mixed muscle containing slow and fast muscle fibres. Innervation is subsequently supplied by the tensor tympani nerve, a purely motor branch of the mandibular division of the trigeminal nerve. It has been speculated that the TT can medialise the stapes into the oval window, resulting in changes in inner ear perilymphatic pressures, which in turn may lead to various inner ear disorders like MD [94]. This seems reasonable, considering that a rise in inner ear pressure has three main routes of escape: the vestibular aqueduct, the round window and the oval window. Most importantly, this pressure change and alteration in ossicular function seems to primarily affect lower frequencies, which aligns with the hearing loss spectrum in MD [95].
Klockhoff described a tensor tympani syndrome characterised by fluctuation in the middle ear impedance and complaints of fullness, tinnitus, and dysacusis, which echoes some of the common findings in MD. Although the role of the TT in otologic disease still remains largely elusive, the best expected markers for TT contraction reported thus far include: a decrease in peak static compliance measured with acoustic tympanometry and a low-frequency conductive hearing loss, with a possible smaller low-frequency SNHL component [96].

d. Spontaneous intracranial hypotension (SIH)
The original discussion of SIH is attributed to Schaltenbrand in 1938. A rare pathology, the annual incidence is estimated at 5 per 100,000 persons [97]. Typically, it results from a cerebrospinal fluid (CSF) leakage associated with an orthostatic headache, the cause of which is unknown but may be associated with spontaneous trauma in context of fragile spinal meninges [98]. Physiologically, there is a balance of pressures between the endolymphatic and perilymphatic compartments, mediated by the CSF. Each compartment is in continuity with the CSF: the perilymph, via the cochlear aqueduct, and the endolymph via the ES. However, if this equilibrium is disrupted in some way, the CSF pressure falls. This in turn is transmitted to the perilymph via the cochlear aqueduct, producing a transitory perilymphatic hypotonia and endolymphatic hydrops, which is clinically comparable to the findings present in MD [99]. Additionally, diffuse intracranial venous engorgement has been described in patients with SIH, which causes irritation of the vestibular and cochlear nerves at the internal acoustic meatus, leading to the triad of hearing loss, tinnitus, and vertigo [100].
There are reports in humans and animals that a CSF leak could lead to compensatory expansion of the endolymphatic space. It is proposed that this expansion is the cause of the associated hearing loss with a CSF leak. Reports in MD patients have shown decreased hearing with shifts of intracranial pressure, but no definitive proof is available [22].

e. Low frequency pressure changes
The effect of MD patients' sensitivity to low frequency pressure changes, such as atmospheric pressure changes, has been attributed to prolonged ELH. Prolonged hydrops, experimentally sustained up to 40 minutes, causes displacement of the organ of Corti toward the scala tympani. This was shown to increase endocochlear potential and increase sensitivity to infrasonic frequencies [22].

Conclusions

Our understanding of MD continues to evolve with scientific improvements in animal model studies, imaging modalities and histologic techniques, as well as further comprehension in the fields of allergy, immunology, endocrinology, and genetics. There are an abundant number of theories relating the clinical signs and symptoms of MD to various predispositions and inflammatory states. Our goal is to provide a comprehensive update regarding the aetiopathologies of MD, which unfortunately remains an idiopathic disease despite medical advancements. It is the authors' impression at this time that endolymphatic hydrops seems to be the most appropriate core principle for the ultimate development of MD. Research about MD is broadly focused, which may provide multiple approaches for exploring therapeutic options for disease sufferers in the future.

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Head and neck

The rising incidence of parotid metastases: our experience from four decades of parotid gland surgery

Incremento dell'incidenza di metastasi alla ghiandola parotide: analisi della nostra esperienza in quattro decenni di chirurgia parotidea

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SUMMARY

Secondary neoplasia in the parotid gland is increasingly frequent. We examined outcomes from 40 years of parotid surgery to analyse patterns for metastasis, review the staging procedure and discuss management. We retrospectively examined 772 consecutive cases of parotid surgery in a university hospital between 1975 and 2015 and assessed changes in incidence and management over four decades. In all, 71% percent of patients were male and 29% were female, with a mean age of 68 years, aged between 23 and 93 years. We diagnosed 683 parotid tumours of which 15.8% (n = 108) were malignant; 44% (n = 48) of all malignant lesions were metastases. The incidence of malignant tumours rose from 8% in the first decade, 14% in the second, 17% in the third to 21% in the fourth. The incidence increased even further from 10% in the first to 57% in the final decade. Most frequent tumours were metastases of squamous cell carcinoma (79%), and the majority of these lesions (87%) arose from above the clavicle, with 30 primary tumours in the skin. In most cases, the skin tumour had been excised between 6 and 24 months prior to parotid metastasis. Management consisted of surgery with neck dissection. 48 patients (67%) received adjuvant therapy, but despite aggressive multimodal treatment, disease progressed in the majority of cases, in 57% squamous cell carcinoma of the skin primaries, 67% of mucosal primaries above the clavicle and 83% of infraclavicular primaries. Parotid malignant tumours are increasing in incidence, mostly due to a rise in metastatic malignant tumours within the parotid gland, most of which are metastases of skin tumours, commonly squamous cell carcinoma. Despite multimodal therapy, their recurrence and progression rate remains high. We propose inclusion in head and neck follow-up in all cases of head and neck skin cancers.

KEY WORDS: Parotid • Surgery • Neoplasm • Metastases

RIASSUNTO

La neoplasia secondaria nella ghiandola parotide è un reperto sempre più frequente nella chirurgia parotidea. Vengono qui presentati i nostri risultati in quaranta anni di chirurgia parotidea, analizzando le modalità di metastasi in pazienti con lesioni metastatiche della ghiandola parotide, le procedure operatorie e la gestione dei pazienti. Sono stati esaminati retrospettivamente 772 casi consecutivi di chirurgia parotide in un ospedale universitario tra il 1975 e il 2015 e valutate le variazioni di incidenza e di gestione della patologia nel corso di quattro decenni (I: 1975-1985; II: 1986-1995; III: 1996-2005; IV: 2006-2015). Sono stati diagnosticati complessivamente 683 tumori della parotide, di cui il 15,8% (n = 108) sono rivelati essere di natura maligna; a loro volta, il 44% (n = 48) di tutte le lesioni maligne si sono rivelate essere metastasi. Si è inoltre potuto constatare come, con l'andare del tempo, i tumori maligni della ghiandola parotide abbiano incrementato la loro incidenza con un aumento dall'8% nel primo decennio, del 14% nel secondo, del 17% nel terzo fino al 21% nel quarto decennio. L'incidenza di metastasi alla ghiandola parotide è altresì ulteriormente aumentata dal 10% nella prima decade fino al 57% nell'ultimo decennio. Il 71% per cento dei pazienti era di sesso maschile e il 29% era di sesso femminile, con un'età compresa tra i 23 ei 93 anni (media di 68 anni). La diagnosi istopatologia più frequente era quella di metastasi di carcinoma a cellule squamose (79%). La grande maggioranza delle lesioni primarie era localizzata in lesioni sopra la clavicola (87%), delle quali 30 tumori primari erano localizzati nel cuoio capelluto e nella cute del collo. Nella maggior parte di questi casi, il tumore primario è stato rimosso tra 6 e 24 mesi prima della metastasi parotidea e i pazienti sono stato seguiti in modo subottimale. La gestione consisteva in intervento chirurgico di dissezione del collo. 48 pazienti (67%) sono stati sottoposti a terapia adiuvante, ma nonostante il trattamento multimodale aggressivo la malattia è progredita nella maggior parte dei casi, nel 57% dei casi di metastasi da carcinoma a cellule squamose cutaneo, nel 67% da metastasi di tumore primario della mucosa sopra la clavicola e l'83% dei casi di metastasi da primitivo infraclaveare. I tumori maligni parotidei registrano un progressivo aumento di incidenza, in gran parte dovuto ad un incremento delle lesioni metastatiche parotidee. I più frequenti tumori primitivi sono melanomi maligni precedentemente asportati, e i carcinomi a cellule squamose del cuoio capelluto e del collo precedentemente operati. Nonostante la terapia multimodale il tasso di recidiva e di progressione rimane alto. È auspicabile per i tumori della testa e del collo un programma di follow-up, come già in atto per i tumori della mucosa della testa e del collo.

PAROLE CHIAVE: *Parotide • Chirurgia • Neoplasia • Metastasi*

Introduction

Malignant tumours of the parotid gland are a rare but a varied group of tumours, comprising of at least 24 histological types of malignant lesions of epithelial or mesenchymal origin [1]. The parotid gland hosts metastases, most commonly from tumours of the head and neck region. The highest proportion of parotid metastases have been reported to arise from squamous cell carcinoma of the skin of the scalp, face and neck, but their frequency varies between populations in different geographical locations with different levels of sun exposure [2-4].

Knowledge about clinical and epidemiological aspects of malignant neoplasms of the parotid gland is scarce compared to carcinomas of the upper aerodigestive tract. This is due to the rarity of such tumours, their variance in histological types and also the fact that salivary gland tumours are often reported without allocation to a particular salivary gland. The majority of reports is based on data collections of clinical centres or institutes for pathology [3 5-8.] Population-based data or data from tumour data banks are rare [1 9-11].

Considering the limitations in which published data can be interpreted, the incidence of a malignant parotid neoplasm is expected to be 1 in 100,000 per year [9-11]. The proportion of primary glandular tumours is thought to be 50-70% [9-11], but this depends on geographical location. In Europe and the United States, the proportion of metastatic tumours in parotid malignancies is reported to be around 25% [5 12]. In sun-exposed populations with a higher risk of skin malignancies in the Southern Hemisphere, data from Australia report the proportion of metastatic parotid tumours arising from skin malignancies to be significantly higher at 60% [2-4 13 14]. Vice versa, only 1 to 3% of cutaneous skin malignancies are thought to metastasise into the parotid or periparotid lymph nodes [15].

While in some patients a primary tumour is diagnosed at the same time as a parotid metastasis [5], the majority of patients with parotid metastasis will present with the metastasis first and may undergo parotid surgery before their primary tumour is diagnosed and staged.

There are numerous studies, all of them retrospective, which attempt try to identify risk factors for metastasis of cutaneous cancers to the parotid, and how to manage them.

By examining outcomes from our practice of 40 years, we looked for patterns and timing of metastases in patients with metastatic tumours located in the parotid gland. We also critically review the staging process and discuss management and survival of patients presenting with parotid metastases. This has helped us establish our current practice of management followed by clinic follow-up with a schedule of non-invasive imaging.

Materials and methods

We retrospectively examined 772 consecutive cases of parotid surgery. All procedures were performed by a Consultant Head and Neck Surgeon in a Head and Neck unit at a university teaching hospital between 1975 and 2015. Either total conservative parotidectomy with facial nerve preservation or superficial parotidectomy were performed. Open parotid biopsies were performed in a few selected cases. Neck dissections were performed contemporaneously in selected cases. Postoperative histopathology examination was performed in-house with samples sent to reference laboratories as appropriate. All patient data were obtained by hand searching of patient records and analysed using a statistical software package (Apache Open Office Calc with R Statistics Package).

Ethics considerations

All investigations and treatments are established clinical practice and were carried out according to accepted practice and in compliance with medical principles of the Declaration of Helsinki and German Federal Law. Informed consent was obtained from all patients prior to treatment. In this retrospective case series, formal ethics approval was not required.

Results

In 772 consecutive parotid surgeries, we diagnosed 683 tumours. Of those, 108 were malignant (15.8%) and 48 were metastases (7.0%) (Fig. 1). Therefore, 44.4% of all malignant parotid tumours (n = 108) were metastases, a higher proportion than primary epithelial parotid tumours at 37.0% (n = 40) and malignant lymphoma at 19.4% (n = 21).

The number of parotid tumours rose steadily over the observation period: we diagnosed 121 parotid tumours in the first decade, 163 in the second, 183 in the third and 215 in the fourth decade (Table I and Fig. 1).

The incidence of parotid malignancies rose similarly over the entire observation period from 10 malignancies between 1975 and 1985 to 46 malignancies between 2005 and 2006 (Table I). This accounted for 8.3% of all parotid tumours between 1975 and 1986 (10 of 121), 13.5% (22 of 163) between 1986 and 1995, 16.9% (31 of 183)

Table I. Numbers of parotid tumours diagnosed between 1975 and 2015.

Number of cases	1975-1985	1986-1995	1996-2005	2006-2015
All	121	163	183	216
Benign	90	121	127	140
Malignant	10	21	31	46
Primary	9	12	19	20
Metastasis	1	9	12	26

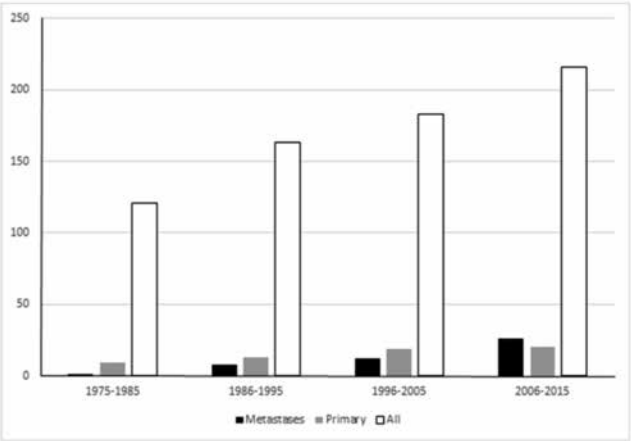

Fig. 1. Incidence of parotid tumours between 1975 and 2015.

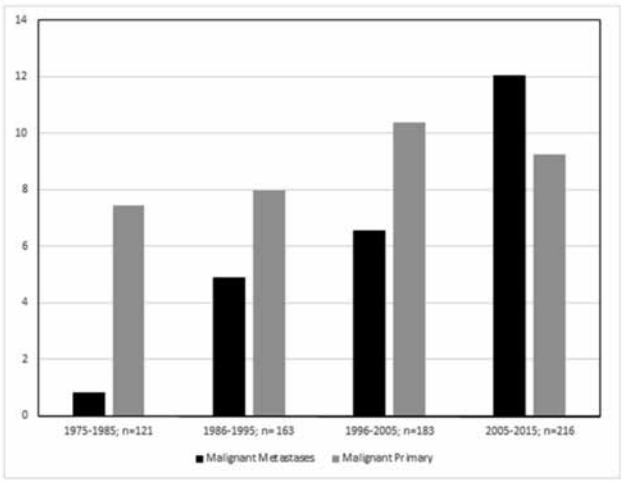

Fig. 2. Incidence of parotid metastases in percent of all parotid tumours diagnosed by decade between 1975 and 2015.

between 1996 and 2005, and 21.3% (46 of 216) of all parotid tumours between 2006 and 2015, demonstrating a nearly three-fold increase in the proportion of parotid malignancies amongst all parotid tumours (Fig. 2).

The proportion of parotid metastases rose out of proportion: in the first decade between 1975 and 1985, the proportion of metastases among malignant parotid tumours was 10% (1 of 10). This rose to 41% (9 of 22) in the second decade between 1986 and 1995 and 39% (12 of 31) in the third decade between 1996 and 2005, and finally reached 57% (26 of 26) in the final decade between 2006 and 2015.

Divided into two 20-year periods, it rose from 31.3% (n = 10 of 32 malignant tumours) in period between 1975 to 1995 to 49.4% (n = 38 of 77 malignant tumours) in the period between 1995 to 2015. Considering all tumours diagnosed during the decade, the number of parotid metastases rose from just under 1% (n = 1 of 121 tumours) to 12% (n = 26 of 215 tumours) (Fig. 2).

Metastatic parotid tumours affected 34 male patients (71%) and 14 female patients (29%) between the ages of 23 and 93 years, with a mean age of 68 years. Six patients were younger than 50 years old at the time of diagnosis.

The most commonly found metastatic tumours were those of a squamous cell carcinoma at 79% (n = 38) followed by malignant melanoma at 12.5% (n = 6) of all metastatic lesions.

Primary tumours were located above the clavicle in 42 of 48 cases (87%), with 30 located in the facial skin or scalp, 9 in the oral cavity or pharynx and 3 in the ear canal. The remaining six primary tumours (13%) were located below the clavicle and arose from primary tumours of the lung (n = 3), kidney (n = 1), distal oesophagus (n = 1) and breast (n = 1).

The period between diagnosis of the primary tumour and the parotid metastasis was 11 months on average (range 0-120 months).

Diagnosis was usually confirmed following histopathological evaluation of parotidectomy specimens. Patients received either a partial parotidectomy (n = 22), total parotidectomy (n = 16), or a radical parotidectomy with facial nerve sacrifice (n = 1, patient had pre-existing facial nerve palsy). Open biopsy alone was performed in 4 patients. In five patients we were unable to determine the exact type of parotidectomy.

Parotidectomy with concurrent excision of the skin tumour was performed in 33% of cases (10 of 30), where staging of the primary tumour revealed a parotid lesion or due to size and histology of the skin lesion.

The excision of a carcinoma of the skin was performed in our patient group in 60% of cases (18 of 30) between 6 and 24 months prior to parotid surgery. These patients were referred to hospital for assessment and excision of a parotid lesion – the association between a previously operated skin tumour and the present parotid lesions was not recognised or unknown to the patient or referring or admitting clinician. This means that a significant number of these patients were operated on primary skin tumours without appropriate staging or that staging was performed, but patients were not referred or followed up appropriately.

We performed a contemporaneous neck dissection on 21 of 48 cases of metastatic parotid tumour (44%). Adjuvant radiotherapy was carried out in 32 of 48 patients (67%).

All patients were observed for at least seven years following parotid surgery, with the exception of those operated on after 2007, who continue to be under observation. Following diagnosis of a metastasis in the parotid gland, we observed tumour progression in 28 of 48 cases (58%). This accounts for 5 of 6 cases of infraclavicular primary tumour (83%), 6 of 9 cases of mucosal squamous cell carcinoma (67%) and 17 of 30 cases of squamous cell carcinoma of the skin (57%) during the observation period.

Discussion

We observed a proportion of 44.4% metastases to the parotid gland in all parotid malignancies over a 40-year period in our group of patients, but there has been an increase from 31% between 1975 and 1995 to 49% between 1995 and 2015. Even though our observations appear to diverge from other European series in that we have observed a higher number of metastatic tumours, it is noted that Bergersen and colleagues reported a similar proportion of parotid metastases nearly 30 years ago from a series of cases in Australia [3]. Similar observations were reported by others in North America more recently, where the proportion of parotid metastases was seen to increase [5 15]. When malignant parotid tumours were recorded in previous epidemiologic studies, a distinction between primary parotid malignancies and parotid metastases was not made [1 9 11].

Metastatic tumours of the parotid gland are more common in older age, the peak incidence in our patient group lies in the 7th and 8th decade. Younger patients are less commonly affected: only six of our 48 patients were younger than 50 years. On the other hand, we found a wide age range between 23 years and 93 years. Patients with metastatic parotid tumours were, in contrast to patients with malignant primary parotid tumours or parotid lymphoma, predominantly male (71%). This may well be due to the higher incidence in skin squamous cell carcinoma and in squamous cell carcinoma of the head and neck in males [7 14 16 17].

In most cases, the primary tumour became manifest prior to the clinical manifestation of the parotid metastasis [7 14 16]. The average period between the diagnosis of the primary tumour and the manifestation of parotid metastasis was 11 months in our group, but there was a wide variety between concurrent diagnosis and a 120 months interval. This also demonstrates the very diverse clinical course.

Squamous cell carcinomas are generally the most frequent carcinomas metastasising into the parotid gland [1 3 5 6 14 16]. In our patient group, squamous cell carcinomas were not just the most common metastatic tumours at 79%, but they also represented the most frequent histological type of tumour at 33%. The predominance of squamous cell carcinoma among parotid metastases has been described in multiple studies from Australia where there is high prevalence of cutaneous squamous cell carcinoma in a predominantly white population [3 13 14]. Further evidence is provided by the largest population based study of the incidence of malignant parotid tumours to date, where the incidence of squamous cell carcinoma amounts to 20% in men and 15% in women, and, as in our group, represents the most common histological type [1]. Since primary squamous cell carcinoma of the parotid gland is rare, it is reasonable to conclude that a significant proportion of these squamous cell carcinomas are metastases [18 19]. A diagnosis of primary parotid carcinoma should be a diagnosis of exclusion depending on histopathological findings, and metastasis should always be considered depending on histological type, and a primary tumour excluded.

Malignant melanoma is the second most common tumour type that metastasises into the parotid gland, and the proportion of primary cutaneous malignant melanoma metastasising into the parotid gland is higher than that of squamous cell carcinoma [6 7 20 21]. Malignant melanomas very rarely arise in the parotid gland as a primary tumour and should generally be considered metastatic spread from a cutaneous melanoma, although mucosal melanoma and choroidal melanoma must also be considered as primary lesions [20 21].

As seen in our patient group, where 87% of primary tumours were located above the clavicle and within the lymphatic drainage area of the parotid lymph nodes, skin tumours of the face and scalp are the most common primary tumours metastasising into the parotid gland [2 14 21 22]. Direct infiltration from the buccal skin can also be observed, as seen in two of our cases of squamous cell carcinoma of the buccal skin.

Reports of parotid metastases of upper aerodigestive tract squamous cell carcinoma are rare compared to those of metastatic cutaneous carcinoma [7 23]. Considering all tumours diagnosed in the upper aerodigestive tract within the observation period, the incidence of parotid metastases in these tumours was less than 1% in our patient group and therefore of little relevance. Metastases of primary tumours located below the clavicle are reported to make up 10-20% of all parotid metastases. As also seen in our patient group, where 13% were metastases of tumours below the clavicle, primary tumours are mostly located in the lung, breast and kidney, and more rarely seen in the gastrointestinal tract, prostate and infraclavicular skin [24-30].

A distinction between primary glandular tumour and metastasis must be made in each case of parotid malignancy. This can be difficult considering the many types of primary tumours that have been described for parotid tumours, but is relevant for therapy and prognosis. When searching for a primary tumour, locations that should be considered first and foremost are the skin of face and scalp and the oral and pharyngeal mucosa, but also the lung, kidneys and breast [3 6 18].

Facial nerve palsies in parotid metastases are comparably rare and in our group of patients we observed two cases of facial nerve weakness [25 30].

Parotid metastatic disease is associated with a high rate of local recurrence and tumour-associated mortality. A metastasis measuring 6 cm or more in diameter and facial nerve palsy are also factors that worsen prognosis. Resection of the parotid metastasis followed by adjuvant radiotherapy is considered the treatment of choice. In patients with parotid metastases of a cutaneous squamous cell carcinoma, neck dissection should always be performed, even in a clinically N0 neck [4 5 13 31]. The patients in our group were primarily cases in whom a

parotid metastasis was diagnosed secondarily, i.e. 6-24 months following diagnosis of a primary tumour. Despite combined treatment and resection of recurrent parotid metastasis, the tumour recurred, either locally or systemically, in 58% of our patients with parotid metastases. We observed a much more favourable course in patients with a clinically N0 neck who underwent parotidectomy and neck dissection prior to a parotid metastasis being diagnosed compared to patients where a parotid metastasis was diagnosed secondarily, and even more so, that the neck and the salivary gland are included in the staging of primary malignant skin tumours. Similarly, Ebrahimi and colleagues reported that an interval of 9 months or less between detection of primary tumour and detection of a metastasis in squamous cell carcinoma of the scalp is an unfavourable prognostic factor [17]. Cutaneous cancers of the head and neck metastasising into the parotid gland may also be associated with increased expression of epidermal growth factor and are particularly aggressive and associated with poor outcome, requiring a different diagnostic regime and surgical and adjuvant management such as radiotherapy [15 31 32]. Parotid metastases of infraclavicular primary tumours are often an expression of disseminated metastasis and carry a poor prognosis. In our cohort, only one of six patients with a parotid metastasis of a previously treated renal cell carcinoma (6 years after nephrectomy) is still alive and recurrence-free four years following parotidectomy. Parotidectomy is rarely considered curative in patients with infraclavicular primary tumours, but it is appropriate for symptom control and should therefore be offered to patients who are fit for surgery. Other than that, primary radio-chemotherapy should be considered depending on sensitivity of the primary tumour [27 33]. Literature following up parotid metastases of mucosal squamous cell carcinoma is very sparse, but prognosis tends to be poor [23]. In patients with malignant melanoma, parotid metastases are a unfavourable prognostic factor [19-21].

Conclusions

Metastatic tumours of the parotid gland have an increasing significance in the spectrum of malignant parotid neoplasia. Parotid metastases are of high prognostic relevance and must be included when stratifying risk and planning treatment. As the majority of parotid metastases are metastases from squamous cell carcinoma of the skin of the head and neck, the majority of which are diagnosed well after treatment of the primary skin tumour, a structured aftercare regimen is required for patients with carcinoma of the skin of the head and neck and possibly for selected patients with infraclavicular primary tumours following primary treatment, which should involve a minimum of clinical otolaryngological examination and ultrasound examination of the neck and salivary glands. By diagnosing and treating such metastases early, tumour recurrence may be prevented but further research is required to assess the impact of early detection of parotid metastasis on survival and recurrence rates.

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HEAD AND NECK

Indications of cone beam CT in head and neck imaging in children

Indicazioni all'esecuzione di una TC cone beam del distretto testa e collo nei bambini

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SUMMARY

For imaging of bony structures, especially for the anterior and lateral skull base in ORL medicine, cone beam computed tomography (CBCT) is an increasingly used alternative to CT, with a lower exposition to plain radiography that makes its use for imaging, particularly in children, very interesting. The aim of this study was to analyse possible indications and settings for CBCT in children and compare them to those of adults. A total of 554 patients (age range 0-18 years, mean age 10.36 years), who underwent CBCT between 01/2004-06/2013 in the ENT department at the university clinic of Marburg were enrolled in this retrospective analysis to evaluate technical parameters and indications. Data on CBCT of all children were compared with previously published data collected from 1730 adults who were diagnosed with the help of CBCT in the ENT department at the university clinic of Marburg, during the years 2012-2013. The most frequent indications of CBCT in children vs. adults were in the anterior skull base region: mid-facial trauma (60.4%) vs. chronic rhinosinusitis (54.8%), disturbed nasal breathing (13.9% vs. 13.0%) and chronic rhinosinusitis (12%) vs. mid-facial trauma (10.8%). For the lateral skull base the main indications were cholesteatoma (20.3%) vs. position control of cochlear implant (CI) electrode (31.2%), chronic otorrhoea (17.5%) vs. cholesteatoma (20.9%), and position control of CI electrode (11.8%) vs. chronic otitis media mesotympanalis (6.8%). CBCT is a suitable imaging modality for bony structures in adults and children. Settings mainly depend on the region of interest. One aim should also be to reduce exposure to radiation in both adults and children.

KEY WORDS: Cone beam computed tomography (CBCT) • Indications CBCT • CBCT dosage • Imaging in children • Imaging paranasal sinus • Imaging temporal bone

RIASSUNTO

La TC cone beam (CBCT) rappresenta un interessante strumento diagnostico specialmente nei bambini per lo studio del basicranio anteriore e laterale, in particolar modo per la bassa esposizione a radiazioni tipica della metodica. Lo scopo del presente studio è stato quello di individuare le potenziali indicazioni per la CBCT nei bambini e il confronto rispetto alle indicazioni nell'adulto. Sono stati analizzati un totale di 554 pazienti (range 0-18 anni, media 10.36) sottoposti a CBCT da Gennaio 2004 a Giugno 2013 presso il Dipartimento di ORL della Clinica Universitaria di Marburg, allo scopo di effettuare un analisi retrospettiva dei parametri utilizzati e delle indicazioni all'esame. I dati provenienti dai bambini sono stati inoltre confrontati con un set di dati di 1730 adulti sottoposti a diagnosi mediante CBCT presso lo stesso dipartimento e già precedentemente pubblicati. Le differenti indicazioni più frequentemente rilevate all'esecuzione dell'esame negli adulti, rispetto ai bambini hanno riguardato il basicranio anteriore, e in particolare: trauma del volto (60.4%) vs. rinosinusite cronica (54.8%), ostruzione respiratoria nasale (13.9% vs. 13.0%) e rinosinusite cronica (12%) vs. trauma del volto (10.8%). Per quanto riguarda il basicranio laterale le indicazioni principali sono state il colesteatoma (20.3%) vs. controllo del posizionamento dell'impianto cocleare (31.2%), otorrea cronica (17.5%) vs. colesteatoma (20.9%) e il controllo del posizionamento dell'impianto cocleare (11.8%) vs. otite media cronica mesotimpanica (6.8%). La CBCT è una metodica efficace per lo studio delle strutture ossee nell'adulto e nei bambini. I parametri di impostazione dipendono principalmente dalla regione oggetto di studio. Uno dei principali obiettivi è ridurre l'esposizione alle radiazioni sia nei bambini che negli adulti.

PAROLE CHIAVE: *Cone beam computed tomography (CBCT) • Indicazioni CBCT • CBCT dose • Imaging nei bambini • Imaging dei seni paranasali • Imaging dell'osso temporale*

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Introduction

For imaging in otorhinolaryngology, different modalities have been established: for example, for the representation of bony structures, computed tomography is widely accepted. The two regions in ORL where CT is mostly applied are the anterior skull base and the lateral skull base.

The main indication for imaging in these regions is the visualisation of pathologies or anatomical variants for planning therapeutic procedures, such as an operation to minimise possible complications. In the case of imaging soft tissue, magnetic resonance imaging (MRI) or sonography is preferred. In the last few years an equivalent alternative has been found, at least for bony structures, namely cone beam computed tomography (CBCT), which, like conventional CT, is based on the application of X-rays.
Penetrating human tissue, X-rays have an ionising effect. Modifications of human genetic material (DNA) can occur that can be carcinogenic for the affected person, or even for future generations when germ cells are affected [1]. However, a major part of this damage can be corrected by the endogenous defence system [2]. This needs to be kept in mind particularly for children, who have a longer life span compared to adults. To evaluate the radiation dose that acts on the human body, the Computed Tomography Dose Index (CTDI) is a reliable value.
CBCT offers a good spatial resolution and detailed reconstruction with a lower irradiation in comparison with CT [3]. Basically, the lower irradiation results in higher ratio of noise. However, in daily routine, the quality of the images is good enough for sufficient diagnostic power [4]. Therefore, it might be a good alternative for tomography, especially in children [5-8]. Another advantage is that CBCT is very fast, usually taking between 9-18 seconds, and therefore it is a good alternative for patients with lower compliance. Furthermore, it is an open device, so that for claustrophobic persons and anxious children in particular, it may be a pleasant alternative to CT.
To date, while most recent studies have looked at the differences between CT and CBCT, there is no clear statement concerning the indications of CBCT in head and neck imaging in children. Therefore, the aim of the present study is to analyse and discuss possible applications of CBCT in children and to compare these indications with those of adults in the current literature [9].

Materials and methods

Within this study all data of between 01/2004-06/2013 of CBCT performed on children (age between 0 and 18 years) was retrospectively analysed. All imaging procedures were performed and indicated by the Department of Neuroradiology in accordance with the patients' clinical background, based on clinical examination. In total, 650 patients fulfilled these criteria. Of these, 96 patients were excluded because the imaging was indicated and conducted by colleagues from oro-maxillofacial surgery. Finally, a total of 554 cases were analysed.
All imaging was performed with a CBCT device 3D Accu-I-Tomo, model MCT-1, type EX-2 F17 (Morita, Kyoto, Japan). This device has a detector of 17 cm width and 12 cm height and allows Field of Views from 4x4 cm up to 12 x 17 cm without any kind of stitching. With the associated software i-Dixel for processing, analyses and archiving (i-Dixel 2.0 Morita, Kyoto, Japan), the demographic and technical information of patients and images, including weighted CTDI (CTDIw), acquisition time, rotational angle, tube current and voltage as parameters for radiation exposure and the Field of View (FOV) were collected. Furthermore, the target region (paranasal sinuses/ anterior skull base, petrous bone/ lateral skull base, other), the use of scout-imaging and the necessity of repetition were evaluated.
Based on clinical charts, indications for radiological imaging were researched and divided into relevant groups.
Data were analysed using the SPSS 17.0 package (SPSS Inc., Chicago, IL, USA) regarding frequency distribution and descriptive statistics. As a comparative test, the two-sided t-test with independent variables was used and a 95% confidence interval was set. Pairwise comparisons were Bonferroni corrected whenever necessary. Statistical significance level was set at $p < 0.05$.

Results

A total of 554 patients were enrolled in the analysis. Mean age was 10.36 ± 5.5 years. The study population consisted of 37.4% females (N = 206) and 62.6% males (N = 348). In 61.6% of cases, imaging was performed at the anterior skull base (208 male versus 133 female), whereas in 38.3% of cases it was at the petrous bone/lateral skull base (139 male versus 73 female). In one patient (0.2%) looking for a foreign body, the region of interest was the neck.
The following data regarding the adjustments of the x-ray tube and examination parameters are summarised in Tables I and II. Regarding the rotational angle of the x-ray tube, there were differences with regards to the target areas found: an angle of 180° was mainly used for 47.8% (n = 163) of the anterior skull base region and for just 8% (n = 17) of the lateral skull base, whereas a rotational angle of 360° was chosen for 92% (n = 195) of the lateral skull base and for 52.2% (n = 178) of the anterior skull base.
Analysing the data of the FOV in 95.3% of the images of the lateral skull base, a 6x6 cm (cylindrical diameter and height) window was used, while for the anterior skull base in 45.5% a 10x10 cm window, followed by a 6x6 cm window (22.8%) and a 10x14 cm window (18.2%) were used.
With respect to the tube voltage, in the total patient cohort a significant difference was found between the lateral and the anterior skull base (82.43 kV vs. 85.06 kV, $p = 0.000$). Also detected was a significant positive correlation between the tube voltage and the age of the patient (lateral skull base: $p = 0.000$; anterior skull base $p = 0.000$). No correlation was found between sex and tube voltage ($p = 0.778$).
Furthermore, significant differences regarding the tube

Table I. Technical parameters in CBCT imaging in children 2004–2013 vs. children 2012-2013.

	Tube current (mA)	Tube voltage (kV)	Rotation angle	CTDI (mGy)
Anterior skull base	4.79	82.43	180° - 47.8% 360° - 52.2%	4.24
Lateral skull base	6.97	85.06	180° - 8% 360° - 92%	6.01

Table II. Examination specifications.

	Scout	Repetition	FOV	Additional imaging	Reason for repetition
Anterior skull base	33.4%	4.7%	14x10 - 18.2% 10x10 - 45.5%	0.3%(1)	3% (10) - motion artefacts 1.5% (5) - incomplete FOV
Lateral skull base	17%	5.5%	6x6 - 95.3% 8x8 - 2.4% 10x10 – 1.4%	3.8%(8)	3.7% (8) - motion artefacts 0.9% (2) - incomplete FOV

current were found for the different target regions, the lateral skull base vs. anterior skull base (6.97 mA vs. 4.79 mA, p = 0.000). A significant negative correlation between age and tube current was found only for the anterior skull base (p=0.000). No correlation was found between the tube current and sex of the patients (p = 0.416 lateral skull base, p = 0.193 anterior skull base).

For the total patient cohort, a significant difference between the CTDI necessary in the lateral skull base versus the anterior skull base was found (6.01 mGy ± 1.26 vs. 4.24 mGy ± 1.92, p=0.000). A positive correlation could furthermore be detected between patient age and the CTDI for anterior skull base imaging (p = 0.005).

During the years 2004-2013, 5.5% of the lateral skull base imaging had to be repeated, whereas the repetition rate of anterior skull base imaging was needed in 4.7% of patients. The most common reason for repetition (in total: 66.67%; lateral skull base: 80%; anterior skull base: 58.82%) was a blurred image due to non-adherence of the patient, followed by an incomplete presentation of the region of interest (33.33%). Imaging repetition was more frequent in the age group 3-7 years (Table II).

In 1.63% (n = 9) of cases additional imaging seemed to be necessary to verify the suspected diagnosis (0.3% (n = 1) of all anterior skull base imaging versus 3.8% (n = 8) of all lateral skull base imaging). The affected age group was mostly the group of adolescents. A retrospective analysis of the additional imaging compared to the initial CBCT imaging showed that in 66.67% (n = 6) no further information could be gained, whereas in 33.3% (n = 3) additional information was given or another diagnosis was made (Table II).

After analysing the primary charts, a total of 26 different indications could be detected. Looking at lateral skull base imaging, a total of 12 different indications could be identified. The most common indication of the whole study collective was epitympanic chronic otitis media (20.3%), followed by otorrhoea of unknown origin in 17.5% and position control of cochlear implant in 11.8% (Table III). For anterior skull base imaging, 10 different indications were determined, led by suspected fractures of the mid face (60.4%), nasal airway obstruction (11.4%) and acute rhinosinusitis (12%) (Table III).

Discussion

The necessity of imaging in children should take into consideration how much it is really required and which structures need to be visualised. Over the last few years the use of conventional CT in the field of imaging bony structures has found strong competition in the form of CBCT.

Offering a good spatial resolution and detailed reconstruction, CBCT has lower irradiation in comparison with CT [6 8] which, in children in particular, is a huge advantage. As the sensitivity of cells towards ionising radiation depends on the rate of mitosis of cells, those cells with a

Table III. Indications of CBCT at the lateral and anterior skull base in paediatric group.

Anterior skull base (N = 341)	Lateral skull base (N = 212)
Mid-facial trauma (60.4%)	Cholesteatoma (20.3%)
Disturbed nasal breathing (13.9%)	Otorrhoea (17.5%)
Chronic rhinosinusitis (12%)	Cochlear implant position control (11.8%)
Cephalgia (5.9%)	Conductive hearing loss (11.8%)
Rhinorrhoea (2.3%)	Suspected mastoiditis (8%)
Tumour of paranasal sinuses (1.8%)	Acute otitis media (6.1%)
Search for focus (1.5%)	Malformation of the ear (5.7%)
Dacryostenosis (0.9%)	Sensorineural hearing loss (4.2%)
Exclusion of focus at paranasal sinuses (0.6%)	Chronic otitis media mesotympanalis (3.8%)
Planned epithesis supply (0.6%)	Tumour of auditory canal (3.3%)
	Otalgia (2.8%)
	Status after ear trauma (1.9%)

high rate of mitosis are more sensitive towards damage caused by ionising radiation because the mitosis growth rate of cells in children is up to 10 times higher than in adults, so their cells are also more sensitive to ionising radiation. The highest sensitivity towards ionising radiation is found in newborns and decreases with age [10]. Another feature in children is that the endogenous mechanisms to control damage caused by radiation is not fully mature and therefore less effective compared to adults. In addition, body proportions in children are different compared with adults – for example, bone marrow is distributed in almost all body parts more homogeneously, the greater part being located in the trunk, which is why bone marrow is especially threatened and the risk of developing leukaemia is high [11]. Also, the risk of developing other cancers induced by radiation over the years is higher in children because compared to adults the manifestation of long-term-effects is more probable as children potentially have a longer life span [12]. Therefore, it is important to strictly establish the indications for x-ray-dependent examinations in children and to minimise the radiation dose. One possible way to reduce the dose is by discussing the need for quality imaging. Bitterwolf et al. demonstrated the potential of optimising irradiation for anterior and lateral skull base examinations through discussion of the clinical need for images [13].

Nevertheless, in frequent cases, an imaging of bony structures is needed to confirm a diagnosis or to plan treatment. This study focused on the evaluation of indications for CBCT in daily otolaryngology imaging in children. The most common indications in the anterior skull region in children were circumscribed mid-facial trauma (60.4%) followed by disturbed nasal breathing (13.9%) and chronic rhinosinusitis (12%). In comparison, in adults the most frequent indication was chronic rhinosinusitis (54.8%), followed by disturbed nasal breathing (13.3%) and mid-facial trauma (10.8%) [9]. These findings correspond to a study in which it was demonstrated that 80% of all imaging of the anterior skull base is based on indications of chronic rhinosinusitis [14 15] and guidelines recommend CBCT as an alternative to conventional CT [16 17]. For the second most frequent indication, i.e. disturbed nasal breathing, the successful use of CBCT was demonstrated [18] and is usually performed preoperatively to predict possible complications that might be a result of individual anatomical features. The third frequent indication of adults and most frequent in children is mid-facial trauma, which refers primarily to fractures of the nasal bone. For this indication, simultaneous fractures of the mid-face bones need to be excluded, which is why a FOV of 14x10 cm was still the most recommended and used window, both in children and adults in the present study [19]. In cases of involvement of the brain or eye, or patients with multiple trauma, CT is first line choice. Regarding imaging of the lateral skull base, the most common indication in children is suspicion of cholesteatoma (20.3%) followed by chronic otorrhoea (17.5%) and cochlear implant electrode position control (11.8%). The CBCT has been shown to give an equivalent visualisation of the middle and inner ear structures compared to CT, which is why it is also recommended in guidelines for chronic otitis media [20 21]. However, in adults, the most frequent indication is position control after cochlear implantation (CI) (31.2%), followed by cholesteatoma (20.9%) and chronic otitis media mesotympanalis (6.8%). The successful diagnostic pathway for evaluating the correct position of the CI electrode has already been demonstrated, which is why it has been established in routine diagnostics [22-25]. In children, this is only the third most frequent indication, which might be based on the fact that CI implantations are more frequent in adults than in children in our clinic, and the fact that paedoatric patients are most commonly aged about one year or younger. At this age, the CBCT available at our department (sitting position) is of no use.

Regarding technical parameters, for the imaging of the anterior skull base in children in the present study, in half of the cases 360° was used and in half a 180° angle was utilised. Due to the fact of twice as many images, the 360° setting results in a higher-quality image and allows more precise visualisation of small structures (e.g. ossicular chain). However, it was shown that the image quality using a rotational angle of 180° is also sufficient, with a 50% reduction in the radiation dose, especially in the lenses and the dosage of the parotid gland [4]. Furthermore, the advantage of a 180° mode is the shorter examination time. The 360° rotational angle was mainly used for lateral skull base imaging in the present study (for adults and children), however, it could be demonstrated that here too a rotational angle of 180° is adequate for sufficient imaging quality [13]. In the future, a rotational angle of 180° should be chosen to shorten the examination time and to reduce the radiation exposure while still achieving sufficient imaging quality.

Other parameters that can reduce the radiation dose are the tube current and/or tube voltage [26] and a focus on dedicated field of views. The dosage should be chosen taking into consideration the region need to be shown. As a result of this, the lateral skull base with smaller bony structures needs a higher dose in comparison to the anterior skull base (6.97 mA vs. 4.79 mA, $p = 0.000$). In the present study, a significant correlation between the tube current and age was also found for the anterior skull base ($p = 0.000$). This demonstrates the consequent use of dose reduction protocols with lower age. The same findings could be detected in analysis of tube voltage (85.06 kV vs. 82.43 kV; $p = 0.000$).

In consideration of this, our standard protocols with the above mentioned machine are 90 kV, 3 mA and 180° for anterior skull base and 90 kV, 8 mA and 180° for the lateral skull base. In small or slightly small children, the tube

current is reduced by 0.5 to 1.5 mA. The field of view (FOV – diameter x height of cylinder) for the anterior skull base was most frequently 10x10 cm, followed by a 6x6 cm window. Theoretically, fractures of the nose could be diagnosed within a FOV of 6x6 cm, the problem being that neighbouring parts of the mid-face bones cannot be evaluated sufficiently and so fractures of the mid face could be overlooked in this setting [18]. Therefore, in our opinion it is recommended to use at least the 10x10 cm FOV. For the lateral skull base, a window of 6x6 cm was mainly used. The FOV should be large enough to show the whole region of interest, but not too large, because local resolution decreases and radiation exposure increases as the size of the FOV increases [27].

The decision on how to proceed in a case of bilateral ear imaging should be performed individually, taking into account the applied radiation exposure, risk of movement artefacts and need for FOV. Comparing the different FOVs used in anterior vs. lateral skull base imaging, the fact that the structures of the paranasal sinuses are larger in contrast to the ear structures should be taken into consideration, which is why a larger FOV could be chosen here.

In the present study, 5.5% of the lateral skull base imaging and 4.7% of the anterior skull base imaging had to be repeated. The most common reason for this was a blurred image as a result of motion artefacts, followed by an incomplete FOV (Table I). Particularly in the age group 3-7 years, image repetition was more frequent. In lateral skull base imaging a rotational angle of 360° was frequently used, which results in a longer examination time (16.87 sec ± 2.5 lateral skull base vs. 13.42 sec ± 4.24 anterior skull base) and thus a higher possibility of motion artefacts because keeping still for a longer time is more difficult, especially for children. Nevertheless, in the comparable group of adults, motion artefacts were also the most common reason for image repetition in lateral skull base [9]. Possibilities for reducing the number of repetitions are the use of positioning aids [28], reduction of examination time and detailed explanation of the importance of a steady head position.

Conclusions

CBCT is a good alternative to conventional CT as an imaging technique of bony structures in children as well as in adults. The most frequent indications for anterior skull base imaging in children are circumscribed mid-facial trauma, disturbed nasal breathing and chronic rhinosinusitis compared to lateral skull base imaging for which the most frequent indications are cholesteatoma, otorrhoea and cochlear implant position control. In case of involvement of the soft tissue (e.g. orbital/ central complications) MRI or CT should be performed. Tube adjustments mainly depend on the region of interest. One aim should be a consequent reduction of radiation exposure by using a rotational angle of 180° on the back of the head.

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HEAD AND NECK

Laryngectomy: what is the impact of the type of surgery on life quality and sexual function?

Laringectomia; qual è l'impatto del tipo di chirurgia sulla qualità di vita e sulla sessualità?

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SUMMARY

The purpose of this study is to compare total and partial larygectomy on private life functions and sexuality in patients with laryngeal cancer. The study included 31 partial laryngectomy patients (Group 1) and 51 total laryngectomy patients (Group 2) who were operated for laryngeal cancer. European Organization for Research and Treatment of Cancer (EORTC) head and neck cancer module (QLQ-H&N35) and Arizona Sexual Experiences Scale (ASEX) forms were filled in by interviewing face to face with patients. HNSW (swallowing), HNSE (senses), HNSP (speech), HNSO (social eating), HNSX (sexuality), HNTE (problems with teeth), HNOM (problems with opening mouth) and HNCO (coughing) scores of EORTC QLQ-H&N35 were significantly higher in group 2 than in group 1. However, according to Arizona test results, there were no significant difference between the two groups.

KEY WORDS: Laryngectomy • Life quality • Sexuality • EORTC QLQ-H&N35 • Arizona Sexual Experiences Scale

RIASSUNTO

Lo scopo del presente studio è stato quello di confrontare gli effetti della laringectomia totale e della laringetomia parziale sulla qualità di vita e sulla sessualità. Lo studio ha incluso 31 pazienti affetti da carcinoma laringeo sottoposti a laringectomia parziale (Gruppo 1) e 51 pazienti sottoposti a laringectomia totale (Gruppo 2). Ai pazienti sono stati somministrati i questionari dedicati dell' EORTC (QLQ-H&N35) e l'Arizona Sexual Experiences Scale (ASEX). I risultati del test EORTC QLQ-H&N35 relativamente alle sezioni HNSW (deglutizione), HNSE (sensi), HNSP (voce), HNSO (alimentazione sociale), HNSX (sessualità), HNTE (problematiche coi denti), HNOM (problemi nell'apertura della bocca) e HNCO (tosse) sono risultati significativamente più alti per il gruppo 2. Tuttavia il test Arizona non ha mostrato differenze significative fra i due gruppi.

PAROLE CHIAVE: *Laringectomia • Qualità di vita • Sessualità • EORTC QLQ-H&N35 • Arizona Sexual Experiences Scale*

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Introduction

Head and neck cancers, and particularly cancers of the larynx, is an issue that affects the daily lives of patients with severe consequences according to the kind of surgery that was performed. Choice of treatment depends on stage at diagnosis; organ sparing surgery such as partial laryngectomy is performed in early stages and total laryngectomy in advanced cases. In order to provide valuable information on how the type of surgery impacts the quality of life and sexual function, we divided our patients into two categories: patients that received partial laryngectomy in which the speech organ, smell sense, taste sense and air passage are preserved and patients who received total laryngectomy in which none of these were preserved. To compare the quality of life in these two patient groups and to investigate the psychophysiological effects objectively, we used European Organization for Research and Treatment of Cancer (EORTC) head and neck cancer module (QLQ-H&N35) which was first established in 1999 [1], and we also used Arizona Sexual Experiences Scale to compare the sexual functions of both patient groups.

Materials and methods

Study design

This is a cross-sectional study. The protocols were approved by the Cerrahpasa Medical Faculty Ethics Committee at Istanbul University. All patients were promised privacy and all patients who were included consented to the study.

Sample

The inclusion criteria for total laryngectomy patients included having completed treatment at least four months before the study, and for total laryngectomy patients, having been decannulated at least four months before the study. Patients with residual or recurrent tumour, psychiatric disease, diabetes or major heart disease, or who declined a face-to-face interview were excluded. The initial sample set consisted of 127 patients who underwent surgery for laryngeal cancer between 2010 and 2013 at the otolaryngology department of single tertiary cancer center. Female patients formed a relatively small number and were excluded in order to obtain a homogenous sample set. The remaining 82 male patients were divided by surgical procedure: partial laryngectomy (Group 1; 31 patients) and total laryngectomy (Group 2; 51 patients). The same clinician carried out all face-to-face interviews. All patients completed the head and neck cancer module of the quality of life questionnaire (QLQ-H&N35) of the European Organization for Research and Treatment of Cancer (EORTC), as well as the Arizona Sexual Experiences Scale (ASEX). Additional demographic data were recorded, including educational level, monthly income, post-operative follow-up duration, treatment modality, and tumour, node and metastases (TNM) stage.

Instruments

ASEX is a questionnaire consisting of five sections on sexual function and a scoring scale between 1 and 5. The sections cover sexual drive, erection, arousal, orgasm and satisfaction. Patients are considered to have severe sexual dysfunction if they score 5 or 6 on a single section, 4 or higher in 3 or more sections, or 19 or more in total [2]. Both patient groups were evaluated and compared for average scores (ASEX1) and the ratios of patients with sexual dysfunction (ASEX2) were calculated.

The QLQ-H&N35 was developed as an addition to the EORTC QLQ C-30, in order to better evaluate the quality of life of cancer patients [1 3]. It consists of 35 questions forming 18 measurements. A lower score indicates better quality of life [4].

Statistical analysis

Statistical analysis was performed using IBM SPSS software version 16.0. Means and standard deviations were calculated for demographic data and questionnaire scores. Group comparisons were made with Student's t-test and verified with Pearson's chi-square test. A p value of less than 0.05 was considered significant.

Results

Socio-demographical profiles

The average age of the partial laryngectomy group (Group 1) was 57.3 years, with a range between 42 and 67 years. In the total laryngectomy group (Group 2), the average age was 63.4 years, with range between 43 and 84 years. Statistical analysis showed no significant difference between the mean age of the groups ($p = 0.093$). The differences in the levels of education and average income between the groups was not significant ($p = 0.084$ and $p = 0.088$, respectively).

Analysis of impairment

The average score on the QLQ-H&N35 was higher in Group 2 than in Group 1 in all sections except weight increase. The sections in which the differences between the average scores reached statistical significance were swallowing (HNSW; Group 1 = 9.4; Group 2 = 21.4; $p = 0.009$), senses (HNSW; Group 1 = 11.6; Group 2 = 47.7; $p = 0.000$), speech (HNSP; Group 1 = 44.6; Group 2 = 59.7; $p = 0.038$), social eating (HNSO; Group 1 = 10.5; Group 2 = 28.8; $p = 0.011$), sexuality (HNSX; Group 1 = 29.0; Group 2 = 54.3; $p = 0.005$), problems with teeth (HNTE; Group 1 = 22.9; Group 2 = 45.5; $p = 0.011$), problems with opening mouth (HNOM; Group 1 = 6.3; Group 2 = 28.6; $p = 0.003$) and coughing (HNCO; Group 1 = 17.0; Group 2 = 49.1; $p = 0.000$) (Table I).

The mean ASEX score was 13.6 ± 5.1 in Group 1 and 4.7 ± 4.2 in Group 2. The difference was not significant (ASEX1: $p = 0.386$). In Group 1, 11 patients of 31 (35.4%) indicated sexual dysfunction, with scores higher than 11. In Group 2, the total was 30 patients of 51 (52.9%). The difference between the groups was remarkable, however, it was not statistically significant (ASEX2: $p = 0.127$). (Table II).

Investigating the correlation between the results of ASEX and HNSX of Group 1 using the Pearson method, it can be observed that HNSX values were positively correlated with both ASEX1 and ASEX2 scores, which indicate sexual dysfunction ($r = 0.771$ and $p = 0.000$; $r = 0.891$ and $p = 0.000$, respectively). The same calculations for Group 2 indicate a high positive correlation between HNSX and ASEX2 ($r = 0.525$ and $p = 0.000$), but no correlation between HNSX and ASEX1 ($r = 0.183$ and $p = 0.199$) (Tables II and IV).

Discussion

The most important outcome regarding the socio-demographic profiles of the patients was the absence of a significant difference between total laryngectomy and partial laryngectomy patients in terms of the mean age of the patients, occupation and average education and income. The homogeneity of the demographic characteristics prevented sociocultural factors from influencing outcomes. The average age was similar to the previous study by Tas et al [5]. The all-male sample set was inconsistent with the literature [5 6], but another study that included only men is also available [2].

Table I. Mean Scores of the EORTC QLQ-H&N35 items and scales of two groups and comparison.

Symptom scales	Group 1 Partial laryngectomy	Group 2 Total laryngectomy	P value
HNPA (Pain)	15.5	18.5	0.449
HNSW (Swallowing)	9.4	21.4	0.009
HNSE (Senses)	11.6	47.7	0.000
HNSP (Speech)	44.6	59.7	0.038
HNSO (Social eating)	10.5	28.8	0.011
HNSC (Social contact)	19.1	32.3	0.055
HNSX (Sexuality)	29.0	54.3	0.005
Symptom Items			
HNTE (Problems with teeth)	22.9	45.5	0.011
HNOM (Problems with opening mouth)	6.3	28.6	0.003
HNDR (Dry mouth)	26.0	31.8	0.425
HNSS (Sticky maliva)	33.1	39.8	0.386
HNCO (Coughing)	17.0	49.1	0.000
HNFI (Feeling ill)	27.1	28.7	0.817
Dichotomous Items			
HNPK (Use of painkillers)	41.9	54.9	0.260
HNNU (Use of nutritional supplements)	11.3	12.3	0.542
HNFE (Use of feeding tube)	12.9	27.4	0.126
HNWL (Weight decrease)	19.3	33.3	0.176
HNWG (Weight increase)	54.8	47.0	0.135

In several studies [5 7 8], the speech parameter (HNSP) of the QLQ-H&N35 questionnaire was considered the most important for indicating quality of life. Other studies validated the QLQH&N35 for reflecting speech problems [2 9]. In the current study, we found significantly lower scores for speech problems in the partial laryngectomy group ($p = 0.038$). The data we obtained is mostly consistent with the literature, although we disagree with the assertion by Müller et al. [8] that the QLQ-H&N35 does not accurately reflect speech difficulties.

When other parameters of the QLQ-H&N35 were considered, it was observed that the patients with total laryngectomy had more problems in swallowing (HNSW) than patients with partial laryngectomy, in addition to teeth (HNTE), opening their mouth (HNOM), sensation (HNSE), coughing (HNCO), social eating (HNSO) and sex (HNSX). Predictably, partial laryngectomy patients scored higher only in the weight increase (HNWG) section. Although they scored lower compared to total laryngectomy patients for pain, dry mouth, sticky saliva, feeling ill, use of painkillers, and trouble with social contact, the differences were not significant. We believe the data we obtained are plausible and self-confirming.

According to the study conducted by Braz et al. [10], problems such as fatigue, smell and taste disorders, and avoidance of eating in social environments, occured more frequently in the total laryngectomy group than in the partial laryngectomy group; however, the difference was significant only for sensory problems. Similarly, Swnaik et al. [11], in their comparison of the quality of life after total and partial laryngectomy, found that only smell and taste disorders were higher in patients with total laryngectomy. Akduman et al. [9] reported that, among all parameters of the QLQ-HN35, only speech problems and coughing scores were higher in total laryngectomy patients compared to partial laryngectomy patients. Furthermore, Fil-

Table II. Mean scores of the Arizona sexual experiences scale of two groups and comparison.

	Group 1 (Partial laryngectomy; n = 31)	Group 2 (Total laryngectomy; n = 51)	P value
ASEX 1	13.6	14.7	0.386
ASEX 2	0.35	0.52	0.127

Table III. Correlation between ASEX and HNSX scores of group 1 (n = 31).

		ASEX 1	ASEX 2	HNSX
ASEX 1	Pearson correlation	1.000	0.713 **	0.771 **
	p		0.000	0.000
ASEX 2	Pearson correlation	0.713 **	1.000	0.891 **
	p	0.000		0.000
HNSX	Pearson correlation	0.771 **	0.891 **	1.000
	p	0.000	0.000	

*** Correlation is significant at the 0.01 level (2-tailed)*
** Correlation is significant at the 0.05 level (2-tailed)*

Table IV. Correlation between ASEX and HNSX scores of group 2 (n = 51).

		HNSX	ASEX 1	ASEX 2
HNSX	Pearson correlation	1.000	0.183	**0.525 ****
	p		0.199	0.000
ASEX 1	Pearson correlation	0.183	1.000	**0.483 ****
	p	0.199		0.000
ASEX 2	Pearson correlation	**0.525 ****	**0.483 ****	1.000
	p	0.000	0.000	

*** Correlation is significant at the 0.01 level (2-tailed).*
** Correlation is significant at the 0.05 level (2-tailed)*

ipovski et al. [2] found that speech, swallowing, sensation and coughing problems, as well as difficulty in establishing social relationships were significantly higher among patients with total laryngectomy. Our study reports significant differences between the two groups in the opening mouth, taste, and sex parameters, although other studies found no difference [2 9 10].

Sexuality following laryngectomy has not been evaluated in depth in previous studies[12]. Considering early investigations on sexual problems, Gardner's 1960 study [13] on laryngectomies is one of the first. In that study, 23% of female patients reported that they felt less feminine and 35% that they felt less attractive post-surgery. In 1980, Myers et al. [14] surveyed 48 laryngectomised patients of whom 82% had been sexually active before the operation. Approximately one in five of these patients felt less attractive, and one-third complained that their relationship was altered.

De Boer [15] divided patients into three groups according to treatment, namely radiation, laryngectomy, or laryngectomy plus neck dissection. The laryngectomy patients reported a 44% reduction in sexual contact. Similarly, Harran and Gavilan [16] studied 111 larynx cancer patients and found that partial laryngectomy patients had sexual problems more often than total laryngectomy patients. The de Boer study also found that women had more problems than men did. In contrast, Singer et al. [12] used the QLQ-H&N35 form to determine the differences between total and partial laryngectomy patients in the frequency of sexual difficulty, and the HNSX score for total laryngectomy patients was significantly higher than for partial laryngectomy patients.

Other recent studies about the psychology of laryngectomised patients focused on the quality of life for the spouses of patients. Offerman et al. [17] and Meyer et al. [18] reported that the spouses of patients who underwent total laryngectomy needed professional psychological support and that the surgery had an effect on their sexual relationships. Although our sample set did not include spouses, we think that our results are in accordance with these studies. We plan to study the spouses of total laryngectomised patients using the same questionnaires as in the current study.

The differences between the two groups in ASEX scores and in the number of patients with sexual dysfunction scores over 11 were not significant. However, we believe it is valuable to know that the average ASEX scores and the number of patients with sexual dysfunction in Group 2 were higher than in Group 1. Yilmaz et al. [19] found results that were similar to ours.

In contrast to studies that found no significant difference between total and partial laryngectomy groups in terms of HNSX [2 10], our data set revealed a highly significant difference in HNSX scores ($p < 0.005$) between the total and partial laryngectomy groups. This differed from other studies that showed significant differences between total and partial laryngectomy groups in terms of HNSX [12]. In our study, while the HNSX scores were significantly different between groups, the ASEX scores showed no sexual function difference. While this is an apparent contradiction, it can be explained by the fact that the QLQH&N35 scale for HNSX primarily reflects libido and sexual enjoyment, and not sexual dysfunction [12]. The ASEX scale shows sexual dysfunction with tested reliability [20].

We also evaluated the relationship of the sex scales with each other using Pearson's correlation and determined a highly significant correlation between the HNSX scale and the ASEX 2 scale ($p = 0.000$) in both the partial laryngectomy and total laryngectomy groups. Between the HNSX scale and ASEX1 scale there was a high correlation in the partial laryngectomy group ($p = 0.000$), but there was no significant correlation in the total laryngectomy group ($p = 0.199$). In both groups, there was a high correlation between ASEX1 and ASEX2 ($p = 0.000$).

These results deserve a special explanation. Primarily, although there was no significant difference in terms of the ASEX scale and there was a significant difference in terms of HNSX, the high correlation of both tests in both groups might be because the HNSX scale does not reflect sexual dysfunction fully, although it includes some elements of

sexual function (libido and sexual enjoyment). Secondly, the detection of the total score from ASEX1 highly correlated with the presence of sexual dysfunction regarding ASEX2 in both groups suggests that ASEX1 could be used as a parameter for sexual dysfunction. Thirdly, the reason for the high correlation of the ASEX1 and HNSX scales in the partial laryngectomy group, while showing no correlation in the total laryngectomy group, might be because of the lack of verbal communication or because the HNSX scale and ASEX1 do not fully reflect sexual dysfunction. Lastly, in light of all these, HNSX may be a more appropriate method to compare these patient groups.

Our sample set was not large. This point can be seen as a weakness, but we think that our results are reliable and compatible with the recent literature. The epidemiological distribution of the study groups was similar and reduced the risk of bias.

Conclusions

These results show that the quality of life for patients who undergo total laryngectomy is lower than for those who undergo partial laryngectomy. Survival is, of course, the most important factor in the follow-up of patients with laryngeal cancer, but the psychosocial sequela of the disease and its treatment should not be underestimated.

The relationship between laryngectomy, sexuality and quality of life is a complex, intertwined issue. Many points remain to be clarified in future studies.

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Maxillofacial surgery

Palate perforation differentiates cocaine-induced midline destructive lesions from granulomatosis with polyangiitis

La perforazione del palato differenzia le lesioni destruenti della linea mediana indotte da cocaina dalla granulomatosi con poliangioite

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SUMMARY

Cocaine abuse occasionally causes extensive destruction of the osteocartilaginous structures of the nose, sinuses and palate, which mimics the clinical picture of other diseases associated with necrotising midfacial lesions. The differentiation of cocaine-induced midline destructive lesions (CIMDL) and limited granulomatosis with polyangiitis (GPA) may be difficult, particularly if patients do not readily admit substance abuse. We studied 10 patients with CIMDL and palate perforation referred to our Unit between 2002 and 2015. All cases underwent nasal endoscopy, sinus CT or MRI and ANCA test. In 8 patients, a nasal biopsy was performed. The PubMed database was searched to review all cases of palate perforation described in patients affected by CIMDL or GPA. All 10 cases presented with septal perforation and inferior turbinate destruction. We found hard palate perforation in 7 patients, soft palate perforation in 2 patients, and perforation of both in one patient. ANCA testing was negative in 8 patients and positive in 2, with C-ANCA and P-ANCA specificity, respectively. A review of the English literature identified palate perforation in 5 patients with GPA and in 73 patients with CIMDL. The presence of palate perforation in patients with MDL may represent a clinical marker that strongly favors CIMDL over GPA.

KEY WORDS: Palatal perforation • Cocaine • Granulomatosis with polyangiitis (GPA)

RIASSUNTO

L' abuso di cocaina può talvolta causare lesioni destruenti della struttura osteocartilaginea del naso, dei seni paranasali, del palato, con caratteristiche cliniche che ricordano altre patologie sistemiche associate a lesioni necrotizzanti centrofacciali. La diagnosi differenziale tra lesioni destruenti della linea mediana indotte da cocaina (CIMDL) e granulomatosi associata a poliangioite (GPA) può essere complessa, in particolare se il paziente non ammette l'abuso di sostanze. 10 pazienti con CIMDL e perforazione palatale sono stati trattati presso la nostra Unità Operativa tra il 2002 ed il 2015. Tutti i casi sono stati sottoposti ad endoscopia nasale, TC o RMN del massiccio facciale ed Anca test. In 8 casi è stata effettuata anche la biopsia nasale. Contestualmente è stata eseguita una revisione della letteratura presente su PubMed riguardante i casi di perforazione palatale in pazienti affetti da CIMDL e GPA. Tutti i 10 pazienti oggetto dello studio presentavano perforazione palatale e distruzione dei turbinati inferiori; inoltre 7 pazienti presentavano perforazione del palato duro , 2 pazienti perforazione del palato molle ed 1 paziente perforazione di entrambi. Gli Anca test erano negativi in 8 pazienti e positivi in 2, sia per C-Anca sia per P-Anca. La revisione della letteratura edita in lingua inglese ha evidenziato perforazioni palatali in 5 pazienti affetti da GPA e in 73 pazienti affetti da CIMDL. La presenza di perforazione palatale in pazienti con lesioni destruenti della linea mediana può rappresentare un nuovo marker clinico a favore delle CIMDL nella diagnosi differenziale con GPA.

PAROLE CHIAVE: *Perforazione del palato • Cocaina • Granulomatosi con poliangioite (GPA)*

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Introduction

The United Nations Office on Drugs and Crime reports that cocaine use has remained stable during the last three years, with 14 to 21 million estimated users per year worldwide. In particular, cocaine use has remained high in North America (5 million), South America (4.5 million), Africa (2.8 million), and Western and Central Europe (4 million) [1]. In the last 2016 European Drug Report, it was estimated that around 17 million adults (15-64 years) have used cocaine at least once in their lifetime with some countries (such as Spain and UK) showing a prevalence of use among young adults (15-34 years) that matches or even exceeds rates in the USA [2].

The most frequently used route of cocaine administration

is intranasal inhalation, or "snorting", and thus adverse effects on the nasal tract are very common [3]. Habitual nasal insufflations of cocaine may cause mucosal lesions, and if cocaine use becomes chronic and compulsive, progressive damage of the mucosa and perichondrium leads to ischaemic necrosis of septal cartilage and perforation of the nasal septum [4]. Occasionally, cocaine-induced lesions cause extensive destruction of the osseocartilaginous structures of nose, sinuses and palate that can mimic other diseases such as tumours, infections and immunological disorders. Several problems have been reported in differentiating cocaine-induced midline destructive lesion (CIMDL) from granulomatosis with polyangiitis (GPA) with limited ear-nose-throat involvement (ENT) [5]. An essential element for achieving correct diagnosis is clinical history, although cocaine abusers rarely admit drug dependency. The presence of a positive ANCA test with either proteinase 3 (PR3) or myeloperoxidase (MPO) specificity facilitates differential diagnosis of GPA from CIMDL, although not in all cases.

In the present study, we focus on patients with CIMDL and palatal perforation and review the available literature to discuss the utility of this type of midface destructive lesion as a possible clinical marker that might orient differential diagnosis.

Materials and methods

A series of 10 patients with CIMDL and palate perforation evaluated at the Department of Otorhinolaryngology of San Raffaele Hospital between February 2002 and October 2015 was retrospectively reviewed. This retrospective study adhered to ethical standards according to the Declaration of Helsinki. The patients ranged in age from 28 to 60 years; there were 8 males and 2 females. Follow-up lasted from 8 to 86 months. The duration of cocaine abuse was available in 7 patients, ranging from 2 to 30 years, at doses varying from 1 to 10 g/week. Demographics and past medical history were collected at the initial visit. It is important to underline that data concerning duration and daily dose of cocaine abuse are difficult to estimate because of poor collaboration between cocaine abusers and physicians. All patients underwent physical examination at the outpatient clinic of our Institute that included inspection of the face, oral cavity and oropharynx, as well as inspection of the nasal cavities and nasopharynx using 30° rigid telescopes (4 mm in diameter). During endoscopy, biopsies and samples for bacterial and fungal cultures were taken. A total of 8 mucosal biopsy specimens were evaluated. Sections were stained with haematoxylin-eosin. Orcein staining was used to evaluate elastic fibres, and periodic-acid Schiff and Ziehl-Nielsen stains were used to identify fungi and mycobacteria, respectively. Ten patients underwent imaging studies; in particular, 7 patients were evaluated using computed tomography (CT) scan, and 3 patients with magnetic resonance imaging (MRI). Sera from 10 patients were tested for ANCA in the laboratory at our Institute. We used indirect immunofluorescence (IIF) microscopy on ethanol-fixed blood donor neutrophils following the standard procedure outlined at the first ANCA workshop [6]. The PubMed database was searched for the available English literature (original papers, case series, and single reports) describing palate perforation in cocaine abusers and in patients suffering from GPA (available at: http://www.actaitalica.it/issues/2017/4-2017/06_TRIMARCHI).

Results

The 10 patients in our study cohort presented with a variable combination of common symptoms, such as epistaxis, oro-nasal regurgitation of solids and liquids, dysphagia, oropharyngeal pain, nasal speech and halitosis. At rhinoscopy, all patients showed necrotising ulcerative lesions, extensive crusting, intranasal destruction of the vomer and perforation of the nasal septum cartilage as well as of the hard and/or soft palate. Eight patients presented destruction of inferior turbinates, 7 of middle turbinates, and one of the right superior turbinate. The medial wall of maxillary sinus was completely reabsorbed in one patient. Oro-nasal communication affected the hard palate in 7 cases, the soft palate in 2 cases, and both the soft and hard palate in one patient. The diameter of the oro-nasal fistula ranged from 1 to 4 cm (Figs. 1, 2).

All patients had positive nasal cultures for *Staphylococcus aureus*. No positive fungal cultures were observed. Eight biopsies were negative for inflammatory, oncological and immunological diseases (2 patients admitted cocaine use, but did not consent to biopsy). One patient showed strong P-ANCA positivity on immunofluorescence with negative ELISA for both anti-PR3 and anti-MPO antibodies. One patient showed C-ANCA positivity on immunofluorescence with positive ELISA for anti-MPO antibodies.

CT scan confirmed the endoscopic features, showing perforation of nasal septum and palate, and destruction of the inferior middle and superior turbinate, whereas MRI revealed areas of abnormal signal in the septal and palate perforation, such as hypointensity of mucosal and submucosal tissue and nonhomogeneous enhancement.

Discussion

CIMDL represents an uncommon complication of habitual intranasal cocaine insufflations [7]. Patients with CIMDL develop extensive destruction of midfacial osseocartilaginous structures, which can resemble different pathological conditions such as oncologic, infectious and immunological diseases [5]. If differential diagnosis between oncologic or infectious disorders and CIMDL is facilitated by histopathological features and microbiological

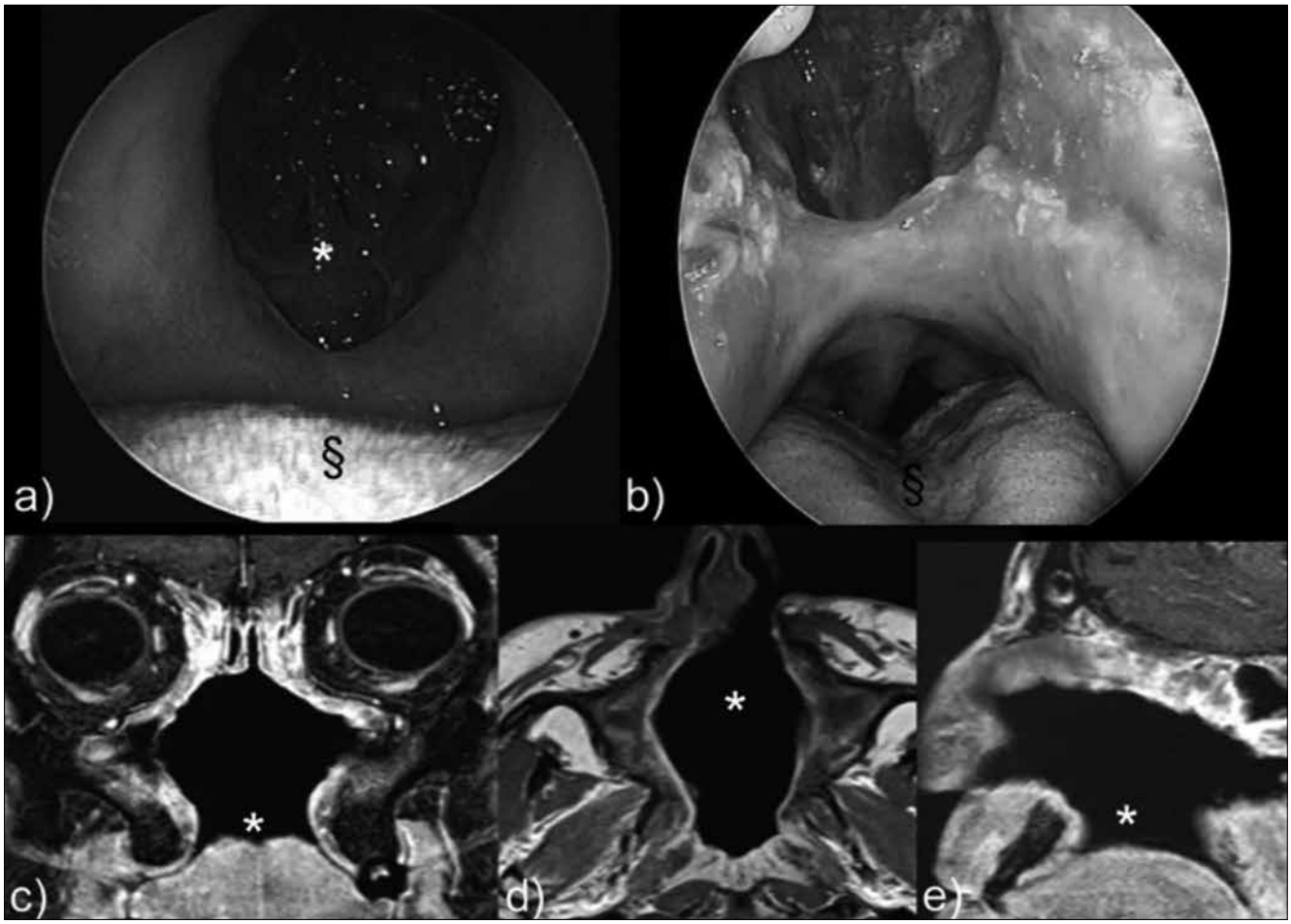


Fig. 1. a) Oral endoscopy (0° rigid fiberscope): large 4 cm palate perforation. **b)** Nasal endoscopy (0° rigid fiberscope): 4 cm hard palate perforation (§). **c)** MRI in the coronal plane shows destruction of the inferior, middle, and superior turbinates on both sides, partial reabsorption of the left medial wall, and palate perforation. **d)** Destruction of the central nasal septum and lateral nasal structures (middle turbinate) is shown by MRI axial study. **e)** Palate perforation (*) is shown in the sagittal plane.

studies, respectively, differentiation between CIMDL and limited ENT GPA may pose several problems. Considering the histological features of CIMDL reported in the literature [5] and in our experience, we frequently found the presence of vascular changes including microabscesses in the venule wall and leukocytoclastic vasculitis, which have been proposed as characteristic features of GPA [8-10]. Consequently, the histologic changes observed in a large proportion of biopsies from patients with CIMDL might be misinterpreted as "consistent with GPA" [8]. Only extravascular changes consisting in giant cells and microscopic foci of deeply located necrosis may be diagnostic of GPA [5-11].

However, as described in a previous study [12], in situ TUNEL assay on biopsy specimens can be useful to demonstrate apoptotic cells because they are highly characteristic features of CIMDL. If histological analysis is non-diagnostic, the next step is ANCA determination, although ANCA test positivity is not always discriminatory between CIMDL and GPA. Anti-neutrophilic cytoplasmic antibodies (ANCAs) directed against proteinase 3 (PR3) or myeloperoxidase (MPO) are sensitive and specific markers for GPA. However, instances of positive ANCA test results have been reported in an unexpectedly large proportion of patients with CIMDL [5]. In order to discriminate between CIMDL and GPA, Wiesner et al. made a detailed analysis of the ANCAs and found a high frequency (84%) of anti-human neutophil elastase (HNE) ANCAs in patients presenting with CIMDL. This finding allowed the authors to conclude that HNE ANCAs are discriminatory, whereas the presence of PR3 ANCAs is not. Consequently, in a clinical setting of necrotising inflammation of the upper respiratory tract, additional testing for HNE ANCAs may be useful in differentiating CIMDL from limited ENT GPA [7]. Unfortunately, this diagnostic method in not commonly available in routine practice. Differential diagnosis is difficult to reach in the case of HNE ANCA negativity, and in this case there are no discriminating elements.

To facilitate diagnosis of CIMDL and reduce the rate of misdiagnosis with other pathological conditions, we propose a diagnostic algorithm that takes into account the

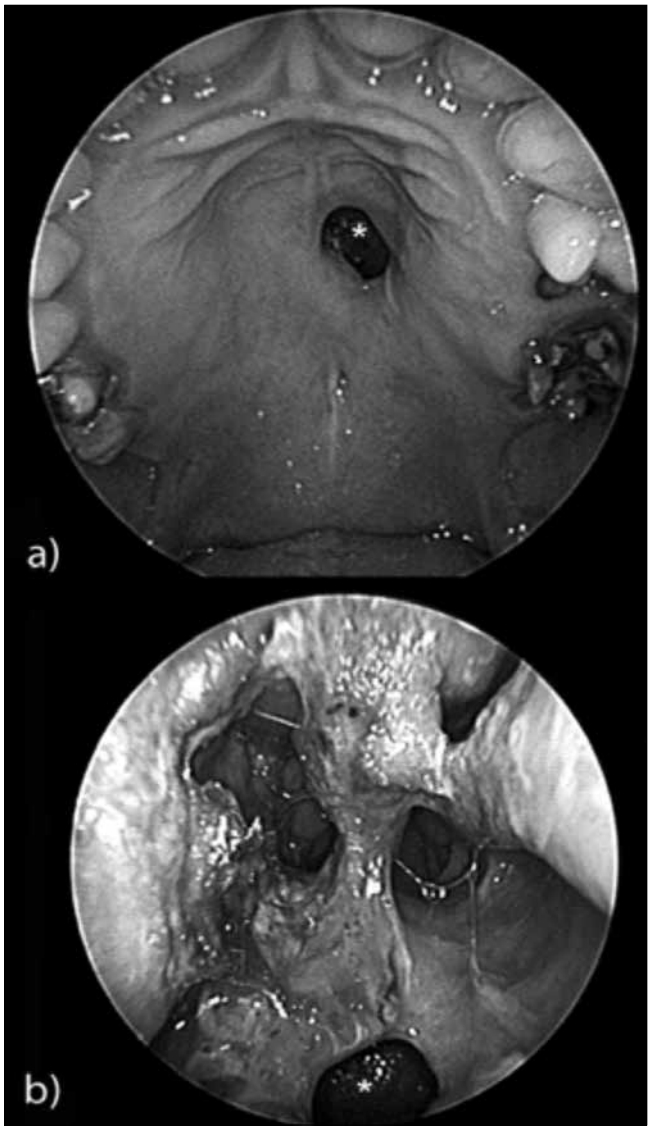


Fig. 2. a) Oral endoscopy (0° rigid fiberscope): a 1 cm hard palate perforation with regular margins (*). **b)** Nasal endoscopy (0° rigid fiberscope): typical nasal crusting in a cocaine abuser with 1 cm hard palate perforation (*).

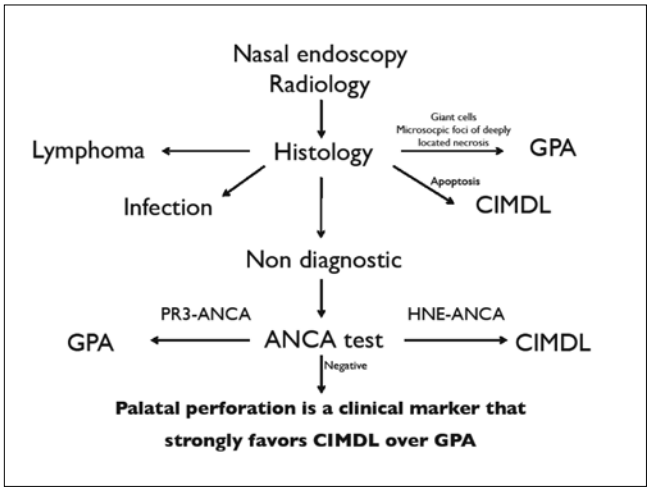
presence of palate perforation. This can help diagnostic choice when clinical doubt is focused on CIMDL and GPA (Fig. 3).

For this reason, we consider palate perforation to be an additional diagnostic element. In our experience, palate perforation is frequently associated with cocaine abuse [5], but we have never observed cases of palate perforation in patients with GPA [13].

From a review of the literature, palate perforation has been described in 73 CIMDL patients, while there are only 5 reports of subjects affected by GPA with palate perforation, for which a few comments are warranted.

Kasifoglu et al. [14] described the case of a 26-year-old woman admitted with nasal septum and palatal destruction. The authors reported indeterminate cANCA positivity and a histopathological diagnosis of GPA, but these elements were not exhaustive for definitive diagnosis because CIMDL could not be excluded. Moreover, the same authors defined palatal destruction as a rare condition in the course of GPA, citing three papers from literature [15-17] in which palatal perforation was not mentioned. Molloy et al. [18] did not present a published case, but indirectly describe their personal GPA experience with one case of palatal perforation in a letter. Manganaro et al. [19] imputed their case of soft palatal loss to GPA without ANCA test positivity or biopsy, and therefore with a debatable diagnosis. Aries et al. [20] presented a case of palatal perforation without biopsy because it was refused by the patient: the final diagnosis relied on non-histological criteria for GPA. In contrast, Sciascia et al. [21] presented the case of a 49-year-old woman with perforation of the midline and no other signs of systemic disease. A biopsy revealed a chronic inflammatory process with giant cells, pathognomonic of GPA.

Fig. 3. Diagnostic algorithm for CIMDL.



Recently, a proportion of idiopathic cases of midline destructive lesion have been attributed to IgG4-related disease (IgG4-RD), a novel systemic fibro-inflammatory condition characterised by tumourous swelling of affected organs and serum IgG4 elevation [22 23]. IgG4-RD was shown to involve midline structures both in the form of mass-forming lesions and nasal or palatal erosions, thereby introducing an additional differential diagnosis to CIMDL. However, in contrast to GPA and CIMDL, the incidence of IgG4-RD is largely unknown and palatal perforation remains an anecdotal observation from a single centre case series that requires further confirmation. In addition, as we recently reported, IgG4-RD might be accurately differentiated from CIMDL thanks to specific histological hallmarks, such as storiform fibrosis, IgG4+ positive plasma cells, and obliterative phlebitis [24].

In conclusion, our experience and the present review of the literature demonstrate that palatal perforation is strongly suggestive of CIMDL and represents an impor-

tant diagnostic element that can enrich diagnostic workup between GPA and CIMDL.

Conclusions

In conclusion, the presence of palate perforation in patients with MDL and negative biopsy and negative ANCA test may represent a clinical marker that strongly favours CIMDL over GPA.

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Phoniatry

Stabilometric findings in patients affected by organic dysphonia before and after phonomicrosurgery

Analisi posturografica in pazienti con disfonia organica prima e dopo fonomicrochirurgia

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SUMMARY

The purpose of this study is to understand if there is any alteration in the posture of patients affected by organic dysphonia and describe possible postural modifications after phonomicrosurgery on the vocal folds. Forty subjects (22 males, 18 females; mean age 32.6 ± 7.5 years) suffering from organic dysphonia (15 cases of polyps, 11 submucosal retention cysts, 10 bilateral fibrous vocal fold nodules and 4 bilateral Reinke's oedema) were examined by open-eye and closed-eye posturography while breathing spontaneously before surgery, 24 hours after surgery and after 6 months. The variables taken into account were: the coordinates of the centre of pressure on both frontal and sagittal planes, length and surface of the track, mean velocity of the oscillations and relative standard deviations, spectral analysis of oscillation frequency, statokinesigram and stabilogram values. No characteristic pathological pattern was seen in basal stabilometry in any of the subgroups (polyps, cysts, Reinke's oedema). Only the subgroup of patients with fibrous vocal fold nodules (8/10; 80%) showed a slight forward shift from the centre of gravity when analysed in both open-eye and closed-eye posturography. A comparison performed within the same subgroup using open-eye and closed-eye posturography before and after surgery revealed no significant difference in any of the parameters being studied. The use of static stabilometry in this study demonstrates the absence of characteristic postural alterations in patients affected by organic dysphonia and also excludes that simple removal of the vocal fold lesion can change posture.

KEY WORDS: Posture • Static stabilometry • Proprioception • Phonomicrosurgery • Organic voice disorders

RIASSUNTO

Lo scopo di questo studio è stato quello di dimostrare se pazienti affetti da disfonia organica presentino alterazioni posturali caratteristiche e se l'intervento di fonomicrochirurgia delle corde vocali determini modificazioni dell'assetto posturale. Sono stati esaminati 40 soggetti (22 maschi, 18 femmine; età media 32,6 ± 7,5 anni) affetti da disfonia organica (15 polipi cordali, 11 cisti da ritenzione sottomucosa, 10 noduli vocali fibrosi bilaterali e 4 edema di Reinke). L'assetto posturale è stato studiato mediante stabilometria statica in respirazione spontanea, ad occhi aperti e ad occhi chiusi, in tre diverse fasi: prima dell'intervento chirurgico, 24 ore dopo la chirurgia e 6 mesi dopo l'intervento. Le variabili prese in considerazione sono state: le coordinate del centro di pressione sul piano frontale e sagittale, la lunghezza e la superficie della traccia, la velocità media delle oscillazioni e le relative deviazioni standard, l'analisi spettrale della frequenza di oscillazione e i valori di statokinesigramma e stabilogramma. Nessun pattern patologico caratteristico veniva rilevato alla stabilometria in condizioni basali nei diversi sottogruppi di pazienti (polipi, cisti, edema di Reinke). Solo il sottogruppo di pazienti con noduli vocali bilaterali fibrosi (8/10; 80%) mostrava un lieve spostamento in avanti del centro di gravità sia ad occhi aperti che ad occhi chiusi. In tutti i sottogruppi non si verificavano modificazioni significative delle variabili stabilometriche ad occhi aperti e ad occhi chiusi, prima e dopo l'intervento chirurgico. L'uso della stabilometria statica, in questo studio, dimostra l'assenza di alterazioni posturali caratteristiche nei casi di disfonia organica ed esclude che la semplice rimozione della lesione cordale, unilaterale o bilaterale, possa determinare variazioni posturali.

PAROLE CHIAVE: *Postura • Stabilometria statica • Propriocezione • Fonomicrochirurgia • Disfonia organica*

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Introduction

There is general agreement in the literature that posture control and voice are related [1-3]; in fact, it has been demonstrated that correct posture is fundamental for quality function of the voice [4-12]. Voice disorders are usually associated with alterations in extra-laryngeal muscle activity, whereas changes in posture can sometimes have a significant role in the genesis and/or maintenance of these voice disorders, in a sort of vicious circle where a change in

extra-laryngeal tension and an inadequate activity of the larynx itself contributes to and influences each other [13].

In recent years, the use of stabilometry for studying posture has permitted overcoming the many limits given by clinical tests alone [3 11-14]. Computerised posturographic studies performed with a stabilometric platform supply extremely sensitive numeric parameters in subjects with purely dysfunctional dysphonia or dysphonia associated with secondary organic disorders, and even in subjects with no primary balance problems. Moreover, using static stabilometry in open-eye, closed-eye and in closed-eye with head backwards, the importance of the individual sensorial inputs (visual, vestibular and cervical proprioceptive) can be assessed, and when the test is performed during natural breathing (not forced) it is possible to study the prevalently reflex component of posture (spinal vestibular reflex: SVR) [13]. In fact, the systems controlling posture, balance and organisation of body movement rely principally on the integration of specific sensorial patterns for their function, followed by the elaboration of specific motor responses that are mainly reflex ones (the most important of which is undoubtedly the SVR).

Our recent studies on subjects with pure dysfunctional dysphonia show how the greater proprioception achieved through speech rehabilitation brings an improvement in the majority of the postural parameters evaluated with static stabilometry [13]. Our studies confirmed what was previously described in the relevant literature.[3] One of these studies evaluated postural variations in a group of subjects with dysfunctional dysphonia, and then compared these variations with the modifications seen in the stabilometric parameters after speech therapy [13]. The results obtained were very encouraging and call attention not only to the importance of stabilometric analysis in subjects with voice disorders associated with postural changes, but also to the fundamental role rehabilitation plays when resolving dysphonia and at the same time improving postural performance. With this in mind, investigation of the postural characteristics of patients with voice disorders who have organic lesions in the vocal folds appears interesting. We therefore submitted subjects with organic dysphonia due to acquired, benign vocal fold lesions to posturographic analysis, performing static stabilometry before and after phonomicrosurgery. Our aim was to understand if there were any postural characteristics particular to the individual organic disorders and to assess if removal of the lesion with phonomicrosurgery is, on its own, sufficient to modify the postural performance of subjects.

Materials and methods

In this study, we assessed 40 patients (22 males and 18 females; mean age 32.6 ± 7.5 years) with organic dysphonia: 15 had a vocal fold polyp, 11 a submucosal retention cyst, 10 bilateral fibrous vocal fold nodules and 4 cases of bilateral Reinke's oedema. The clinical characteristics of patients are summarised in Table I. All subjects were submitted to a posturographic test using a static stabilometric platform (S.Ve.P. AMPLIFON-Amplaid, Milan, Italy), inviting patients to stand upright during the test and breathe normally. The test was carried out with the patients' eyes both open (OE) and closed (CE) to eliminate visual afferents and enhance proprioceptive faculties. The posturographic test was carried out in basal conditions and then repeated 24 hours after phonosurgical removal of the vocal fold lesion. Moreover, the posturographic test was repeated at 6 months after surgery under the same conditions as the baseline and 24 hour control. The following parameters were considered: pressure centre coordinates on the frontal (X; right-left) (minimum X, maximum X, mean X) and sagittal (Y; forward/backward) (minimum Y, maximum Y, mean Y) areas; total length of the recording in mm (L); surface of the helix containing 90% of the points sampled (S); mean velocity (VEL) and relative SD; Fourier fast transform (FFT) for oscillations on the X and Y axes separately; statokinesigram describing the area within which the centre of gravity projects with respect to the floor, and stabilogram which reveals the time taken for the pressure centre to shift on both the X and Y axes.

Each patient underwent accurate phoniatric and otorhinolaryngoiatric anamnesis, general ENT examination,

Table I. Clinical characteristics of the study group.

Study Group	Patients	Sex (M/F)	Age (yrs)	LPR*
	n = 40	**22M/18F**	**32.6 ± 7.5**	**NO**
Subgroups	Patients	Sex (M/F)	Age (yrs)	LPR*
Polyps	n = 15 15/40 (37.5%)	10M/5F	29.9 ± 6.4	NO
Acquired cysts	n = 11 11/40 (27.5%)	7M/4F	32.1 ± 7.3	NO
Bilateral nodules	n = 10 10/40 (25%)	2M/8F	33.3 ± 6.6	NO
Reinke's oedema	n = 4 4/40 (10%)	3M/1F	42.8 ± 7.4	NO

**LPR = Signs of laryngopharyngeal reflux*

flexible fiberoptic rhino-pharyngo-laryngoscopy, videolaryngostroboscopy, electro-acoustic voice tests including spectrography and analysis of the vocal signal with the multidimensional voice program (MDVP). Vocal signal was acquired by asking the patient to pronounce a sustained [a] vowel. All patients had been suffering from chronic dysphonia for at least six months and diagnosis of organic lesion of the vocal fold was made for at least three months in all study subjects.

All patients remarked that their voice disorder limited their social or working life. The subjective degree of severity of the condition was evaluated using the Voice Handicap Index (VHI) questionnaire, which each patient filled in before surgical treatment [15]. The perceptive evaluation of voice was scored against the GRBAS Scale[16]. The acoustic analysis, perceptual analysis and patient's self-assessment were performed before and 6 months after surgery.

The tests carried out with flexible fiberoptic endoscopy and rigid videolaryngostroboscopy (70°) revealed organic damage in the glottic plane of all the subjects in the study. None of the patients showed signs of posterior inflammation due to laryngo-pharyngeal reflux, whereas they all showed some degree of tentative compensation by the supraglottic structures to aid closure of the glottis during phonation, since closure was faulty because of the organic lesion on the vocal fold. In the 5 cases with submucosal cyst, stroboscopic light revealed an interruption of mucosal wave on the site of the lesion.

After accurate anamnesis and orthopaedic examination, all patients with orthopaedic disorders or known postural defects (varus/valgus foot, scoliosis, previous orthopaedic surgery of any kind, etc.) were excluded from the study. Additionally, those who showed balance disorders during anamnesis and/or were classified positive upon oto-neurological examination were excluded from the study. To evaluate the possible presence of oto-neurological diseases, the following tests were performed: accurate oto-neurological assessment, liminal tonal audiometry, investigation of spontaneous and provoked nystagmus by videonystagmography and vestibular caloric balance. Other exclusion criteria were systemic disease, alcohol abuse, psychiatric disorder and vision less than 10/10.

Seven subjects were excluded from the study: 3 cases were affected by oto-neurological diseases (1 case of Menière's disease, 1 case of recurrent paroxysmal positional vertigo and 1 case of recent vestibular neuronitis), 2 cases were affected by scoliosis, 1 case was affected by whiplash injury with functional limitation of the cervical spine, while 1 case was affected by diabetes mellitus type I. Therefore, considering the inclusion and exclusion criteria, 40 subjects were included in the study group.

None of the patients had undergone previous speech rehabilitation/therapy. Even the 10 patients with fibrous nodules had never been submitted to rehabilitation treatment since, at diagnosis, patients chose surgical treatment after all therapeutic options had been explained to them.

After surgical treatment, the study group was not submitted to speech therapy either because it was not advisable or because the patients refused it.

Surgical treatment

The phonomicrosurgery procedure was performed under general anaesthesia using specific instruments for endolaryngeal phonosurgery and according to the methods described in the national and international literature [17 18].

Statistical analysis

All numeric parameters are expressed in medians. A comparison was performed between several parameters at different times, before and after surgical treatment. The comparison (before open-eye *vs* after open-eye mode; before closed-eye *vs* after closed-eye mode; after 24 h *vs* after 6 months surgery) was carried out considering the median of the different parameters with a Wilcoxon non-parametric test and considering the same parameters for the percentage of pathological patients using a chi^2 Test. The parameters resulting above normal range with this instrument were considered pathological. All tests were considered significant with $p < 0.05$. StatView 5 release 5.0.1 was used to process data.

Results

Control laryngostroboscopy carried out at one month and 6 months after phonomicrosurgery demonstrated the absence of organic lesions in all the subjects.

The results of acoustic analysis (MDVP), perceptual analysis (GRBAS) and VHI performed before and 6 months after surgical treatment are summarised in Tables II, III and IV.

Stabilometric study

Basal conditions (Pre-OE and Pre-CE)

In basal conditions (before phonomicrosurgery), no characteristic pathological stabilometric pattern was seen within the individual groups (polyps, cysts and Reinke's oedema). An anterior shift from the centre of gravity was seen in 8 of 10 patients with fibrous vocal nodules (80%) in both open-eye and closed-eye tests. Such an anterior shift from the centre of gravity was evident at analysis of the posturographic trace and, in particular, of the statokinesigram.

Pre-OE vs Post-OE1 and Pre-CE vs Post-CE1 (Follow-up at 24 h) and Pre-OE vs Post-OE2 and Pre-CE vs Post-CE2 (follow-up at 6 months)

A comparison performed within the individual groups (polyps, nodules, cysts and Reinke's oedema) before and after surgery (after 24 hours and after 6 months) in open-eye (Pre-OE *vs* Post-OE1; Pre-OE *vs* Post-OE2) and

Table II. Results of the acoustic analysis (MDVP) for Jitter %, Shimmer %, NHR and SPI parameters, before and 6 months after phonomicrosurgery.

POLYPS			
	Pre	Post	p
Jitter %	2.23 ± 0.32	0.31 ± 0.36	p < 0.01
Shimmer %	3.34 ± 0.82	1.92 ± 0.71	
NHR	0.14 ± 0.12	0.09 ± 0.06	
SPI	26.43 ± 4.24	8.11 ± 4.13	
NODULES			
	Pre	Post	p
Jitter %	1.73 ± 0.21	0.91 ± 0.22	p < 0.01
Shimmer %	4.15 ± 0.84	2.13 ± 0.41	
NHR	0.12 ± 0.02	0.06 ± 0.02	
SPI	16.36 ± 3.83	4.92 ± 1.63	
CYSTS			
	Pre	Post	p
Jitter %	1.97 ± 0.44	0.52 ± 0.31	p < 0.01
Shimmer %	5.26 ± 0.85	0.33 ± 0.01	
NHR	0.18 ± 0.31	0.08 ± 0.06	
SPI	16.94 ± 3.93	11.12 ± 1.63	
REINKE'S OEDEMA			
	Pre	Post	p
Jitter %	4.55 ± 1.25	1.23 ± 0.61	p < 0.01
Shimmer %	11.46 ± 3.23	3.82 ± 1.31	
NHR	0.25 ± 0.14	0.12 ± 0.04	
SPI	12.86 ± 3.67	6.25 ± 1.24	

closed-eye manner (Pre-CE *vs* Post-CE1; Pre-CE *vs* Post-CE2) showed that there were no statistically significant differences in any of the parameters studied. Even the stabilometric tests performed after surgery in the 10 subjects with vocal nodules detected no shifts from the centre of gravity and showed no substantial modifications compared to basal conditions in the parameters studied.

Post-OE1 (24h) vs Post-OE2 (6 months) and Post-CE1 (24h) vs Post-CE2 (6 months)

A comparison performed within the individual groups after surgery (24h) *vs* follow-up (6 months) in open-eye (Post-OE1 *vs* Post-OE2) and closed-eye manner (Post-CE1 *vs* Post-CE2) showed that there were no statistically significant differences in any of the parameters studied.

Table IV. Results of the perceptual analysis (GRBAS) before and 6 months after phonomicrosurgery.

POLYPS			
	Pre	Post	p
G	1.7 ± 0.6	0.2 ± 0.3	p < 0.0001
R	1.2 ± 0.5	0.1 ± 0.2	
B	1.4 ± 0.6	0.1 ± 0.2	
A	0.9 ± 0.3	0.1 ± 0.2	
S	0.7 ± 0.6	0.2 ± 0.3	p = 0.04
NODULES			
	Pre	Post	p
G	1.4 ± 0.4	0.2 ± 0.3	p < 0.001
R	1.2 ± 0.3	0.1 ± 0.1	
B	1.7 ± 0.6	0.2 ± 0.2	
A	1.1 ± 0.8	0.2 ± 0.4	
S	1.4 ± 0.6	0.2 ± 0.2	
CYSTS			
	Pre	Post	p
G	1.9 ± 0.8	0.3 ± 0.4	p < 0.001
R	1.5 ± 0.7	0.3 ± 0.5	
B	1.6 ± 0.6	0.2 ± 0.2	
A	1.2 ± 0.4	0.1 ± 0.2	
S	1.1 ± 0.8	0.2 ± 0.2	
REINKE'S OEDEMA			
	Pre	Post	p
G	1.9 ± 0.7	0.4 ± 0.1	p < 0.005
R	2.0 ± 0.5	0.5 ± 0.5	
B	0.6 ± 0.1	0.2 ± 0.2	NS
A	1.2 ± 0.5	0.3 ± 0.1	p < 0.005
S	1.5 ± 0.6	0.3 ± 0.2	

The results are summarised for each subgroup in Tables V and VI.

Discussion

It is now acknowledged that pure dysfunctional dysphonia or the types associated with secondary larynx disorders (with vocal fold lesions) are related to modified respiratory dynamics and particular postural characteristics [19]. Thanks to computerised posturographic studies, it is now possible to accurately evaluate the numerical parameters and graphics that reflect even the slightest modification

Table III. Results of patient self-assessment (VHI), before and 6 months after phonomicrosurgery.

	Pre	Post	p
Polyps	37.2 ± 16.6 (18-73)	9.3 ± 3.2 (4-14)	p < 0.0001
Nodules	32.1 ± 12.5 (15-56)	11.8 ± 5.3 (4-19)	p < 0.001
Cysts	41.5 ± 15.9 (22-71)	10.9 ± 4.9 (3-20)	p < 0.0001
Reinke's oedema	33.3 ± 6.7 (27-40)	16.8 ± 2.8 (14-20)	p = 0.004
Total (N = 40)	36.7 ± 14.7 (15-73)	11.1 ± 4.5 (3-20)	p < 0.0001

Table V. Pre-OE, Post-OE1 (after 24h), Post-OE2 (after 6 months): values of each parameter in the *open-eye* mode study, before and after phonomicrosurgery (median). Pre-OE N (%), Post-OE1 (after 24h) and Post-OE2 (after 6 months) N (%): number of pathological patients and the relative percentage for each parameter. p1: statistical significance of the pre- vs post-therapy comparison referring to the median (Wilcoxon). p2: statistical significance of the pre- vs post-therapy comparison referring to the number of pathological patients (Chi^2).

POLYPS (N = 15)								
	Pre-OE	Post-OE1	Post-OE2	p1	Pre-OE N° (%)	Post-OE1 N° (%)	Post-OE2 N° (%)	p2
Xmin	-9.89	-8.56	-10.1	NS	1 (6%)	2 (12%)	1 (6%)	NS
Xmax	5.21	3.49	4.24	NS	2 (12%)	1 (6%)	1 (6%)	NS
Xmed	-2.89	-3.28	-2.48	NS	1 (6%)	1 (6%)	1 (6%)	NS
SD (X)	0.23	0.22	0.24	NS	-	-	-	-
Ymin	-34.62	-30.57	-33.61	NS	1 (6%)	0	0	NS
Ymax	-29.67	-27.93	-30.35	NS	0	0	0	NS
Ymed	-32.59	-34.51	-32.81	NS	0	0	0	-
SD (Y)	0.29	0.27	0.32	NS	-	-	-	NS
L	194.45	201.56	203.39	NS	1 (6%)	1 (6%)	0	NS
S	141.78	135.69	138.93	NS	2 (12%)	2 (12%)	2 (12%)	NS
FFTx	0.04	0.04	0.04	NS	-	-	-	-
FFTy	0.08	0.04	0.04	NS	-	-	-	-
VEL	12.44	11.35	13.82	NS	-	-	-	-
SD(VEL)	4.43	4.09	4.93	NS	3 (18%)	2 (12%)	2 (12%)	NS
NODULES (N = 10)								
	Pre-OE	Post-OE1	Post-OE2	p1	Pre-OE N°(%)	Post-OE1 N°(%)	Post-OE2 N°(%)	p2
Xmin	-9.79	-9.54	-10.56	NS	2 (20%)	2 (20%)	1 (10%)	NS
Xmax	4,11	3.82	5.34	NS	1 (10%)	1 (10%)	1 (10%)	NS
Xmed	-1.39	-1.03	-2.62	NS	1 (10%)	1 (10%)	1 (10%)	NS
SD (X)	0.26	0.24	0.22	NS	-	-	-	-
Ymin	-57.52	-55.31	-52.83	NS	1 (10%)	1 (10%)	1 (10%)	NS
Ymax	-38.02	-34.80	-36.81	NS	2 (20%)	2 (20%)	2 (20%)	NS
Ymed	-47.34	-45.59	-44.21	NS	1 (10%)	1 (10%)	2 (20%)	-
SD (Y)	0.32	0.30	0.30	NS	-	-	-	NS
L	252.36	248.81	261.78	NS	1 (10%)	1 (10%)	1 (10%)	NS
S	150.12	148.9	154.87	NS	3 (30%)	3 (30%)	3 (30%)	NS
FFTx	0.08	0.08	0.08	NS	-	-	-	-
FFTy	0.08	0.08	0.08	NS	-	-	-	-
VEL	11.65	11.92	13.03	NS	-	-	-	-
SD(VEL)	11.33	10.52	11.04	NS	4 (40%)	3 (30%)	3 (30%)	NS
CYSTS (N = 11)								
	Pre-OE	Post-OE1	Post-OE2	p1	Pre-OE N°(%)	Post-OE1 N°(%)	Post-OE2 N°(%)	p2
Xmin	2.44	3.69	4.35	NS	1 (9%)	1 (9%)	0	NS
Xmax	12.69	14.82	16.92	NS	2 (18%)	1 (9%)	1 (9%)	NS
Xmed	8.51	6.91	8.34	NS	1 (9%)	1 (9%)	1 (9%)	NS
SD (X)	0.30	0.29	0.24	NS	-	-	-	-
Ymin	-49.50	-44.30	-51.91	NS	0	0	0	NS
Ymax	-31.39	-38.31	-43.72	NS	1 (9%)	2 (18%)	1 (9%)	NS
Ymed	-40.49	-41.08	-44.45	NS	0	0	0	-
SD (Y)	0.33	0.31	0.30	NS	-	-	-	NS
L	229.31	212.83	259.93	NS	1 (9%)	1 (9%)	1 (9%)	NS
S	132.28	149.72	151.78	NS	2 (18%)	1 (9%)	2 (18%)	NS
FFTx	0.04	0.06	0.08	NS	-	-	-	-
FFTy	0.04	0.04	0.04	NS	-	-	-	-
VEL	11.56	12.83	13.35	NS	-	-	-	-
SD(VEL)	6.89	7.31	5.21	NS	2 (18%)	2 (18%)	1 (9%)	NS

Tab. V continues

Tab. V follows

	REINKE'S OEDEMA (N = 4)							
	Pre-OE1	Post-OE1	Post-OE2	p1	Pre-OE N° (%)	Post-OE1 N° (%)	Post-OE2 N° (%)	p2
Xmin	-6.32	-7.02	-9.23	NS	0	0	0	NS
Xmax	3.68	2.07	4.45	NS	0	0	0	NS
Xmed	-1.02	-2.82	-3.69	NS	1 (25%)	1 (25%)	0	NS
SD (X)	0.20	0.22	0.20	NS	-	-	-	-
Ymin	-51.2	-50.79	-59.38	NS	1 (25%)	1 (25%)	1 (25%)	NS
Ymax	-31.30	-26.89	-26.51	NS	0	0	0	NS
Ymed	-45.19	-41.79	-49.42	NS	0	0	0	-
SD (Y)	0.39	0.37	0.35	NS	-	-	-	NS
L	239.06	230.92	221.38	NS	1 (25%)	1 (25%)	-	NS
S	108.72	121.28	118.92	NS	0	0	0	NS
FFTx	0.04	0.04	0.04	NS	-	-	-	-
FFTy	0.04	0.04	0.04	NS	-	-	-	-
VEL	11.44	10.72	15.59	NS	-	-	-	-
SD(VEL)	7.37	6.81	8.12	NS	2 (50%)	2 (50%)	1 (25%)	NS

Table VI. Pre- and Post- therapy values considering the above parameters in the closed-eye mode (CE).

	POLYPS (N=15)							
	Pre-CE	Post-CE1	Post-CE2	p1	Pre-CE N°(%)	Post-CE1 N°(%)	Post-CE2 N°(%)	p2
Xmin	-14.25	-12.97	-10.12	NS	1 (6%)	1 (6%)	0	NS
Xmax	7.29	6.92	12.56	NS	2 (12%)	2 (12%)	1 (6%)	NS
Xmed	-4.38	-3.83	-1.98	NS	1 (6%)	1 (6%)	2 (12%)	NS
SD (X)	0.30	0.28	0.35	NS	-	-	-	-
Ymin	-47.49	-45.41	-54.36	NS	1 (6%)	1 (6%)	1 (6%)	NS
Ymax	-41.31	-40.29	-48.05	NS	1 (6%)	1 (6%)	1 (6%)	NS
Ymed	-45.21	-40.49	-52.79	NS	0	0	0	-
SD (Y)	0.30	0.29	0.30	NS	-	-	-	NS
L	403.38	383.549	409.93	NS	2 (12%)	2 (12%)	2 (12%)	NS
S	326.45	319.38	312.57	NS	2 (12%)	1 (6%)	1 (6%)	NS
FFTx	0.04	0.04	0.04	NS	-	-	-	-
FFTy	0.08	0.08	0.06	NS	-	-	-	-
VEL	15.36	14.85	18.45	NS	-	-	-	-
SD(VEL)	9.45	8.87	10.45	NS	3 (18%)	3 (18%)	2 (12%)	NS
	NODULES (N=10)							
	Pre-CE	Post-CE1	Post-CE2	p1	Pre-CE N°(%)	Post-CE1 N°(%)	Post-CE2 N°(%)	p2
Xmin	-16.78	-15.38	-17.45	NS	1 (10%)	2 (20%)	2 (20%)	NS
Xmax	8.31	7.46	9.69	NS	2 (20%)	1 (10%)	2 (20%)	NS
Xmed	-5.38	-4.13	-6.38	NS	2 (20%)	2 (20%)	2 (20%)	NS
SD (X)	0.40	0.38	0.40	NS	-	-	-	-
Ymin	-63.34	-60.34	65.91	NS	2 (20%)	2 (20%)	2 (20%)	NS
Ymax	-45.29	-40.39	-50.23	NS	2 (20%)	2 (20%)	2 (20%)	NS
Ymed	-54.82	-53.78	-49.36	NS	2 (20%)	2 (20%)	3 (30%)	-
SD (Y)	0.40	0.41	0.40	NS	-	-	-	NS
L	503.26	482.29	492.91	NS	2 (20%)	2 (20%)	2 (20%)	NS
S	327.12	303.92	336.43	NS	3 (30%)	3 (30%)	3 (30%)	NS
FFTx	0.08	0.08	0.08	NS	-	-	-	-
FFTy	0.08	0.08	0.06	NS	-	-	-	-
VEL	16.23	14.38	16.36	NS	-	-	-	-
SD(VEL)	11.36	10.38	12.65	NS	5 (50%)	4 (40%)	4 (40%)	NS

Tab. VI continues

Tab. VI follows

CYSTS (N = 11)								
	Pre-CE	Post-CE1	Post-CE2	p1	Pre-CE N° (%)	Post-CE1 N° (%)	Post-CE2 N° (%)	p2
Xmin	-4.28	-2.89	-4.35	NS	2 (18%)	1 (9%)	2 (18%)	NS
Xmax	14.3	11.29	9.13	NS	2 (18%)	1 (9%)	1 (9%)	NS
Xmed	6.16	5.29	3.69	NS	1 (9%)	1 (9%)	1 (9%)	NS
SD (X)	0.25	0.26	0.28	NS	-	-	-	-
Ymin	-72.38	-70.31	-65.5	NS	0	0	0	NS
Ymax	-50.39	-48.34	-49.1	NS	2 (18%)	2 (18%)	2 (18%)	NS
Ymed	-62.14	-59.29	-57.49	NS	1 (9%)	1 (9%)	1 (9%)	-
SD (Y)	0.42	0.40	0.36	NS	-	-	-	NS
L	501.34	490.29	505.39	NS	1 (9%)	1 (9%)	1 (9%)	NS
S	298.56	257.82	282.31	NS	2 (18%)	1 (9%)	2 (18%)	NS
FFTx	0.04	0.04	0.04	NS	-	-	-	-
FFTy	0.04	0.04	0.03	NS	-	-	-	-
VEL	12.76	12.08	12.23	NS	-	-	-	-
SD(VEL)	10.89	11,31	11.41	NS	2 (18%)	2 (18%)	2 (18%)	NS
REINKE'S OEDEMA (N = 4)								
	Pre-CE	Post-CE1	Post-CE2	p1	Pre-CE N° (%)	Post-CE1 N° (%)	Post-CE2 N° (%)	p2
Xmin	-11.91	-10.93	-10.6	NS	0	0	0	NS
Xmax	19.18	18.92	15.19	NS	0	0	0	NS
Xmed	-0.48	1.39	1.21	NS	1 (25%)	1(25%)	1 (25%)	NS
SD (X)	0.45	0.41	0.36	NS	-	-	-	-
Ymin	-77.74	-74.92	-70.76	NS	1 (25%)	1 (25%)	1 (25%)	NS
Ymax	-26.40	-25.93	-32.98	NS	0	0	1 (25%)	NS
Ymed	-42.98	-40.38	-49.39	NS	0	0	0	-
SD (Y)	0.70	0.66	0.54	NS	-	-	-	NS
L	612.27	603.38	598.49	NS	1 (25%)	1 (25%)	1 (25%)	NS
S	321.78	355.98	343.05	NS	0	0	0	NS
FFTx	0.12	0.12	0.14	NS	-	-	-	-
FFTy	0.12	0.12	0.12	NS	-	-	-	-
VEL	23.27	22.79	19.49	NS	-	-	-	-
SD(VEL)	11.41	10.96	10.62	NS	2 (50%)	2 (50%)	2 (50%)	NS

in posture. In fact, static stabilometry performed in basal conditions has been able to reveal postural modifications associated with voice disorders, which showed significant variations in the stabilometric parameters after speech rehabilitation [3 13]. On the other hand, there are no studies aimed at discovering whether these postural alterations are present even in cases of organic dysphonia and if removal of the lesion through phonomicrosurgery can, on its own, bring about substantial changes in postural performance. Hence, we submitted a heterogeneous group of patients with organic dysphonia (vocal fold polyps, nodules, acquired submucosal cysts and Reinke's oedema) to static stabilometry to see if there were any postural characteristics that were typical to the individual organic disorder, and to assess if phonomicrosurgery alone is sufficient to modify the posture of patients.

In basal conditions, none of the subgroups studied (polyps, cysts and Reinke's oedema) showed any characteristic pathological stabilometric pattern. In fact, the majority of parameters were within the normal range, with no significant deviations from the centre of gravity. Only eight patients (8/10; 80%) in the subgroup with bilateral nodules on the vocal folds showed a forward shift from the centre of gravity, and pathological S and SD VEL values both in open-eye and closed-eye conditions, attesting the postural characteristics of subjects with pure dysfunctional dysphonia [13]. This confirms what has already been acknowledged; that is, vocal fold nodules may be, at least in some cases, the direct consequence of long-standing dysfunctional dysphonia that has been inadequately treated. Hence, patients with vocal fold nodules display a stabilometric pattern both in the open-eye and closed-eye examinations that is similar to what is seen in patients with pure dysfunctional dysphonia; on the contrary, however, the

parameters of the former subjects do not improve significantly at 24 hours after surgery. While the majority of the stabilometric parameters improve significantly in subjects with pure dysfunctional dysphonia after rehabilitation therapy [3 13], the group with vocal fold nodules continue to have modified posture at 24 hours and 6 months after phonosurgery and manifest no significant variations. From a postural point of view, this fact indirectly confirms the importance of giving adequate and sufficiently lengthy rehabilitation treatment to patients with dysfunctional dysphonia associated with altered posture. On the other hand, the static stabilometric results obtained both in basal conditions and after phonomicrosurgery in cases of polyps, cysts and Reinke's oedema demonstrate how modified postural performance in these circumstances is much less pronounced and not so distinctive. One would assume that, immediately after surgery, the situation remains the same as before, while a longer follow-up can show some changes in postural control, related to voice amelioration. The follow-up at 6 months contradicts this hypothesis: in fact, the stabilometric parameters 6 months after surgery do not change in a statistically significant way as formerly observed at 24 hours after surgery (Fig. 1).

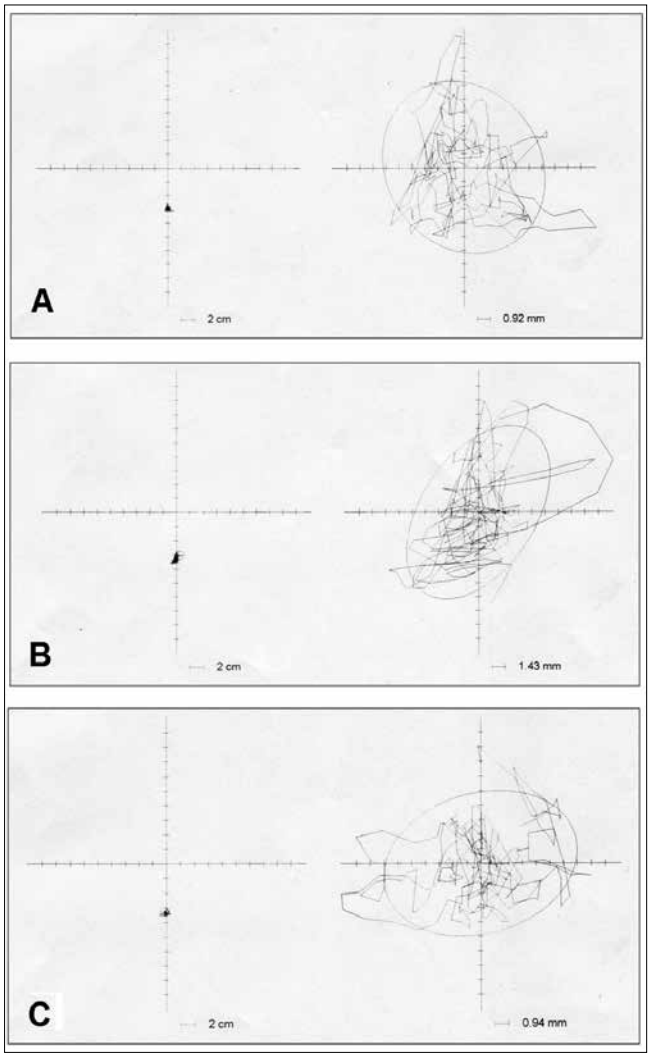

Fig. 1. Stabilometric finding (statokinesigram) of a patient with submucosal retention cyst in the closed-eye mode in basal conditions (A), 24 h after phonomicrosurgery (B) and 6 months after surgery (C). No characteristic pathological pattern was seen in basal conditions; a comparison performed before and after surgery (after 24h and after 6 months), revealed no significant difference in the statokinesigram pattern.

Conclusions

Thanks to static stabilometry it is possible to define the absence of postural alterations in subjects with organic disorders on the glottis plane that are not secondary to problems of a dysfunctional nature. Moreover, this study demonstrates how simple surgical removal of the vocal fold lesion does lead to modification of posture.

In spite of the fact that the results obtained refer to an extremely heterogeneous group, from both a pathophysiological and a clinical point of view, and that the statistical analysis was performed on a restricted number of subjects within each individual subgroup, it is important to again stress how important it is to submit dysphonic subjects with no signs of vertigo to stabilometric analysis.

This study is in line with what has been reported in previous studies [3 13], namely, that skilfully performed speech rehabilitation therapy is fundamental for correcting both voice disorders and altered posture in cases of dysfunctional dysphonia. The results obtained in this study will have to be confirmed in the future, taking into account a larger patient population and a lengthier follow-up.

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Rhinology

Approach to the correction of drooping tip: common problems and solutions

Approccio alla correzione della punta cadente: problemi comuni e soluzioni

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SUMMARY

The drooping tip deformity is both a bothersome aesthetic feature and functional impairment of the nose. Both static and dynamic factors may affect tip appearance and it seems logical to take into account these factors when planning correction of drooping tip. Many studies have examined this topic, but its treatment remains controversial. In order to make nasal tip surgery successful, it is useful to identify the keystone anatomical characteristics of the tip itself. Naso-labial angle, nostril axis, tip rotation angle according to Frankfort plane and columellar-facial angle may be measured to assess nasal tip position. The present study focuses on the authors' personal experience on the key anatomic changes of the nose that deserve correction and on the main surgical steps needed to achieve consistent results when dealing with a drooping tip. Pre- and post-operative nasal tip rotation and projection were studied. Correction of the drooping tip was accomplished by an open or closed septorhinoplasty approach according to patient's needs. The surgical techniques mostly employed for tip repositioning was septum straightening (41/41) and tongue-in-groove (36/41 cases) (87.8%). A columellar strut was used in 8/41 (19.51%) cases. LLC cephalic resection was applied in 29/41 patients (70.73%), LLC re-orienting sutures were made in 18/41 cases (43.9%) and lateral crural overlay was needed in 2/41 (4.8%). The key anatomic changes of the nose that deserve correction and the surgical steps needed to ease the often intriguing pre-operative decision-making process are reviewed.

KEY WORDS: Drooping tip • Rhinoplasty • Tip surgery • Tip measurements

RIASSUNTO

La punta cadente è una fastidiosa deformità estetica e funzionale del naso. L'aspetto della punta è influenzato da aspetti sia statici che dinamici. Per questo motivo, appare logico tenere in considerazione questi fattori nel pianificare la correzione chirurgica di questa deformità. Molti studi hanno affrontato questo argomento, ma il trattamento resta controverso. Per rendere efficace la chirurgia della punta appare indispensabile identificare le caratteristiche anatomiche fondamentali della punta stessa. Diversi angoli e misure possono essere calcolati per definire la posizione della punta tra cui: l'angolo nasolabiale, l'asse della narice, l'angolo di rotazione della punta in rapporto al piano di Francoforte, l'angolo columellare-facciale. L'obiettivo di questo studio è focalizzare l'attenzione sulla nostra esperienza personale sulle alterazioni anatomiche del naso che meritano una correzione e sulle procedure chirurgiche necessarie per ottenere risultati soddisfacenti nel trattamento della punta cadente. Nel presente studio sono stati presi in considerazione la proiezione e la rotazione della punta pre e post-operatorie. La correzione della punta cadente è stata ottenuta mediante settorinoplastica aperta o chiusa a seconda dei casi. La tecnica prevalentemente usata per riposizionare la punta è risultata essere il raddrizzamento del setto (41/41 casi) e la tecnica Tongue-in-groove (36/41 casi) (87,6%). Lo strut columellare è stato impiegato in 8/41 pazienti (19,51%). Resezioni cefaliche delle cartilagini alari sono state applicate in 29/41 pazienti (70,73%). Suture per ri-orientare le cartilagini alari sono state impiegate in 18/41 casi (43,9%). Il Lateral crural overlay è stato necessario in 2/41 casi (4,8%). Il presente articolo rivaluta le principali varianti anatomiche del naso che meritano correzione e le tecniche chirurgiche utilizzabili per semplificare il processo decisionale preoperatorio.

PAROLE CHIAVE: *Rinoplastica • Punta cadente • Chirurgia della punta • Misurazioni della punta*

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Introduction

The drooping tip deformity is both a bothersome aesthetic feature and functional impairment of the nose. Aesthetically, the distally displaced tip gives an aged and unpleasant look, and sometimes the tip also descends or "plunges" during smiling. Functionally these conditions may affect the nasal patency due to incompetence of the internal nasal valve that is stenotised by tip malposition. Both static and dynamic factors may affect tip appearance: the former linked to the malposition and incorrect shape of the nasal septum, upper and lower lateral cartilages and the ligaments in between, the latter derive from the dynamic action of the depressor septi nasi and levator

labii superioris alaeque nasi muscles. When dynamic factors are involved drooping of the nasal tip, elevation and shortening of the upper lip, and increased maxillary gingival visibility occur during smiling [1].

It seems logical to take into account static and dynamic factors along with ancillary causes when planning correction of drooping tip [2]. Many studies have examined this topic, but its treatment remains controversial [3]. In order to make nasal tip surgery successful, we believe that it is useful to identify the key anatomical characteristics of the tip itself.

The method to evaluate tip position is not uniform across different studies. Naso-labial angle, nostril axis and columellar-facial angle may be measured to assess nasal tip position. Although not entirely accurate, the nasolabial angle is often considered synonymous with nasal tip rotation. Patients with drooping tip have a nasolabial angle that is sharper than expected. The columellar-facial angle seems most likely to yield consistent measurements of nasal tip rotation [4]. More recently three angles were measured on lateral view (tip angle, nasolabial angle, and columella inclination angle) and changes in static and smiling positions were also compared [5].

The aim of the present study is to focus on the personal experience regarding the key anatomic changes of the nose that deserve correction and on the main surgical steps needed to achieve consistent results when dealing with a drooping tip.

Materials and methods

From a consecutive series of primary septorhinoplasties performed from January 1st, 2010 to December 31st, 2012 in Caucasian patients, we selected 41 cases presenting a drooping tip. A drooping tip was diagnosed in case of a nasolabial angle less than 90-95° in men and less than 100-105° in women.

We retrospectively analysed photographs of 17 men and 24 women (21-57 years of age) submitted to septorhinoplasty. Exclusion criteria consisted of a history of facial surgery or injury and an abnormal facial expression.

Photographs were obtained according to techniques of standardised clinical photography: hair covering the face, hair bands, hairpins, and eyeglasses were removed, a constant brightness and exposure were used. The patient was placed on fabric background. The distance between the patient and the camera was fixed at 50 cm. The subject was also instructed to keep his or her jaw in a relaxed position and eyes level with the horizontal line. Lateral photographs with the Frankfort horizontal plane parallel to the ground were taken. We used a commercially available computer program (Golden Ratio software ver. 3.1, copyright by Markus Welz, Germany) for photograph measurements. Measurements were performed by two experienced examiners, and the mean was calculated.

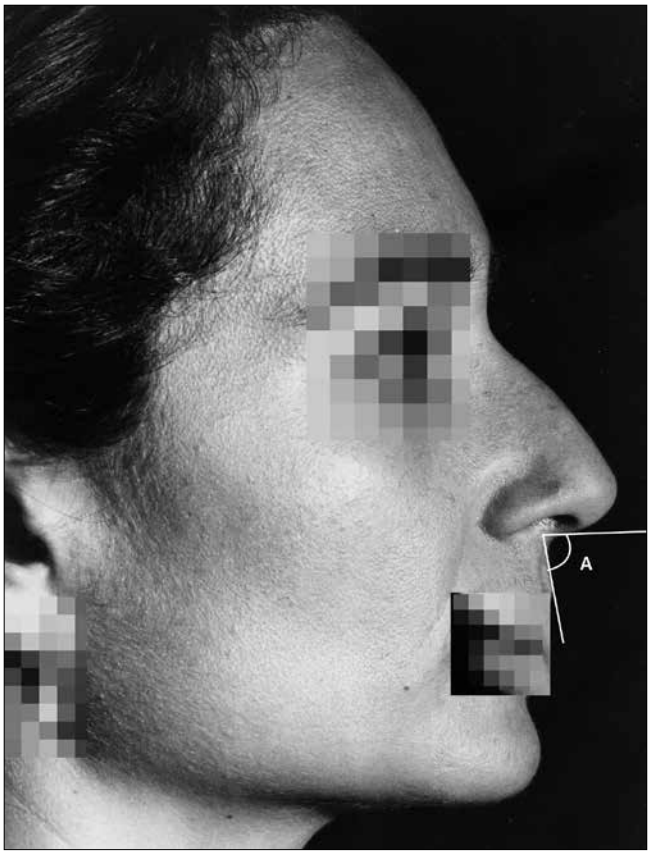

Fig. 1. A) Naso-labial angle.

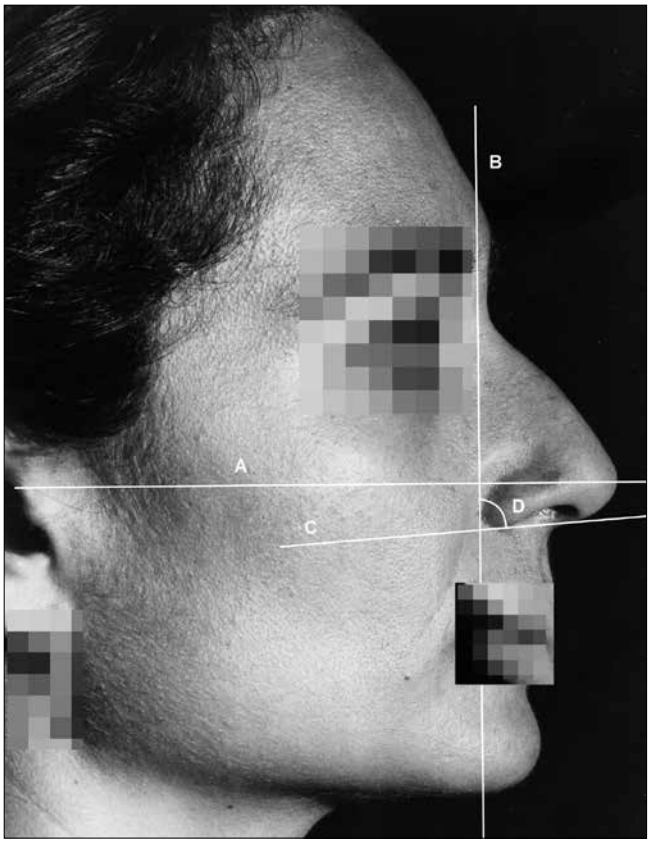

Fig. 2. A) Frankfort horizontal plane; B) Line perpendicular to Frankfort plane; C) line parallel to columella; D) columellar-facial angle.

Pre- and post-operative nasal tip rotation and projection were studied. Tip rotation was evaluated by measuring the nasolabial angle (Fig. 1): on profile view it was assessed as the angle between the upper lip and the columella. Rotation of the nose refers to nasal tip position relative to an imaginary arc on profile view of the face. A normal nasolabial angle in a male is 90-95°, while normal in a female it is 100-105°. Alternatively, nasal tip rotation was based on use of what is termed the Frankfort horizontal plane, by a line drawn from the lower rim of the bony eye socket toward the ear canal. A second line was drawn in parallel to the columella. The angle created by the intersection of these two lines was considered a reliable measure of the nasal tip rotation. A range of 0-15° in males and 15-30° in females is considered ideal. A third angle was also explored: it was drawn by the line parallel to the columella intersected with the alar line, which is a line running perpendicular to the Frankfort plane. The alar line runs through the alar-facial crease, which is where the nasal base attaches to the cheek. (Fig. 2) The latter was developed to avoid the need of measuring a pre-operative "negative" angle between the columella and the Frankfort plane (due the preoperative plunging of the tip) and a "positive" post-operative angle (Figs. 3, 4).

Nasal tip projection was assessed by the Goode method. A measurement was taken from the nasal tip to the alar line ("A") and compared to the distance from the nasal tip to the nasal starting point ("B"). The ratio of "A" to "B" is a measure of tip projection and should ideally be 0.55-0.60 in most patients. A lower ratio was considered as an underprojected tip.

Malposition and incorrect shape of the nasal septum, upper and lower lateral cartilages, and the dynamic action of the depressor septi nasi and levator labii superioris alaeque nasi muscles, were checked to assess the surgical steps needed for tip correction. Changes of tip, subnasale and alar crease were also noted in both static and smiling positions.

Correction of drooping tip was accomplished by closed or open septorhinoplasty approach according to the needs: inter-cartilaginous incision was used for access to the nasal dorsum and full transfix incision of the membranous septum for septal correction in closed approaches, alternatively inverted V columellar incision prolonged as marginal incision in open approaches were employed. Cephalic alar cartilages resection and their re-orientation by sutures or lateral crural interruption and overlapping were performed [6] (as necessary according to the pre-intraoperative evaluation of LLC length). Correction of the septal inferior border length and shape were obtained by careful wedge resection of the same in a triangular, anteriorly-based fashion, taking care not to de-project the tip. Before final suturing, the redundant vestibular skin and mucosa, when present, were excised to avoid nasal valve obstruction.

In case of dynamic nasal tip changes during smiling for

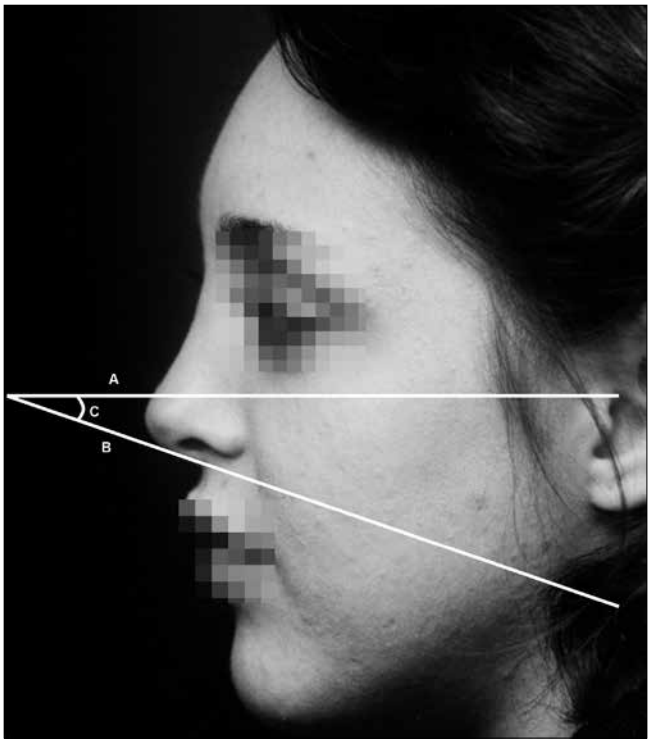

Fig. 3. A) Frankfort horizontal plane; B) line parallel to columella; C) Tip rotation angle.

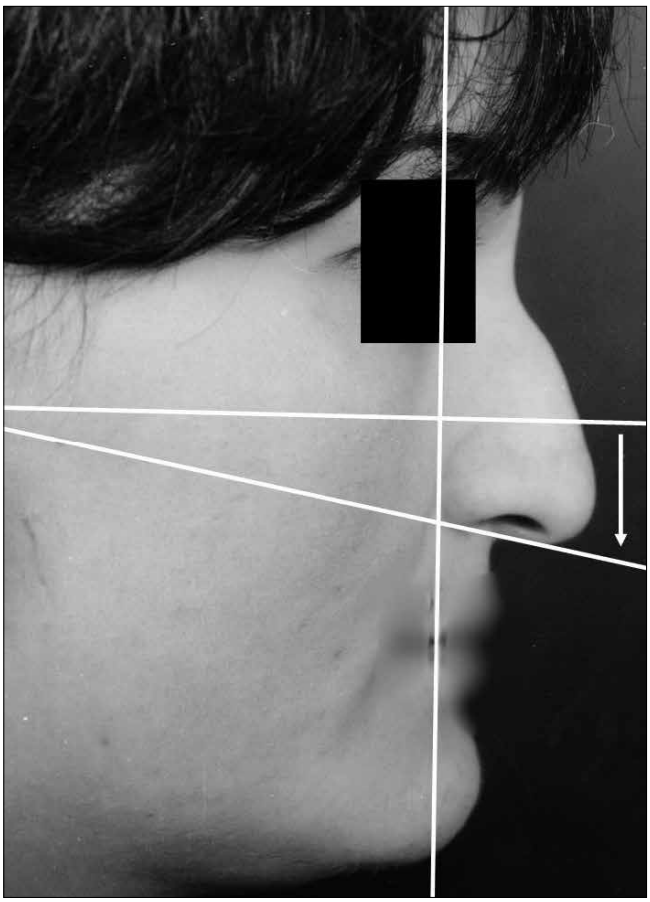

Fig. 4. In drooping tips the Frankfort plane and the line parallel to columella do not encounter between themselves, so that it is not possible to correctly calculate the tip rotation with this method.

depressor septi muscle action, muscle excision just below the footplates of the medial crura when felt necessary was carried out. Counteraction of the residual depressor septi muscle action, as well as the scar contracture pulling down the newly positioned tip, was always considered mandatory: either a strong columellar strut graft placed between the medial crura or a Tongue-in-Groove [7] fixation of the medial crura to the caudal septum, or both, were applied. Correction of the residual (if present) columellar-labial acute angle was achieved using a columellar strut graft extending to the nasal spine and/or by plumping graft of the pre-spinal area. All grafting material was autologous septal cartilage.

Results

The surgical technique mostly employed for tip repositioning was septum straightening and shortening (41/41) and Tongue-in-groove (36/41 cases) (87.8%) (Figs. 5-6). A columellar strut was used in 8/41 cases (19.51%) (Figs. 7, 8). LLC cephalic resection was applied in 29/41 patients (70.73%) and LLC re-orienting sutures were made in 18/41 cases (43.9%). Lateral crural overlay was needed in 2/41 (4.8%) to correct excessive LLC length (Figs. 9, 10).

Both hyper- or normo-dynamic nasal tip ptosis were corrected in all patients as shown by the nasal angles pre- and post-operative measures reported in Tables I-III: post-operative angles were reported as matching the value considered as "ideal" or improved, but not completely corresponding to the normal value. For the naso-labial angle and for tip rotation, calculated according to the Frankfort plane, an increase in the angle value was considered as improvement; on the contrary, a decrease was the goal on the columellar-facial angle. No major or late complications (36 months follow-up)

Table I. Pre- and post-operative results.

Naso-labial angle	Pre-operative	Post-operative
Mean + SD	77.338 ± 15.094	93.924 ± 8.954 *
Normal value (n/N)	0/41	19/41
Improved tip position (n/N)	-	22/41

p < 0.001

Table II. Pre- and post-operative results.

Columellar-facial angle	Pre-operative	Post-operative
Mean + SD	92.406 ± 4.552	81.95 ± 5.414 *
Normal value (n/N)	2/41	21/41
Improved tip position (n/N)	-	20/41

p < 0.001

Table III. Pre- and post-operative results.

Tip rotation angle	Pre-operative	Post-operative
Mean + SD	-2.357 ± 4.579	8.051 ± 5.414 *
Normal value (n/N)	2/41	21/41
Improved tip position (n/N)	-	20/41

p < 0.001

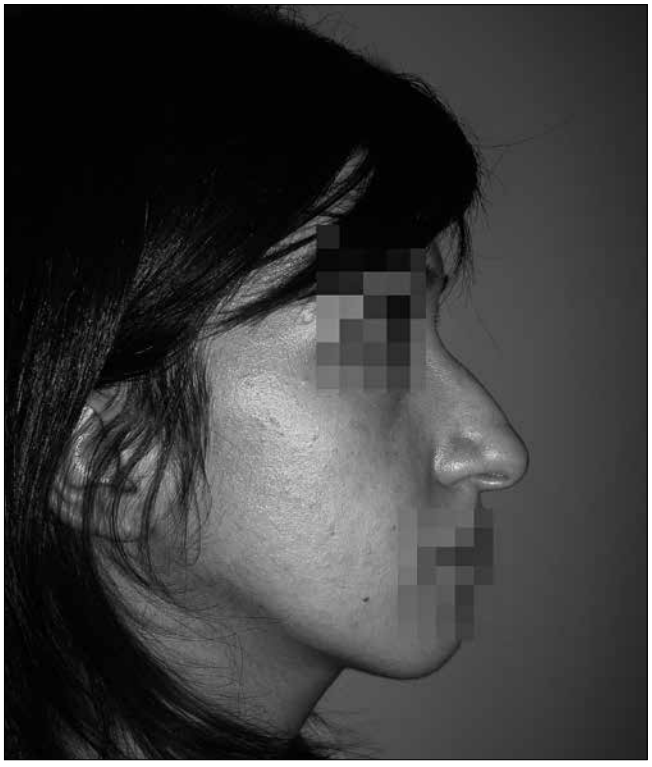

Fig. 5. Tongue-in-Groove (pre-operative image).

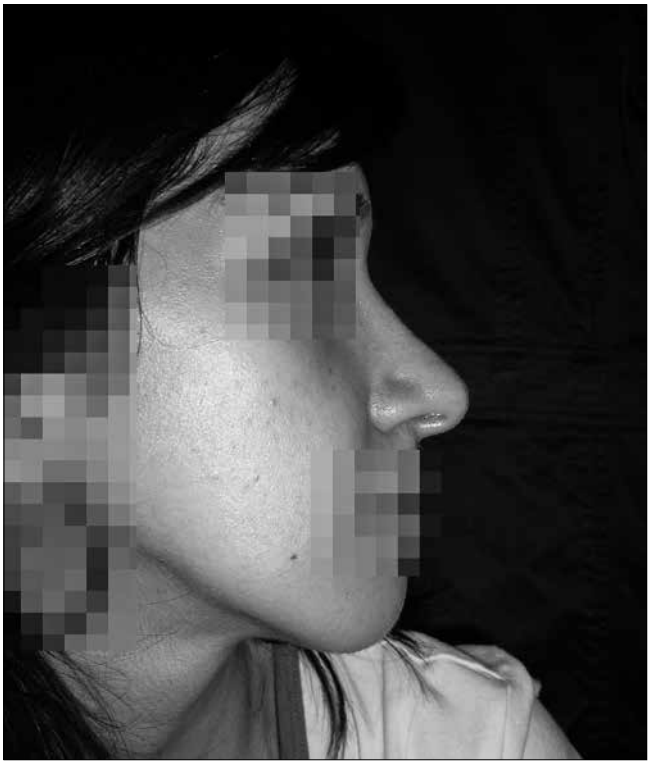

Fig. 6. Tongue-in-Groove (post-operative image).

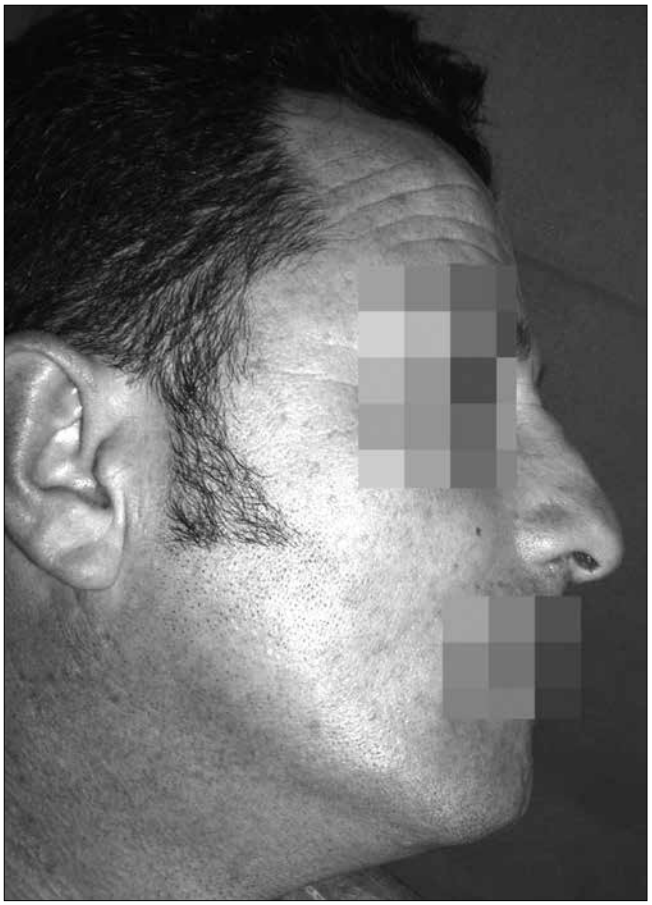

Fig. 7. Columellar strut (pre-operative image).

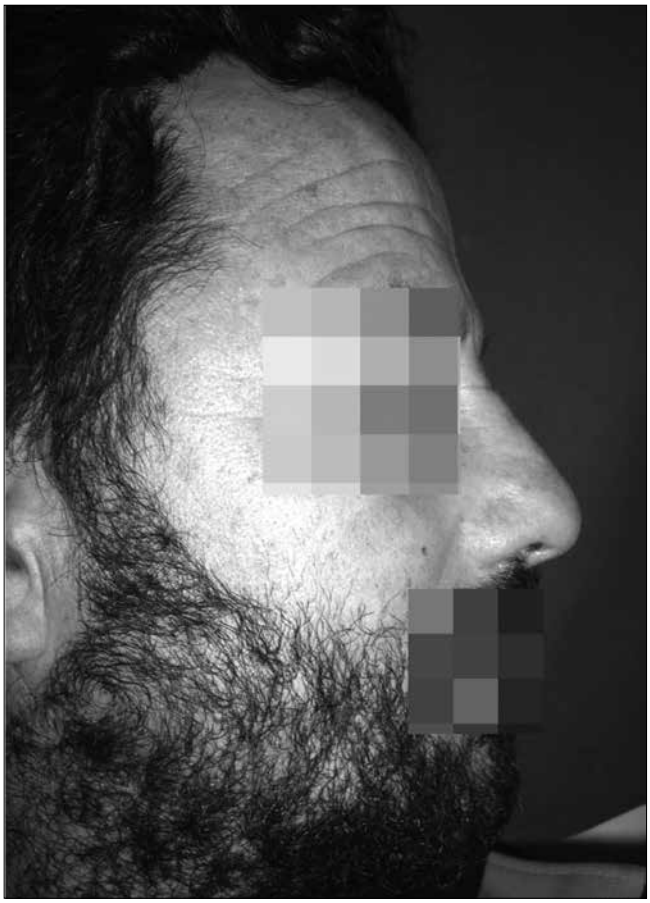

Fig. 8. Columellar strut (post-operative image).

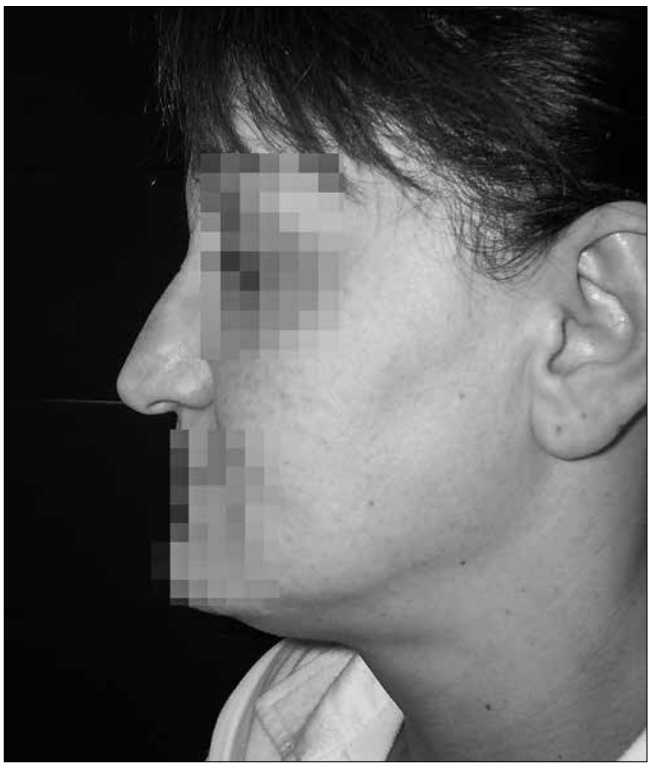

Fig. 9. Lateral crural overlay (pre-operative image).

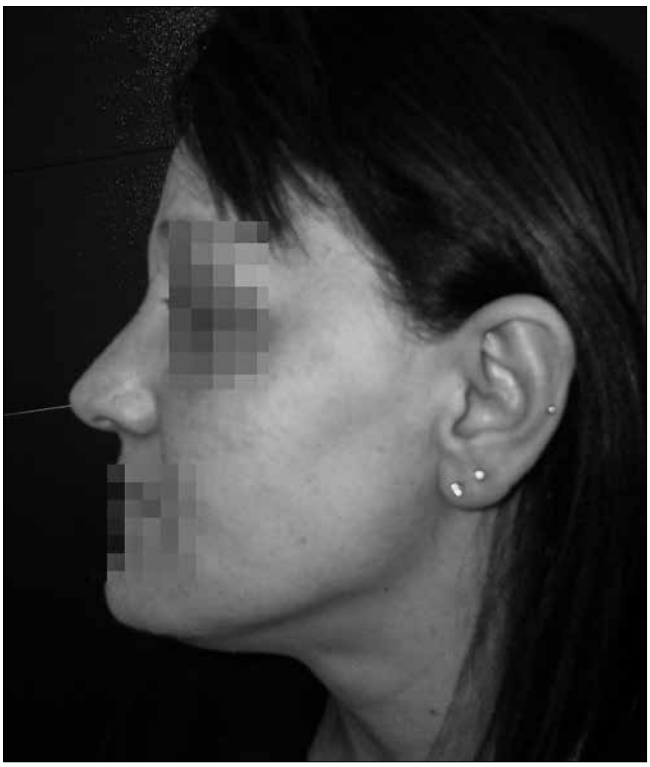

Fig. 10. Lateral crural overlay (post-operative image).

Table IV. Pre- and post-operative results.

Tip projection (Goode Ratio)	Pre-operative	Post-operative
Mean + SD	0.638 ± 0.054	0.647 ± 0.061 (n.s.)
Normal value (n/N)	13/41	15/41
Underprojection (n/N)	1/41	0/41
Overprojection (n/N)	27/41	26/41

Table V. Major and minor nasal tip supporting mechanisms (from Sajjadian, Guyuron, 2009 [10], mod.).

Major tip supporting mechanisms	Minor tip supporting mechanisms
Shape, resilience and size of the lower lateral cartilage	Attachment of the paired domes, nasal spine and membranous septum
Attachment between the septum and upper lateral cartilage	Attachments of the lateral crura to the piriform aperture
Attachment between the septum and medial crus	
Anterocaudal septum	

were recorded. Minor complications were rarely observed (two cases of minor infection around the stitches in the columellar area, quickly resolved without consequences) in the early postoperative period. Resection of the depressor septi also corrected the upper lip length and gingival show during smiling in 4/41 cases. The columellar width was not grossly reduced by depressor septi resection or increased by columellar strut grafting (8 cases). Residual correction of the columellar-labial junction when needed (8/41 patients) was always achieved by pre-spinal plumping graft positioning. Tip projection analysis (Table IV) revealed that preoperatively there were 13/41 patients (31.7%) showing a normal projection according to Goode's ratio, with 1/41 underprojecting tip (2.4%) and 27/41 overprojecting tip (65.8%). After surgery there were no patients with underprojection, while there were 26/41 overprojecting (63.4%) and 15/41 (36.6%) in the normal range.

Discussion

Patients undergoing primary rhinoplasty have been reported to exhibit, in the majority of cases (61%), a need for increased tip support and to a lesser degree (46%) the need for correction of alar cartilage malposition [8]. In a selected subgroup of cases such as patients affected by drooping tip these percentages are expected to be higher and thus the need for significant correction of the tip itself, even if this correction is somewhat controversial [9]. There are several tip supporting mechanisms in the nose (Table V) [10]. Due to the multifactorial causes of drooping tip, the surgical strategy of intervention must take into account different manoeuvers aimed to correct the static and dynamic alterations that may be present in each single case. Straightforward evaluation of the patient's anatomy will suggest the surgical steps to be applied. One key step is re-establishment of a correct tip position in accordance with its length, projection and shape obtained by framework modifications.

According to the tripod theory, pulling vectors act on lateral LLC crura suspending the tip and pushing forces act on the medial LLC supporting the tip itself: their concurrent action determines the tip position [11]. Cues then arise to determine whether improving the pushing effect or enhancing the pulling forces would be more efficient to correct the drooping tip to gain adequate and stable upward rotation.

Constantian (2004) reported inadequate tip projection and convex lateral crura be more common among patients with malpositioned lateral crura (78% and 61%, respectively) than in patients with orthotopic lateral crura (57% and 20%, respectively). In our Caucasian drooping tip patients, the hypo-projecting tip associated with arched, convex nostrils accounted for a minority of cases, while Goode's Ratio showed mostly overprojecting tips.

In Asian patients, Park (2014) recently highlighted four relevant factors in this surgery: first of all, the alar cartilage or nasal septal cartilage problem should be corrected. Alar cartilage shape and orientation must therefore be revised and properly restored to give the tip a good projection and position: re-shaping/re-orienting of the lower lateral cartilages by cephalic resection and stitching is therefore advised. Additionally, correction of the septal inferior border length and shape must be achieved to straighten the nostril profile and let the tip lift upwards. Patients with true ptosis of the tip for excessive nasal length will benefit from septum antero-inferior shortening by cartilage and membranous septum removal, while cases with tip over-projection may need lateral crura shortening if they are too long. In this case, excessive shortening must be avoided to skip tip de-projection [10]. Among the former factors, the hypoprojection correction seems secondary in our series of Caucasians.

Once reshaped, the framework itself needs to be reinforced in order to warrant a persistent and adequate tip projection that may be jeopardised by some residual downward pulling of the tip exerted by the scar contracture over time and by the residual muscular activity of the depressor septi. Columellar strut, batten grafts and the tongue-in-groove technique all seem valuable for this goal [8 12].

In our experience, the simplest and most effective way to re-position and maintain the correct tip rotation is to restore the pushing effect of the medial crura on the nasal tip itself.

The tongue-in-groove technique associated with septum antero-inferior realigning and wedge shortening is a simple and reliable way to gain upward rotation of the tip while maintaining adequate projection; it was successfully employed in 36/41 (87.8%) cases. A columellar strut was used in only 8/41 (19.5%) cases: specifically, in one case of un-

derprojection associated with drooping tip, one case of open approach and whenever it was felt necessary that stronger support for the tip was needed. The upward pull exerted by LLC lateral crura was reinforced by cephalic resection with/without stitching of the same in 29 cases (70.7%), stitching was mainly used for re-shaping purposes; "major" procedures (e.g. LLC lateral crus interruption-resuturing) were needed in only 2 patients (4.8%) of the present series of unselected drooping tip cases. Therefore, aggressive procedures on the LLC seem to be reserved to very selected and specific indications: excessively long lateral crura may give rise to an unpleasant "arched" nostril profile when the upward lift of the tip is carried out conservatively without concomitant shortening of the length of the lateral crus.

It must also be taken into account that a "plunging tip" may sometimes be due to an optical illusion: during smiling, the real position of the tip is steady, but alar crease and subnasale elevate while the alar rim straightens. Kosins demonstrated that objectively the tip moves less than 1 mm and less than 1° [5]. "…When a person smiles, the functional unit is activated by a combination of two forces acting simultaneously in opposite directions that rotate the tip caudally and elevate the nasal base. The levator moves the alar base upward and the depressor pulls the tip caudally..." [9]. The depressor septi muscle originates from the alveolar bone and inserts the footplates of the medial crus and caudal septum and interdigitates with the medial fascicles and orbicularis oris [3]. Since the depressor septi is responsible for smiling deformity, correction of the same helps to improve both it and the tip-lip relationship [13]. An intranasal or open approach resection of this muscle has been shown to be effective in correcting a drooping nasal tip because it prevents the inferior pull of the tip during smiling [1 3]; in our series this was the case in 4/41 patients (9.7%). Dissecting free from the accessories and sectioning the muscle and, if necessary, the accessory cartilages of the lower laterals has also been suggested because it benefits the "tense nose" aspect and smiling deformity [14].

Final refining steps include the redundant soft tissues of the nasal vestibule such as the mucosa and submucosa deserve trimming to help prevention of relapses of the falling tip after correction as well as nasal valve obstruction [2]. Plumping grafts in the pre-maxillary area were successfully used in 4/41 (9.7%) cases to improve the prespinal region projection when an acute naso-labial angle is present, as correction of the columellar base retraction is aesthetically pleasant and helps to support the nasal tip [15]. Our personal experience on the key anatomic changes of the nose that deserve correction and on the main surgical steps needed to achieve consistent results when dealing with a drooping tip have shown that correction of the drooping tip by closed rhinoplasty approach both in primary and revision cases may be achieved in a vast majority of situations. A sequential approach encompasses careful straightening and shortening of the septal anterior-inferior edge and its fixation to the medial LLC crura as pivotal point to warrant stable "pillar" for tip repositioning, concomitant cephalic alar cartilage resection and re-orientation by stitching may ease the tip upward rotation and reinforce tip supporting mechanisms. Dynamic nasal tip changes during smiling for depressor septi hyper-action, if present, can be successfully addressed by muscle excision. Counteraction of the residual depressor septi muscle action and scar contracture need columellar strut grafting if severe underprojection is present or when an open approach is used; alternatively, a Tongue-in-Groove fixation of the medial crura in our experience was satisfactorily applied in the majority of cases. We favour the use of this procedure because it is quick, simple and avoids possible complications due to grafting of the columella (i.e. infection, re-absorption, dislocation, extrusion of the strut). Ancillary procedures may refine the results by skin and mucosa trimming and naso-labial angle adjunctive widening by the use of pre-spinal plumping graft. Grafting material can be autologous (e.g. septal cartilage, conchal cartilage, etc.) or alloplastic. Several alloplastic materials have been used in surgery. In general, they shorten the duration of surgery, reduce trauma to the donor region and are readily available. The main drawback is tissue response, which may lead to extrusion and/or poor resistance to infection over time [17].

Finally, to prevent respiratory problems that can cause dissatisfaction to the patient despite a pleasant aesthetic outcome, inferior turbinoplasty is a simple adjuvant procedure to prevent nasal obstruction after rhinoplasty [18]. In the present series, turbinoplasty by coblation was routinely adopted during septorhinoplasty.

Conclusions

The present review of our personal experience on the key anatomic changes of the nose that deserve correction and on the main surgical steps needed to achieve consistent correction of the drooping tip highlights the surgical strategies that are reliable and the clinical observations that ease the often intriguing pre-operative decision-making process.

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Rhinology

Cerebrospinal fluid rhinorrhoea following transsphenoidal surgery for pituitary adenoma: experience in a Chinese centre

Rinoliquorrea dopo chirurgia dell'adenoma ipofisario con approccio transfenoidale: esperienza in un centro cinese

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SUMMARY

The aim of this study was to elucidate the risk factors for cerebrospinal fluid (CSF) rhinorrhoea following transsphenoidal surgery and discuss its prevention and treatments. We retrospectively reviewed 474 consecutive cases of pituitary adenoma treated with 485 transsphenoidal surgical procedures from January 2008 to December 2011 in our department. We analysed the incidence of intra- and post-operative CSF leakage and outcomes of various repair strategies. Intra-operative CSF leakage was encountered in 85 cases (17.9%), and post-operative CSF rhinorrhoea in 13 cases (2.7%). Seven of the 13 patients with post-operative CSF rhinorrhoea did not experience intra-operative CSF leakage; three of these patients had adrenocorticotropic hormone-secreting adenomas. Of the remaining 6 patients with both intra- and post-operative CSF leakage, 2 were treated for giant invasive prolactinomas, and 2 had previously undergone transsphenoidal surgery. In eight patients, the leak was resolved by lumbar puncture, lumbar external drainage, resting in a semi-reclining position, or other conservative treatment. Two CSF leaks were repaired with gelatine foam and fibrin glue using a transsphenoidal approach, and two with autologous fat graft and sellar floor reconstruction using a transnasal endoscopic approach. After undergoing two transnasal endoscopic repairs, one patient with post-operative CSF rhinorrhoea was successfully treated by further lumbar subarachnoid drainage. In conclusion, procedures using gelatine foam, fibrin glue and autologous fat graft are common and effective techniques for the management of CSF rhinorrhoea after transsphenoidal surgery. When a CSF leak is detected during transsphenoidal surgery, thorough sellar reconstruction and long-term follow-up are necessary.

KEY WORDS: Pituitary adenoma • Cerebrospinal fluid rhinorrhea • Sellar reconstruction

RIASSUNTO

Lo scopo del presente studio è stato quello di chiarire i fattori di rischio della rinoliquorrea a seguito di un approccio transfenoidale e di discuterne la prevenzione e il trattamento. Abbiamo revisionato retrospettivamente 474 casi consecutivi di adenoma ipofisario trattati con 485 procedure chirurgiche per via transfenoidale da Gennaio 2008 a Dicembre 2011 nel nostro dipartimento. Abbiamo analizzato l'incidenza di fuoriuscita di liquor cefalorachidiano intraoperatoriamente e nel postoperatorio, e la riuscita di varie strategie di riparazione. Abbiamo riscontrato fuoriuscita di liquor intraoperatoriamente in 85 casi (17.9%) e postoperatoriamente in 13 casi (2.7%). Sette dei 13 pazienti con rinoliquorrea postoperatoria non avevano mostrato fuoriuscita di liquor intraoperatoriamente; tre di questi pazienti avevano adenomi secernenti ADH. Dei rimanenti 6 pazienti con fuoriuscita di liquor sia intra che postoperatoria, 2 erano stati trattati per prolattinoma gigante e invasivo e 2 erano già stati sottoposti in passato a chirurgia trasnfenoidale. In 8 pazienti la fuoriuscita è stata risolta mediante puntura lombare, drenaggio lombare, riposo in posizione semi-reclinata o altri trattamenti conservativi. Due casi sono stati trattati mediante schiuma di gelatina e colla di fibrina utilizzando un approccio transfenoidale e due con grasso autologo e ricostruzione del pavimento della sella utilizzando un approccio transnasale endoscopico. Dopo essere stato sottoposto a due tentativi di riparazione per via transasale, un paziente è stato trattato con successo mediante un ulteriore drenaggio subaracnoideo. In conclusone le procedure che fanno uso di schiuma di gelatina, colla di fibrina e impianti di grasso autologo sono efficaci ai fini del trattamento della rinoliquorrea postoperatoria in pazienti sottoposti a chirurgia transfenoidale. Quando viene rilevata una perdita di liquido cefalorachidiano in corso di chirurgia transfenoidale, un'appropriata ricostruzione del pavimento della sella e un follow up a lungo termine sono necessari.

PAROLE CHIAVE: *Adenoma ipofisario • Rinoliquorrea • Ricostruzione della sella*

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Introduction

Persistent cerebrospinal fluid (CSF) leakage is the leading cause of morbidity following transsphenoidal surgery (TSS) for pituitary adenomas [1]. CSF leakage can lead to headache and meningitis. Although various repair methods have been described, a national survey of complications following TSS found that the incidence of postoperative CSF leak remains high at 3.9% [2]. The economic and psychological burden for patients with CSF rhinorrhoea is enormous. In our study, we aimed to elucidate the risk factors for CSF rhinorrhoea following TSS and discuss its prevention and treatment. Our objective was to analyse the incidence of CSF fistula after TSS to remove tumours in the sellar region, discuss factors associated with CSF leakage and describe a method for sellar closure.

Materials and methods

Patients

We retrospectively reviewed 474 consecutive cases of pituitary adenomas treated by 485 TSS procedures from January 2008 to December 2011 at the Department of Neurosurgery, Shanghai Changzheng Hospital. Written approval for this study was obtained from the ethics committee of Shanghai Second Military Medical University. All patients or their family members provided written consent for study participation in accordance with the ethics committee standards during hospital stay or outpatient follow-up. We obtained information about patient demographics, tumour type, degree of resection (gross total resection or subtotal resection), intra- and post-operative CSF leakage, and repair strategy. Various techniques of sellar closure and indications for each specific condition were retrospectively reviewed. Potential risk factors for post-operative CSF rhinorrhoea were analysed.

Diagnosis of CSF fistula

The diagnostic algorithm for patients with suspected postoperative CSF fistula was pre-operative nasal endoscopy, β-trace protein test (followed by a β-2-transferrin test when necessary to confirm CSF fistula), and 1-mm computed tomography scan slices of the paranasal sinus and anterior cranial base in the axial and coronal planes.

Tumour removal technique

Because endoscopy was unpopular in our department during this period, all patients underwent pituitary adenoma resection by microscopic endonasal TSS. After accessing the sella using a microscopic approach, a fine needle was used to puncture the sellar dura before performing the dual incision to prevent an aneurysm. The tumour was resected using a pseudocapsular technique.

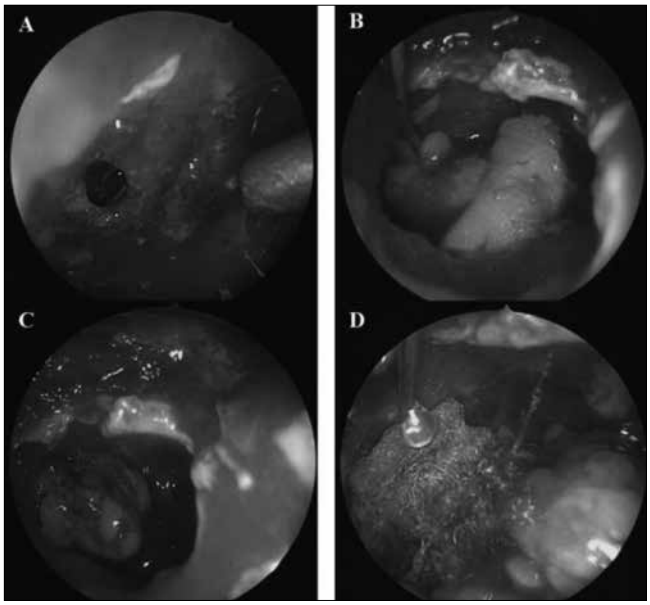

Fig. 1. A) Identify the arachnoid defect laceration. **B**, **C)** Embed the dumbbell-shaped autologous fat in the defect. **D)** The fat graft was covered immediately with fibrin glue and surgicel.

CSF leakage repair techniques

The Valsalva manoeuvre was performed by an anaesthetist to determine whether intra-operative leakage had occurred. If intra-operative CSF leakage was detected, we usually first confirmed the arachnoid leak and then repaired it using one of the following strategies. If the arachnoid laceration was small and the CSF flow rate was low, a piece of Gelfoam covered with Surgicel was placed into the defect and covered with Surgicel and fibrin glue as an overlay graft. The sphenoid sinus was then packed with Gelfoam to support the graft. If the arachnoid laceration was large and the CSF flow rate was high, autologous fat harvested from the lower abdomen was formed into a dumbbell shape and embedded in the defect. The fat graft was then covered immediately with fibrin glue and Gelfoam (Fig. 1). An artificial cerebral dura mater patch and septal cartilage were used to reconstruct the sellar floor. The sphenoid sinus was also packed with fat graft and collagen sponge. External CSF lumbar drainage was kept for 2 to 4 days. Patients were discharged from the clinic 1 to 2 days after surgery with a scheduled date for the next appointment.

Statistical analysis

Fisher's exact test was used to compare the odds of CSF leakage. Results are expressed as mean ± SEM. $P < 0.05$ was considered significant.

Results

Patient and tumour characteristics

A total of 474 patients (214 males and 260 females) who underwent 485 TSS procedures for resection of pituitary

Table I. Summary of clinical characteristics and CSF leakage in 474 cases treated with resection of pituitary adenomas.

		CSF Leak		
Features	**N = 474**	**Intraop**	**Postop**	**P-value**
Gender				0.181
Male	214	36	3	
Female	260	49	10	
Age				0.245
< 50 years	182	38	7	
≥ 50 years	292	47	6	
Tumour type				0.157
Non-functioning	295	40	6	
GH	50	15	0	
PRL	91	18	3	
ACTH	29	12	4	
TSH	5	0	0	
GH-PRL	4	0	0	
Knosp grade				
0	115	17	2	
I	214	25	1	
II	102	16	4	
IV				
Repeated surgery				
Yes	11	5	2	
No	0	6	0	
Extent of resection				0.916
GTR	424	51	8	
STR	50	34	5	

adenomas met the inclusion criteria for this study. Mean age at the time of surgery was 49 ± 15 years (range 14-87 years). Non-functional adenomas accounted for 62.2% of cases, and invasive adenomas for 26% of cases (Table I). Eleven patients (2.3%) underwent repeat operations because of tumour recurrence.

CSF leakage

Intra-operative CSF leakage was detected in 85 cases (17.9%), and post-operative CSF rhinorrhoea in 13 cases (2.7%) (Table I). Our results showed that none of the clinicopathological features, such as gender, age, tumour type, Knosp grade, repeated surgery, or extent of resection correlated with intra- or post-operative CSF leakage.

Seven of the 13 patients with post-operative CSF rhinorrhoea did not experience intra-operative CSF leakage (Table II); three of these patients had adrenocorticotropic hormone (ACTH)-secreting adenomas. Of the remaining 6 patients who experienced both intra- and post-operative CSF leakage, 2 had giant invasive prolactinomas and 2 had previously undergone TSS. Eight patients were successfully treated by lumbar puncture, lumbar external drainage, resting in a semi-reclining position, or other conservative treatment. In two patients the leak was repaired with gelatine foam and fibrin glue through a transsphenoidal approach, and in two patients the leak was repaired with autologous fat graft and sellar floor reconstruction using a transnasal endoscopic approach. One patient with post-operative CSF underwent two transnasal endoscopic repairs, but the leak was resolved only after further lumbar subarachnoid drainage.

β-trace protein test for CSF fistula

Laboratory assessment of CSF leakage by quantifying β-trace protein in nasal secretions offers a great diagnostic advantage. This test is highly sensitive and is more specific and much less expensive than β-2 transferrin testing [3]. In this study, the β-trace protein test was used for all patients. In cases in which there was a doubt about interpretation, the result was confirmed with the β-2 transferrin test.

Exemplary case

In a 70-year-old male patient with a microadenoma, we mistook the sellar floor and punctured the dura in the clival direction during the transsphenoidal tumour resection. Although we repaired the dura puncture thoroughly with gelatine foam and fibrin glue, CSF rhinorrhoea was detected 4 days after the operation. The situation did not improve with conservative treatment, and the patient developed tension pneumocephalus. Two neuroendoscopy procedures failed to repair the defect, but the CSF rhinorrhoea resolved with further lumbar puncture drainage. During hospitalisation, the patient was diagnosed with a refractory intracranial infection. When a combination of vancomycin and ceftriaxone did not control the infection, we treated the patient with linezolid and meropenem along with daily intrathecal injections of vancomycin (20 mg). The man was discharged without any neurological deficits.

Follow-up

Follow-up of asymptomatic patients consisted of nasal endoscopy and imaging evaluations once a month for the first 3 months, then twice yearly for the first year and once yearly for the following 2 years. Median follow-up time was 5.2 years (range 3.5-7 years). In two patients, CSF rhinorrhoea recurred but was subsequently resolved by resting in a semi-reclining position.

Discussion

Post-operative CSF fistula rates after microscopic or endoscopic TSS procedures range from 0.5% to 15% [4], which is consistent with the rate of 2.7% in the present study. Intra-operative CSF fistula rates are higher, ranging from 18.1% to 53.2% [4]. Similarly, the rate of 17.9% in the present study is consistent with these previous reports. According to Shiley et al., the incidence of post-

Table II. The clinicopathological features of 13 patients with post-op CSF leakage.

Case no	Age	Gender	Subtype	Tumour size (mm)	Knosp grade	Surgical technique of intraop CSF leakage	Treatment of postop leakage
1	40	F	NF	38.5	IV	Gelatin foam	Semireclining + LP
2	56	F	ACTH	60	IV	No CSF leakage	Semireclining
3	44	F	ACTH	7	0	Gelatin foam + Fibrin Glue	Semireclining
4	56	F	ACTH	25	II	No CSF leakage	Semireclining
5	22	F	PRL	31	II	Gelatin foam + Fibrin Glue	TSS repair
6	68	M	NF	41	II	Fibrin Glue	TSS repair
7	43	M	PRL	28	III	No CSF leakage	Semireclining
8	46	F	NF	14	II	Gelatin foam	Semireclining
9	48	F	PRL	23	III	Gelatin foam + Fibrin Glue	Endoscopy
10	48	F	ACTH	30	I	No CSF leakage	Semireclining + LP
11	53	F	NF	25	III	No CSF leakage	Semireclining
12	53	F	NF	24	III	No CSF leakage	Semireclining
13	70	M	NF	9	0	No CSF leakage	Endoscopy + LP

operative CSF fistula is 6 times greater in patients who experience intra-operative CSF fistula [4]. For this reason, it is important to identify dural defects through meticulous haemostasis and use of the Valsalva manoeuvre and Trendelenburg position [5 6].

Regarding the risk of CSF fistula associated with specific tumour types, Tamasauskas et al. reported higher rates of post-operative CSF fistula in patients with growth hormone-producing adenomas [7], whereas Shiley et al [4] reported higher CSF fistula rates in patients with non-adenomatous disease (e.g., craniopharyngioma). However, of the 13 patients with post-operative CSF rhinorrhoea in our case series, 4 had ACTH-secreting adenomas, 3 had prolactinomas and 6 had non-functional macroadenomas. Two patients had undergone TSS previously. Our findings are similar to those of other studies. Nishioka et al. retrospectively reviewed 200 consecutive cases of TSS for sellar lesions and observed intra-operative CSF leakage in 19.0% of cases [8]. The risk of post-operative CSF rhinorrhoea was significantly increased in patients who underwent prior TSS, radiotherapy, or both. Macroadenomas (particularly those with suprasellar extension), repeat TSS, intra-operative leaks and even elevated body mass index have previously been reported as predictors of post-operative CSF rhinorrhoea [9 10].

The primary reconstruction technique uses autologous grafts (e.g., fascia lata) or a pedicled nasoseptal flap to reconstruct the skull base when a CSF leak occurs during or after surgery [11 12]. However, due to the unpopularity of endoscopy and unfamiliarity with this reconstruction method in our department during the study period, we used alternative repair methods and also obtained excellent results. Most patients in this study chose conservative methods for CSF rhinorrhoea repair, with surgical repair used only if conservative treatment failed. Our strategies often eliminated the need for additional surgery; however, conservative treatment may increase the risk of infection, duration of hospitalisation and economic and psychological burden on the patient. Presutti et al. [13] suggested that surgical repair should be performed as soon as general clinical conditions allow if diagnostic assessments have detected CSF rhinorrhoea and identified the exact site of the leak. They concluded that clinical presentation and office-based endoscopic nasal exam were of primary importance to evaluate suspected CSF leaks. Prospective randomised controlled studies are needed to clarify the optimal approach and time window for surgical repair of CSF rhinorrhoea.

Couldwell et al. reported no incidence of postoperative CSF rhinorrhea if no intraoperative leak was encountered during transphenoidal surgery [14]. Nevertheless, post-operative CSF rhinorrhoea without intra-operative leakage although rare, does occur. In seven of the 13 patients (53.8%) with post-operative CSF rhinorrhoea in our study, an intra-operative leak was not detected. One possible reason for this finding is that the enlarged sella from a macroadenoma leads to expansion and possible incompetence of the diaphragma sellae and exposed arachnoid membrane. Insertion of an autologous fat graft in the sella turcica may be a feasible and effective surgical method in this scenario [15].

Endoscopic endonasal pituitary surgery differs from the transsphenoidal microsurgery in the following aspects: plane vision, close-up view, no nasal speculum, endonasal approach and ample vision field [16]. Microscopy features a three-dimensional visualisation, wider view and use of a transnasal speculum. Use of the endoscope during TSS is important in that it allows maximum tumoural excision and better visualisation of a small CSF fistula. Because of the enhanced illumination and visualisation of lesions, endoscopic surgery for CSF rhinorrhoea is more reliable and convenient than traditional TSS. In addition, we found that the endoscopic approach enables precise confirmation of the leakage site, sufficient exposure, minimal invasiveness and high rate of success. Although endoscopy was underutilised initially in our department, we subsequently used endoscopy to repair CSF leakage with excellent results. We therefore strongly recommend

endoscopy for surgical repair as well as tumour removal. Limitations of this study include its small sample size and retrospective design. Prospective multicentre studies with larger cohorts of patients are needed to confirm our results regarding risk factors for CSF rhinorrhoea and optimal repair strategies following TSS.

Conclusions

In conclusion, repair strategies using gelatin foam, fibrin glue and autologous fat are common and effective techniques for the management of CSF rhinorrhoea after TSS. The repair strategy should be individualised to each patient. Endoscopic repair of CSF leak is superior to the traditional TSS approach.

Acknowledgments

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Audiology

A mild phenotype of sensorineural hearing loss and palmoplantar keratoderma caused by a novel GJB2 dominant mutation

Fenotipo lieve di sordità neurosensoriale e cheratoderma palmo-plantare causato da una nuova mutazione dominante di GJB2

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SUMMARY

Dominant *GJB2* mutations are known to cause a syndromic form of sensorineural hearing loss associated with palmo-plantar skin manifestations. We present the genotype/phenotype correlations of a new *GJB2* mutation identified in three generations of an Italian family (proband, mother and grandfather) whose members are affected by sensorineural hearing impairment associated with adult-onset palmoplantar keratoderma. In all affected members we identified a new heterozygous *GJB2* mutation (c.66G > T, p.Lys22Asn) whose segregation, population frequency and *in silico* prediction analysis have suggested a pathogenic role. The p.Lys22Asn *GJB2* mutation causes a dominant form of hearing loss associated with variable expression of palmoplantar keratoderma, representing a model of full penetrance, with an age-dependent effect on the phenotype.

KEY WORDS: Hearing Loss • Sensorineural • Keratoderma • Palmoplantar • Gap junction beta-2 protein, human

RIASSUNTO

Le mutazioni dominanti del gene GJB2 sono causa di forme di sordità neurosensoriale sindromiche associate a manifestazioni cutanee palmo-plantari. In questo lavoro viene descritta la correlazione genotipo / fenotipo di una nuova mutazione nel gene GJB2 identificata in tre generazioni di una famiglia italiana (probando, madre e nonno) i cui membri presentano ipoacusia neurosensoriale associata a cheratoderma palmo-plantare ad insorgenza nell'età adulta. Una nuova mutazione di GJB2 (c.66G > T, p.Lys22Asn) allo stato eterozigote è stata identificata in tutti membri affetti. La segregazione della mutazione, la sua frequenza nella popolazione generale e predizioni in silico ne attribuiscono un ruolo patogenetico. La mutazione p.Lys22Asn GJB2 determina una forma di sordità dominante associata ad un'espressione variabile di cheratoderma palmo-plantare, rappresentando un modello di penetranza completa con effetto età-dipendente sul fenotipo.

PAROLE CHIAVE: *Sordità neurosensoriale • Cheratoderma palmo-plantare • GJB2*

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Introduction

Biallelic mutations in the *GJB2* gene (MIM #121011), encoding the gap junction protein Connexin 26, have been associated with non-syndromic hearing impairment (HI) of different degrees and audiometric patterns depending on the type (truncating vs non-truncating) and localization of the gene mutations [1 2]. Dominant mutations in the *GJB2* and in its contiguous homolog *GJB6* have been also described in cases showing non-syndromic HI [3 4] and in those with syndromic forms, characterised by an association between HI and skin manifestations, which in turn have been phenotypically dissected into palmo-plantar keratoderma-deafness (PPKD, MIM #148350), hystrixlike ichthyosis-deafness (HID, MIM #602540), Bart–Pumphrey (MIM #149200), keratitis-ichthyosis-deafness (KID, MIM #148210) and Vohwinkel (MIM #124500) syndromes [5 6]. The association between deafness and skin diseases has been proven as mutation specific, with about 20 causative *GJB2* gene variants described to date, mainly affecting extracellular domain 1 of the connexin 26 protein [7].

In the present report we describe a new *GJB2* mutation, c.66G > T (p.Lys22Asn), identified in an Italian pedigree with carriers showing moderate, progressive sensorineu-

ral HI and age-dependent palmoplantar keratoderma suggesting full penetrance and variable expression.

Materials and methods

Patients were recruited at Modena University Hospital and evaluated by otolaryngologists and medical geneticists. Clinical, auditory and genetic data, including family medical histories with special care towards deafness and age of HI onset were collected. Hearing thresholds were measured by pure tone audiometry at the frequencies of 0.25, 0.5, 1, 2, 3, 4 and 6.8 kHz; auditory brainstem response (ABR) was performed in case of asymmetry. Analysis of the *GJB2* gene was performed on DNA extracted from blood after informed consent, as previously described [8].

The study was approved by the local Ethics Committee (Protocol No. 108/14).

Results

The proband (III-2, Fig. 1) is a 7-year-old child presenting asymmetric bilateral high-frequency sensorineural HI, with a threshold around 15 dB at 250-4000Hz, sloping down to 60 dB at the 8000 Hz frequencies (Fig. 1) in the right ear, while the left ear had a slope to 40 db at 2000-4000 hz, reaching 60 db at 8000 Hz. Among the relatives, his half-sister (same mother, different father) had a unilateral sensorineural HI, which was limited to 8000 Hz with a threshold around 70 dB, presently involving only the right ear. The mother (clinical diagnosis of HI around 9 years of age) and maternal grandfather both had similar, but more severe audiometric patterns, which were referred to as progressive through the years (Fig. 1 reports their audiograms performed at 46 and 78 years of age, respectively).

Dermatological examination of the adult affected members of the family (patient II-2, and patient I-1 of Fig. 1) showed a variable expression of adult-onset palmoplantar keratoderma, which was diffuse on the palms and soles without any involvement of the dorsal side of the hands, feet or of the nails and a friction-associated denuded area of the fingertips (Fig. 2, panel B). Neither children had the palmo-plantar phenotype.

Sequencing analysis of the *GJB2* gene revealed a novel heterozygous variant, c.66G>T, p.Lys22Asn (Fig. 3A) (ClinVar ID 242831, http://www.ncbi.nlm.nih.gov/clinvar/), which was present in patients III-2, III-1, II-2, I-1, all showing some degree of HI, thus suggesting an autosomal dominant pattern of inheritance. The mutation, falling in the transmembrane domain of the connexin 26 protein (Fig. 3 B), has not been previously reported in the medical literature, is not present in the public disease databases (Leiden Open variant Database [9], Deafness Variation Database, The Molecular Otolaryngology and Renal Research Laboratories, The University of Iowa), or as a variant in the general population (Ensembl [10]; 1000 Genomes Project Consortium [11], Exome Variant Server). The Polymorphism Phenotyping v2 [12], Provean [13], Mutation Tester [14] tools, which were used to predict the possible impact of the amino acid substitution on the structure and function of the protein, classified the variant as pathogenic (Polyphen-2 prediction: probably damaging with a score of 1.000, sensitivity: 0.00; specificity: 1.00; Provean prediction deleterious with a score of -2.716; Mutation tester prediction: disease causing prob > 0.99).

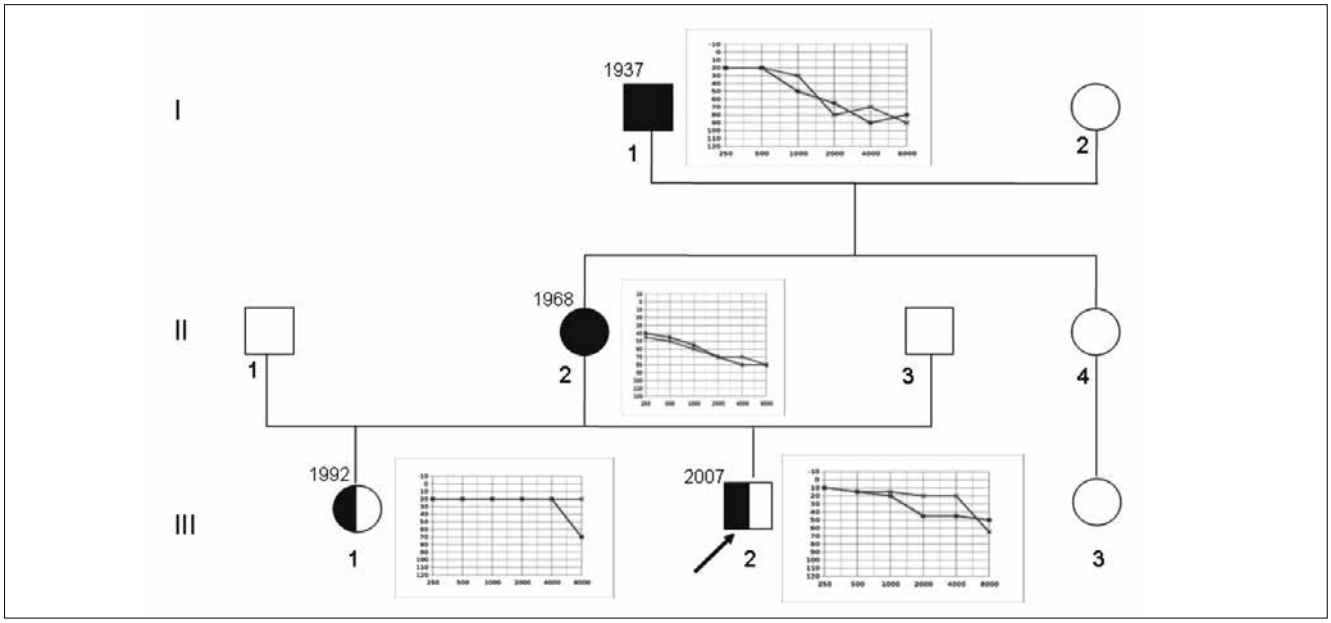

Fig. 1. Genealogical tree of the family under study. Hearing impairment and PKK is indicated by solid-filled shapes. Half-shaded symbols denote non-syndromic HI. The audiograms were obtained at age 78, 46, 23, 7 for patients I-1 , II-2, III-1, III-2, respectively. The arrow indicates the proband.

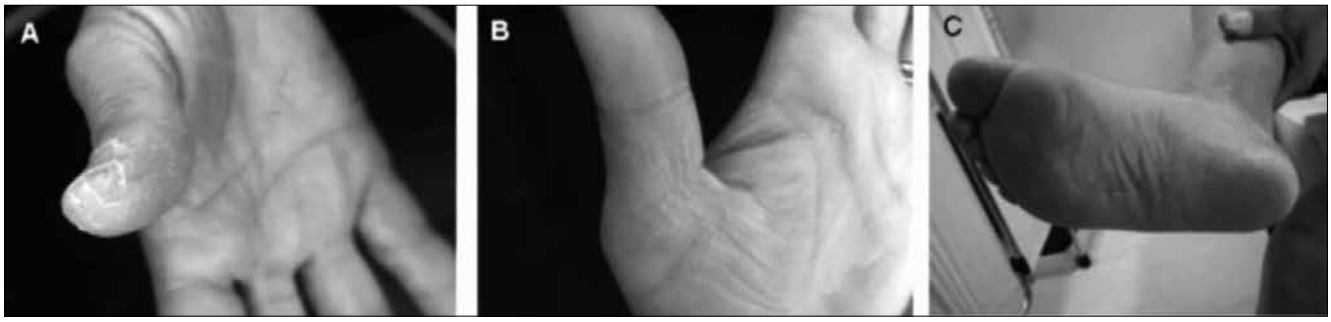

Fig. 2. Skin changes of the hands (A and B) and feet (C) of patient II-2 in Figure 1, demonstrating a palmoplantar keratoderma with a friction-associated denuded area of the thumb fingertip.

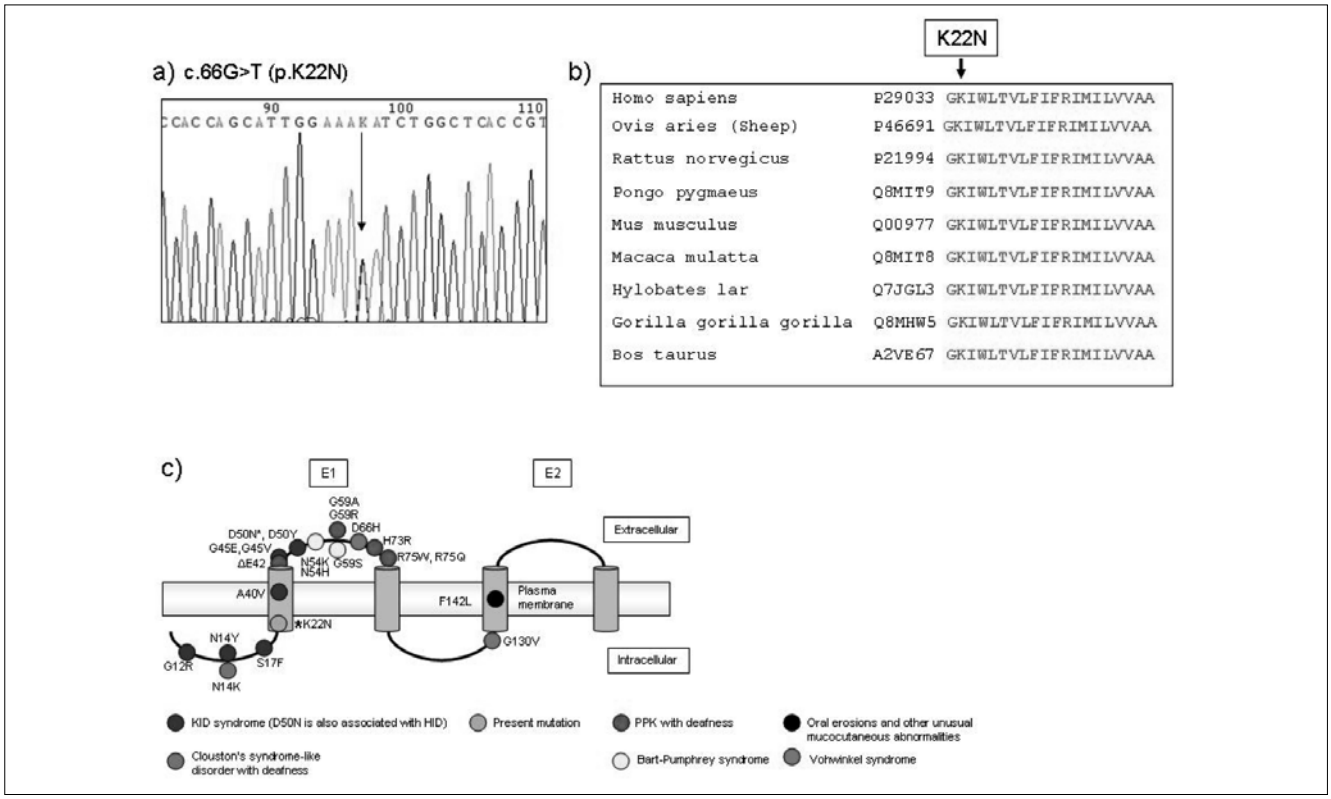

Fig. 3. a) Proband's chromatograms of *GJB2*. The arrow indicates the position of the c.66G>T, p.Lys22Asn mutation. b) Comparison of amino acid sequences of GJB2 among diverse species, showing that the first transmembrane domain (from aa 21 to aa 40) is highly conserved. c) GJB2-associated syndromes and reported causative mutations. E1 and E2, extracellular domains 1 and 2, respectively; PPK, palmoplantarkeratoderma; KID, keratitis–ichthyosis–deafness.

Discussion

We report a novel *GJB2* dominant mutation identified in an Italian pedigree, associated with childhood-onset, progressive neurosensorial HI and palmoplantar keratoderma, which was observed only in the adult affected members of the family. Different from the other keratoderma/deafness causing mutations, the p.Lys22Asn GJB2 variant resides in the transmembrane domain (TM) of the Cx26 protein, which contributes to cell-to-cell interaction at the level of the connexin hemichannels [15]. In one of the TM domains, only one other mutation has been described so far, namely p.Phe142Leu in which the affected child presented an unusual dermatologic phenotype characterised by vast erythematous patches on the trunk and mucosae without keratoderma [16]. The reported phenotype of the family falls into the spectrum of the dominant *GJB2* mutations described so far, since it progressively affects the auditory function starting from the highest frequencies in a mild and non-symmetrical fashion (Fig. 1, patients III-1 and III-2) and finally arrives to a moderate to severe degree of HI in the adult affected members of the family (patient I-1, Fig. 1). The dermatological features also appear mild, adult-onset and progressive, in keeping with the hypothesis of the p.Lys22Asn variant as a mild modifier of skin homeostasis with a gene dosage effect becoming apparent only with ageing.

Although a functional confirmation of the weak pathogenic potential of the variant is needed for definitive

evidence, the presented genotype/phenotype correlations show that the p.Lys22Asn can be considered as a variant with full but age-dependent penetrance, which initially causes an auditory and dermatological phenotype just above the threshold for clinical detection and becomes more evident with ageing, simulating the paradigm of other multifactorial disorders, like age-related hearing loss itself, which has been associated with the susceptibility effect produced by low-penetrance genes [17].

Conclusions

In conclusion, based on patients' phenotype, mutation segregation, population frequency and *in silico* prediction analysis, we suggest that the p.Lys22Asn variant is the cause of the dominant form of hearing loss associated with a variable expression of palmoplantar keratoderma in the family under study and represents a model of full penetrance, with an age-dependent effect on the phenotype.

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Web resources

Online Mendelian Inheritance in Man (OMIM), http://www.omim.org/
Deafness Variation Database, http://deafnessvariationdatabase.org/, accessed April 5 2016
Molecular Otolaryngology and Renal Research Laboratories, http://www.medicine.uiowa.edu/morl/
Exome Sequencing Project http://evs.gs.washington.edu/EVS/, accessed April 5 2016

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Audiology

Temporal changes in impedance of implanted adults for various cochlear segments

Variazioni nel tempo dell'impedenza degli elettrodi nelle diverse partizioni cocleari in adulti con impianto cocleare

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SUMMARY

Electrode impedance (EI) is the first objective assessment carried out during the surgical procedure and follow-up of cochlear implanted patients. This measure provides information on the integrity of electrodes and on the surrounding environment. It is one of the main factors responsible for energy consumption of the cochlear implant (CI). The aim of our study is to investigate changes over time in EI in adult recipients implanted with the perimodiolar array by comparing differences in various cochlear segments. In addition, we explore the relationship between these objective measures and subjective measures such as T-level and C-level. We studied 28 adult patients. Impedance values (IVs) were calculated in "common-ground" (CG) and in monopolar (M1+2) mode for electrode groups in basal middle and apical segments. We found significant decreases in IVs between activation and 1 month. We obtained higher values for basal impedance, whereas lower IVs were found for apical electrodes at all observation times. Statistical pairing over time between impedance and T/C values showed significant correlation for both global impedance (GI) and T-C levels at CG and M1+2 mode up to 6 months. Segregated statistical analysis also showed a significant and prolonged correlation of basal IVs and fitting parameters. The higher basal impedance over time can be explained by the higher proportion of newly formed tissue in this region. The linear correlation of impedances with the fitting parameters become not significant after 3/6 months for the apical and middle segments and remained significant only for the basal region over time. This behaviour underlines the importance of persistence in intra-cochlear factors in influencing fitting parameters in the basal segment.

KEY WORDS: Cochlear implant • Impedance • Perimodiolar array • Cochleostomy • Cochlear segments

RIASSUNTO

La prima valutazione oggettiva effettuata durante la procedura chirurgica e nel follow-up dei pazienti sottoposti ad impianto cocleare è la misura dell'impedenza degli elettrodi. Tale misura fornisce informazioni sia sull'integrità degli elettrodi sia sul mezzo circostante gli stessi ed è uno dei principali fattori responsabili dei consumi energetici dell'impianto cocleare. In questo studio abbiamo valutato in pazienti adulti con impianto cocleare e array perimodiolare, le variazioni nel tempo dell'impedenza degli elettrodi, valutando le differenze nelle varie partizioni cocleari (basale, medio e apicale) e correlandone i valori ai principali parametri psicoacustici del mappaggio: livelli di T e C. Abbiamo testato 28 pazienti adulti impiantati presso il nostro Dipartimento tra il 2009 e il 2014, tutti impiantati per via cocleostomica con un array perimodiolare completamente inserito, utilizzando la tecnica chirurgia "soft surgery". Le impedenze medie sono state misurate in modalità "common-ground" e "MP1+2" per i seguenti segmenti di array: basale (dall'elettrodo n.1 al n.7); mediale (dal n.8 al n.14); apicale (dal n.15 al n.22). L'analisi della varianza (ANOVA) è stata effettuata per valutare le tendenze nelle misure ripetute. Il livello di significatività accettato in tale studio è p<0.05 corretto con metodo Bonferroni. I risultati hanno mostrato una significativa riduzione globale delle impedenze dall'attivazione fino a 1 mese e un valore più alto nel tempo dell' impedenza nel segmento basale dell'array rispetto al segmento apicale e medio. L'analisi statistica temporale della correlazione tra i valori dell'impedenza globale e i livelli di T e C ha mostrato una correlazione significativa fino a sei mesi sia per le impedenze registrate in common-ground che in modalità MP1+2. L'analisi statistica dei vari segmenti cocleari ha mostrato inoltre una significativa correlazione dell'impedenza nel segmento basale e i parametri del fitting fino ad un anno di follow-up. In conclusione gli alti valori dell' impedenza nel segmento basale nel tempo possono essere spiegati con la formazione di fibrosi endococleare dopo l'inserimento dell'array, fenomeno maggiore nel segmento basale della coclea, limitato invece nelle regioni apicali e medie. La correlazione lineare dei valori dell'impedenza con i livelli di T e C diventa infatti statisticamente non significativa dopo tre/sei mesi nei segmenti apicali e medi e resta significativa fino ad un anno per il tratto basale. Questo comportamento sottolinea l'importanza nel tempo dell'influenza dei fattori intra-cocleari sui parametri del fitting nella porzione cocleare basale.

PAROLE CHIAVE: *Impianto cocleare • Impedenza • Elettrodo perimodiolare • Cocleostomia • Segmenti cocleari*

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Introduction

Cochlear implants are helpful tools for hearing function of people with severe to profound hearing loss by means of an electrode system stimulating remaining intra-cochlear neuronal cells. The considerable interest from the scientific community and manufacturers in the fields of bioelectrical and physiological engineering of the ear has led to many studies on implants that have clarified hitherto unknown aspects of the functioning of the cochlea [1 2]. Certainly, the structure of a cochlea stimulated by an electrode in situ that delivers the current is totally different from a normal cochlea for mechanical, electrical and bioelectric reasons.

It seems evident that the first critical point of the sequential process from sound stimulus to auditory comprehension can be identified in the cochlea-electrode interface and in the number of residual cells activated by the current output.

The latter variable is not quantifiable except in post-mortem studies, and even in these cases there is no consistent evidence for a correlation between residual ganglion cells and auditory performance [3-5]. Evidence from animal research shows that reductions and/or changes in the composition of perilymphatic fluid or adjacent electrode structures, as well as tissue modifications, lead to elevation of the contact impedance: this variation interferes with the efficiency and quality of neural stimulation [6]. Other works report that the histological structure of an implanted patient's cochlea changes in a typical pattern as a result of injury to the lateral wall in the region 8-15 mm from the round window, and it is often accompanied by new fibrous tissue and bone growth that can change the electrical conduction [7]. Under experimental conditions, deaf implanted cochleae compared to non-implanted deaf cochleae show great variations in the basal turn in terms of the number of hair cells, peripheral processes and damage to the stria and spiral ligament [8]. Measurement of cochlear electrode impedance provides information on the integrity of the array with the electrical surrounding medium. Impedance is opposition to current flow and is made up of capacitance and resistance; the first is related to the characteristics of electrode/fluids interfaces, and the second occurs when electrons pass through a medium and lose energy, which depends on the properties of the materials. Capacitance and resistance cannot simply be summed to achieve a total resistance. Clark [9] found a positive correlation between the grading of tissue around the electrode and impedance. In addition, electric flow affects electrode impedance: it is a common finding that without stimulation impedance increases.

Electric impedance seems to be primarily related to resistive structure of fluids and tissues around electrodes [10].

Other electrophysiological tests for cochlear implant evaluation are Electrical Advisory Brainstem Response (EABR) and Neural Response Telemetry and Stapedial Reflex. Our choice for recording impedance changes over time is motivated by several important factors: impedance is an objective intra-cochlear measure that provides information on the integrity of electrodes, on the surrounding environment and is one of the main factors responsible for the energy consumption of the cochlear implant. It is not influenced by number of surviving nerve VIII fibres.

The current steering from an electrode to a non-inert biological system can modify the system itself. Thus, the current intensity regulation necessary to deliver minimum or maximum sensations can vary over time because the reactive conditions of the biological system vary themselves. In fact, from a practical standpoint during the starting phases of the fitting, the same current level can provoke inferior acoustic sensations over time compared to successive follow-ups which are corrected with an increase of the energy pulses. Thus, even impedance variations can influence T- and C-levels if coupled to retro-cochlear factors. We wished to investigate this in a cohort of patients where a variability of the couples impedance/current exists, and if there exists a relationship between impedance values and subjective sensations.

In the literature there are several studies about changes over time in electrical stimulation levels and electrode impedance values in children [11-13] and in patients implanted with a straight array [14]. Most of these studies evaluated a short follow-up period [15 16], even though there are a some studies where impedances in the various cochlear segments have been analysed. In our study, in addition to previous studies, we evaluated the impedance variations over time only in adult patients implanted with a perimodiolar cochlear implant system with a longer follow-up (compared to the 12 weeks of Busby [15] or 9 months by Wermeskerken [16]). Furthermore, we assessed differences in the various cochlear segments by evaluating the correlation to the main fitting psychoacoustic parameters. In summary, our study purposes are:

1) Statistical evolution over time of impedance.
2) Statistical pairing over time between impedance and T/C values.
3) Segregated statistical analysis for apical, middle and basal electrodes over time.

Materials and methods

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation (D.L. 24 giugno 2003, n. 211 Attuazione della direttiva 2001/20/CE relativa all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico. G.U. n. 184 del 9-8-2003- Suppl. n. 130) and with the Helsinki Declaration of 1975, as revised in 2008.

Twenty-eight adult patients implanted at our Department were studied with an age between 18 and 58 years, 16 males and 12 females, 23 perilingually and 5 postlingually deafened, implanted in the period between 2009 and 2014. Aetiology of deafness included: meningitis (n = 1), neonatal sepsis (n = 1), neonatal hypoxia (n = 2), neonatal jaundice (n = 2), rubella during pregnancy (n = 1), postnatal measles (n = 1), genetic (n = 4), multiple sclerosis (n = 1), stroke (n = 1), unknown (n = 14). Aetiology of deafness remained unknown in 50% cases, while in 28.57% was due to environmental factors, 14.28% to genetic causes and 7.14% to other clinical features.

Our study protocol included repeated assessments, post-implant, at the following intervals: at time of activation, approximately 30 days post-surgery (mean 28.5 days) (t0); and postactivation, 1 month (t1); 3 months (t3); 6 months (t6) and one year (t12).

All subjects were good implant users (daily on-time > 10 hours). No differences were noted between perilingually or postlingually CI users regarding daily time of use.

In every case, the same type of perimodiolar array was implanted, the Cochlear™ Nucleus® CI24RE-CA (22 intracochlear electrodes along the array and 2 extra-cochlear electrodes). We used the same surgical technique (cochleostomy), performing manual and progressive introduction of the array, removing the stylet and, at the end, always using recommended precautions of soft surgery for this type of device and always using topical steroids (betametasone) over the cochleostomy site and to soak the electrode before cochlear insertion [17-20].

Patients with an incomplete electrode array insertion, cochlear malformations or impedance values for one or more electrodes of greater than 20 kΩ at any time during the follow-up period were excluded as well as cases with bilateral implants.

All processors were fitted with consistent parameters using the ACE strategy, with the same default fitting parameters for stimulation rate (stimulation frequency) = 900 pps (pulses per second) and pulse widths (the amount of time the stimulator delivers current, expressed in microseconds (μs) per phase of the biphasic current pulse) = 25 μsec.

Electrode impedances were measured using software supplied by the manufacturer. The measurement stimuli were biphasic current pulses presented using a current level of 100 clinical units, which are approximately 76 μA, and with pulse duration of 25 μs/phase.

At the beginning of each session, the electrical impedances in kΩ and the subjective values of T-level and C-level for each electrode were measured. Average values were calculated for the impedances measured in "common-ground" (CG) mode and in monopolar (M1+2) mode. In CG, the impedance is measured between an intra-cochlear electrode and all other intra-cochlear electrodes coupled in parallel: such a measure is only related to cochlear variables. In M1+2 mode, the impedance is measured between the intra-cochlear electrode and the sum of two reference electrodes placed one under temporal muscle and the other over the body of implant at the level of the temporal bone. This monopolar stimulation is used as default in clinical conditions by the ACE strategy.

Mean values were evaluated for electrode array segments as follows: basal (from No. 1 to 7); middle (from No. 8 to 14); and apical (from No. 15 to 22).

Mean impedances were evaluated for the different time intervals of observation and by statistical comparison of the temporal evolution of the values of T-level and C-level over time. The statistical test employed was the Student's t-test. T- and C-level were evaluated as standard procedure with a subjective approach [21] to be independent from any objective measure which could be influenced by impedances themselves, software a priori, or other.

Impedances and T- and C-level variations were compared by using the linear regression test. The probability level used was $p < 0.05$ and Bonferroni corrected. Regressions were calculated between mean T- and C-level and impedances for each observation period, as well as for each cochlear segment.

The array used in this study has different electrode surfaces according to their position along the cochlea. The largest surface areas are located in the basal region, while the smallest are located in the apical region: basal electrode (1-10) area is 0.230 mm^2 , middle electrode (11-16) area is 0.223 mm^2, apical one (17-22) is 0.212 mm^2 (data reported with permission of manufacturer).

To avoid that a difference in behaviour of the basal impedances compared to middle and apical ones could be due to the electrode surface, the impedance values were corrected by the area multiplicative factor.

Results

Raw data of T/C and impedance values are reported in Table I.

Statistical evolution over time of global impedance

The results showed an overall trend for the impedances with a significant variation between t0 and t1, similar to those reported by Busby [15]. An analysis of variance (ANOVA) was performed to evaluate trends in the repeated measures, and unexpected significant late reduction could be identified only in M1+2 (Fig. 1a).

Statistical pairing over time between global impedance and T/C values

Statistical pairing over time between impedance and T/C values showed significant correlation between global impedance (GI) and T-levels up to t6 and between GI and C-levels up to t6 for impedances calculated in CG mode. The same times of significant correlations were noted if

Table I. Impedance values (corrected per electrode surface), T-level. C-levels for basal-middle-apical segregations; (mean ± standard deviation).

Mean ± std. dev.			t0	t1	t3	t6	t12
Impedances	CG	Basal	2.93 ± 0.51	1.76 ± 0.41	1.79 ± 0.45	1.83 ± 0.44	1.88 ± 0.43
		Middle	2.77 ± 0.61	1.51 ± 0.40	1.47 ± 0.38	1.47 ± 0.44	1.44 ± 0.35
		Apical	2.48 ± 0.65	1.40 ± 0.38	1.33 ± 0.37	1.34 ± 0.42	1.22 ± 0.34
	MP1+2	Basal	3.02 ± 0.45	1.97 ± 0.40	2.00 ± 0.43	2.10 ± 0.47	2.14 ± 0.44
		Middle	2.93 ± 0.59	1.79 ± 0.38	1.76 ± 0.36	1.82 ± 0.48	1.76 ± 0.36
		Apical	2.64 ± 0.60	1.66 ± 0.38	1.60 ± 0.37	1.65 ± 0.46	1.50 ± 0.37
T-level		Basal	111.78 ± 25.25	135.88 ± 21.14	145.71 ± 15.82	146.32 ± 14.09	147.22 ± 14.94
Middle			107.64 ± 24.55	131.11 ± 21.87	143.08 ± 16.92	144.36 ± 14.79	146.55 ± 13.52
Apical			106.92 ± 25.03	130.95 ± 22.85	142.59 ± 17.23	143.00 ± 16.30	147.02 ± 14.12
C-level		BASAL	148.21 ± 17.52	183.61 ± 19.38	193.76 ± 15.48	194.91 ± 11.75	195.97 ± 11.66
Middle			145.69 ± 16.81	183.73 ± 21.37	195.26 ± 16.70	197.31 ± 12.47	199.68 ± 10.97
Apical			142.51 ± 17.57	181.16 ± 23.16	192.85 ± 17.64	194.76 ± 16.23	199.31 ± 13.94

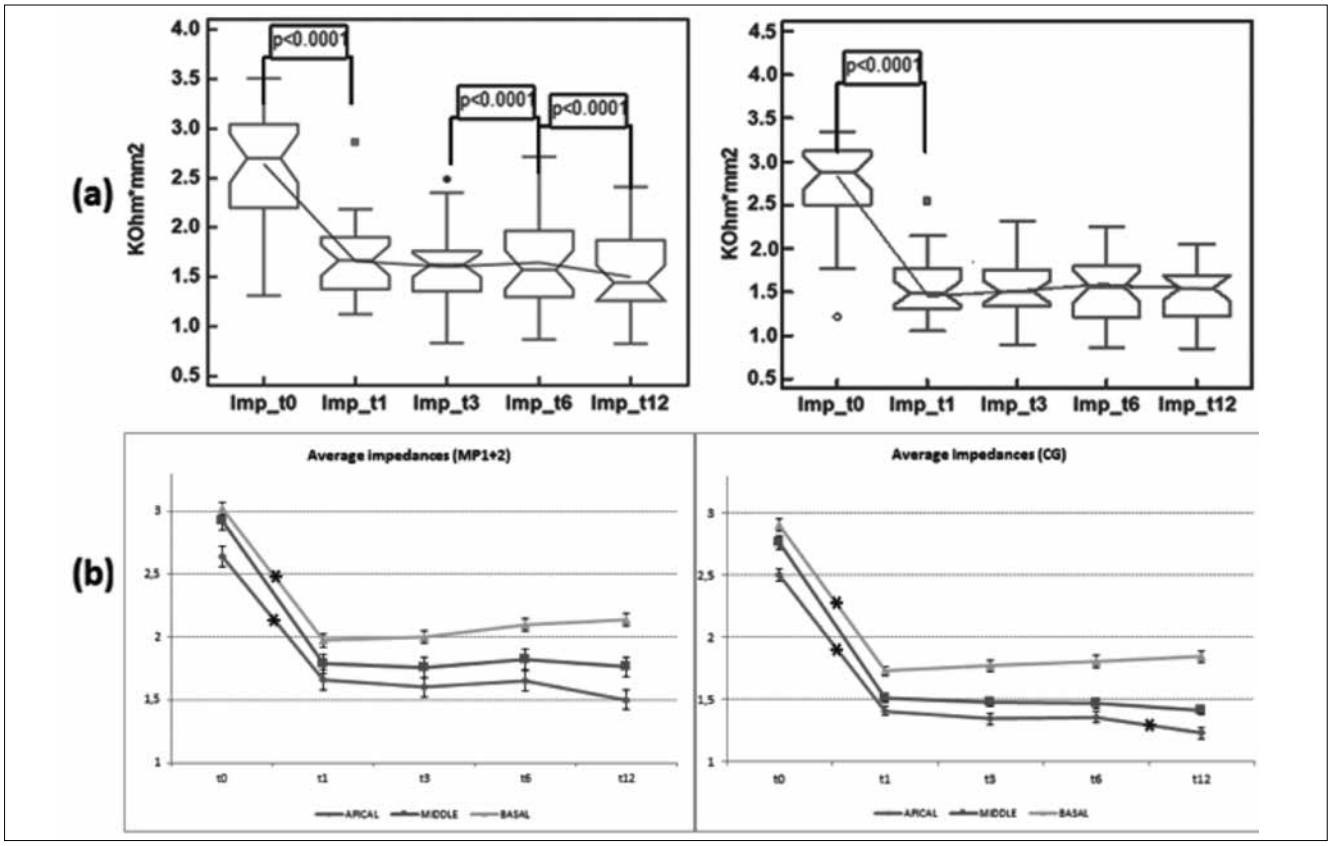

Fig. 1a. Top-left: overall change of impedance corrected by surface in MP1+2 mode; Top-right: overall change of impedance corrected by surface in CG mode; n = 28, significant time differences are shown. The middle line represents the median. In the notched box-and-whisker plot, confidence intervals for the medians are provided by means of notches surrounding the medians. The vertical line extends from the minimum to the maximum value, excluding outside (smaller/larger than the lower/higher quartile ±1.5 times the interquartile range) and far outside values (smaller/larger than the lower/higher quartile ±3 times the interquartile range). **b.** Time sequence of the impedances corrected by surface in MP1+2 mode (lower-left) and in CG mode (lower -right) differentiated by apical, middle and basal electrodes. Asterisk (*) = significant variations.

impedances were calculated in M1+2 mode (Table II) and Figures 2a and 2b.

Segregated statistical analysis for apical, middle and basal electrodes over time

We conducted the same statistical analysis for each cochlear region by differentiating electrodes into their basal, middle and apical segments.

The results presented for the corresponding array segments (Table I and Fig. 3) showed that the absolute values of the basal impedances are much higher at all evaluation times with significant differences with respect to apical

Table II. significant correlations (p<0.05 Bonferroni corrected) for T- and C-levels in CG mode and in M1+2 mode.

Sensation levels	Cochlear segment	Significant correlations with impedance at different time points	
		Common Ground	MP1+2
C	Global	t1 - t3 - t6	t1 - t3 - t6
T	Global	t1 - t3 - t6	t1 - t3 - t6
C	Apical	t1 - t3	t1 - t3 - t6
	Middle	t1 - t3	t1 - t3 - t6
	Basal	t0 - t1 - t3 - t12	t1 - t3 - t6
T	Apical	t1 - t3	t1 - t3 - t6
	Middle	t1 - t3	t1 - t3 - t6
	Basal	t1 - t3 - t6 - t12	t1 - t3 - t6

and middle segments. A clear correlation between T-level, C- level and impedances in M1+2 were shown from t1 up to t6 for the apical, middle and basal segments. In CG mode, T and C correlates up to t3 for apical and middle segments, but a surprising positive correlation was observed up to t12 between basal electrodes versus T and C. A clear correlation between T-level, C-level and impedances in M1+2 were shown from t1 up to t6 (Table II).

A remarkable difference between CG and M1+2 was the prolonged significance up to t12 for the basal electrodes (Table II).

The p values of t tests for impedances, evaluated at different time points, were significant between basal and apical electrode segments and between basal and middle segments at each interval over the observation period (Table III). Less significant differences were observed for comparison of impedances in apical versus middle segments when compared in CG mode (excluded t0 and t12 at MP1+2) (Fig. 3).

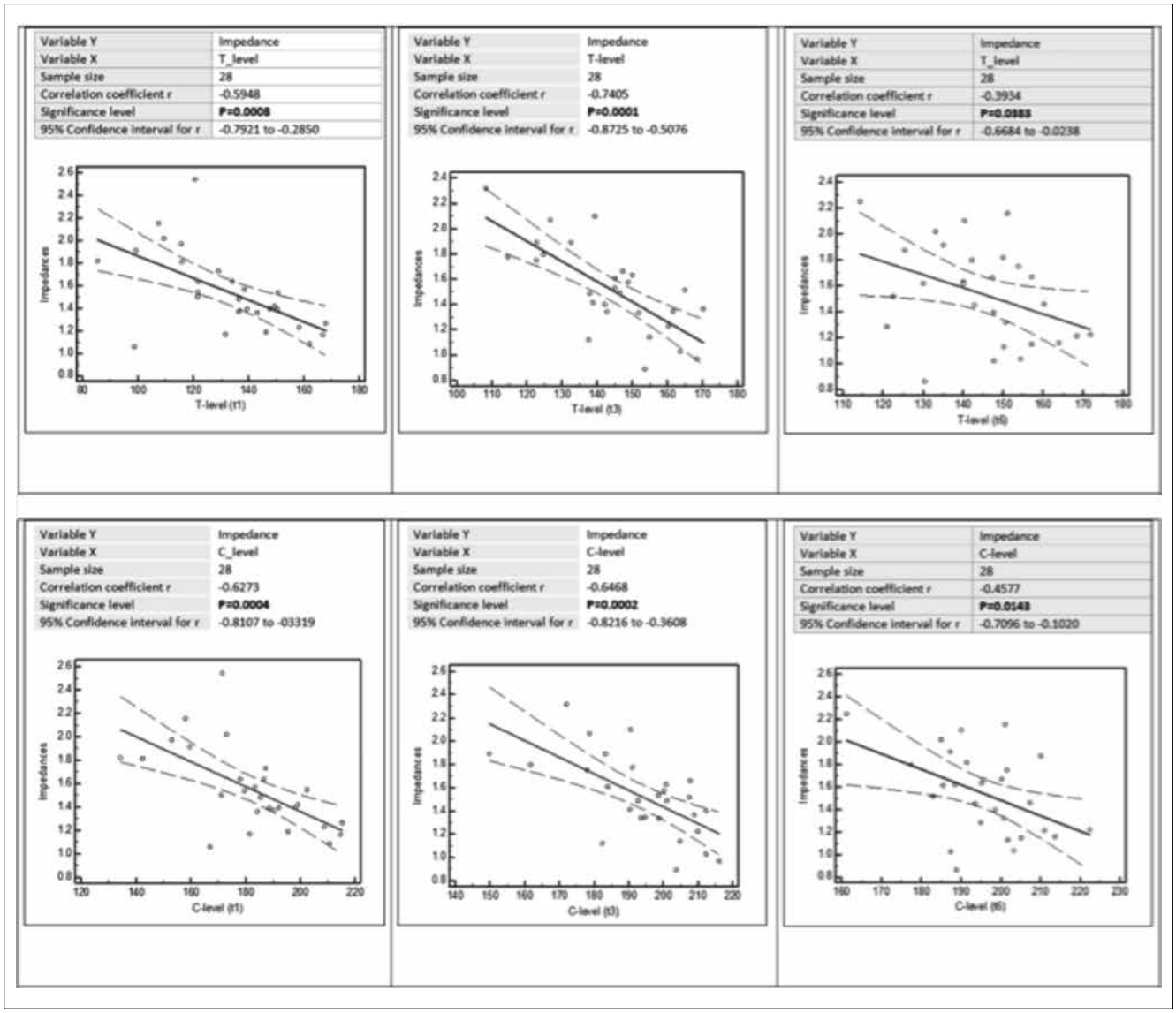

Fig. 2a. Linear correlations between T-level and global impedance; significant values at t1, t3 and t6. **b.** Linear correlations between C-level and global impedance; significant values at t1, t3 and t6.

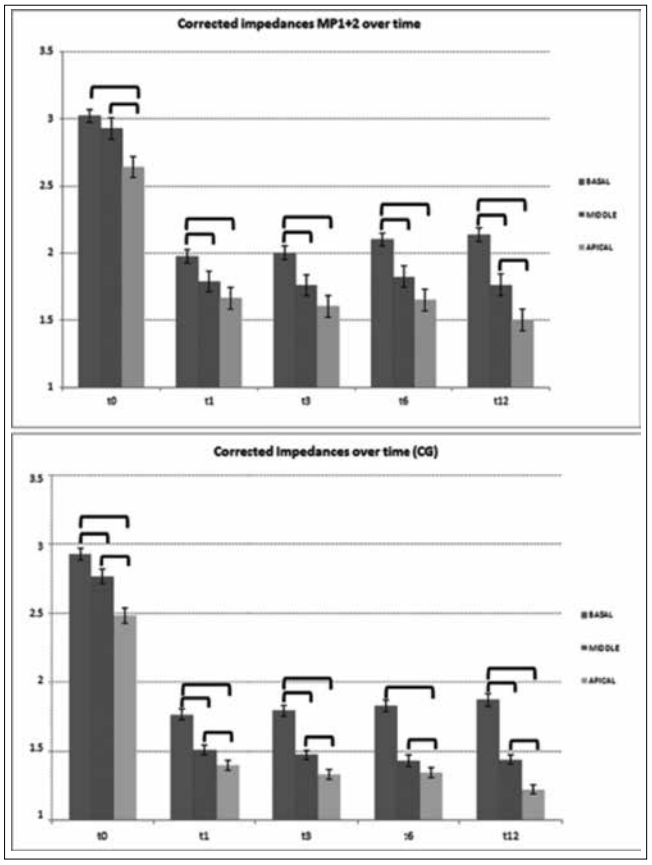

Fig. 3. Histograms depicting average values of the impedances in M1+2 and CG mode in the various cochlear segments and at various evaluation times; in brackets, groups with significant variations.

Discussion

Statistical evolution of global impedance over time

The evaluation of our impedance data overall agrees with literature reports [15 16 22 23]; where the maximum values are recorded at t0 followed by a decrease immediately after activation of the sound processor.

In experimental animal studies, the impedance changes reduce around the 45th day [24]. In humans, a reduction in the average impedances was observed during the first weeks and although impedances tended to increase with the use of the cochlear implant, no statistically significant differences were found between the following months [25].

The variation of global impedance became statistically significant after three months only in Mp1+2 (Fig.1a). We may speculate that extra-cochlear fibrosis around the case electrode is more pronounced and late than around the intra-cochlear one.

Statistical pairing over time between global impedance and T/C values

In our data, there is an evident inverse correlation between impedances and T-level values: high impedance values correspond to lower electrical intensity (Fig. 2). This behaviour is in strong agreement with the relationship of these variables stated by Ohm's law (R = V/I) and other findings in the literature [15]. According to Kawano [26], T-values correlate especially with the amount of fibrous tissue and also with new bone. Global T- and C-levels correlate with IV until t6 in M1+2 and in CG mode (Table II and Figs. 2a and 2b).We may speculate that intra-cochlear variables influenced global T and C values up to t6.

Segregated statistical analysis for apical, middle and basal electrodes over time

Our segregated data over time showed a slight increase, although not significant, in basal impedance over time (Table I and Fig. 1b) and a slight decrease for the apical segment at t12 (Fig. 1b), with no consistent pattern for the middle electrode segment.

The behaviour of the higher basal impedances compared to middle and apical ones (Fig. 3) agree with the data by Busby [15] even if a different electrode array was used.

The higher basal impedance suggests the intervention of biological, intra-cochlear factors that may act in a different way depending on the cochlear regions. In the basal cochlear segment, a relative increase of impedance may be explained by a consistent production of scar tissue. Instead, in the apical region, the lower impedance may be due to a progressive adherence of conductive molecules that lead to an increase of a virtual electrical surface and thus to the decrease of impedance [27]. Probably both capacitive and resistive components of impedance change inside the cochlea, with prevalence of resistive in basal and conductive in apical.

Henkin [13] found no differences between impedances among cochlear segments, but their data are not directly comparable to our study because the population and implants are different; they evaluated a paediatric population with lateral wall implant, while our study considered adults with a perimodiolar array.

Molisz [28] found differences between the impedances among cochlear segments: the mid-portion and apical electrodes showed a decrease in impedance values in the first 6 postoperative months and stabilisation in the later course. The impedance of basal electrodes increased during the first 6 postoperative months and stabilised later on, but remained higher than the mid and the apical electrode impedance. In our study, we found similar results.

Kumar [29] estimated that 75% of the electric current delivered by a cochlear implant is dispersed longitudinally in the scala tympani without stimulating the cells of the spiral ganglion. This large energy dispersion could be the basis for histological findings, while on the contrary, Fayad [8] hypothesised that this is due to surgical trauma alone. It is known that the cochleostomy procedure for insertion of the array causes immediate changes in the microstructure of the cochlea, such as trauma to the lateral wall, destruction of the spiral ligament and stria and damage in the lamina spiralis, basilar membrane, or modiolus [30 31].

Table III. (a) CG mean differences (Δ) and p-value for basal-middle-apical segregations at different time-points and **(b)** MP1+2 mean differences (Δ) and p-value for basal-middle-apical segregations at different time-points; ns=not significant values.

A	Δ Impedance	T-test	Δ Impedance	T-test	Δ Impedance	T-test
CG mode	Basal-Apical:Δ	Basal vs. Apical: p	Basal-Middle:Δ	Basal vs. Middle: p	Apical-Middle:Δ	Apical vs. Middle: p
t0	0.4472	4.00E-09	0.1617	4.56E-04	-0.2855	1.98E-04
t1	0.3647	1.68E-08	0.2533	1.02E-10	-0.1114	ns
t3	0.4572	1.04E-12	0.3148	2.06E-13	-0.1424	8.76E-03
t6	0.4886	1.35E-12	0.3571	1.05E-10	-0.1315	ns
t12	0.6568	4.20E-20	0.4402	1.69E-17	-0.2166	5.47E-05

B	Δ Impedance	T-test	Δ Impedance	T-test	Δ Impedance	T-test
MP1+2 mode	Basal-Apical:Δ	Basal vs. Apical: p	Basal-Middle:Δ	Basal vs. Middle: P	Apical-Middle:Δ	Apical vs. Middle: p
t0	0.3807	0.003	0.0929	Ns	-0.2878	0.048
t1	0.3124	<0.0001	0.1863	<0.001	-0.1261	ns
t3	0.4010	<0.0001	0.2413	<0.003	-0.1598	ns
t6	0.4504	<0.0001	0.2776	<0.0018	-0.1728	ns
t12	0.6339	<0.0001	0.3736	<0.0001	-0.2603	0.01

Late changes may originate from host reactions to the presence of the array and involve inflammation, fibrosis and bony tissue growth. Trauma to the insertion site may also be introduced by bone dust coming into contact with the perilymph, which may contribute to fibrosis and osteoneogenesis [9 32].

Our data indicating an higher basal segment impedances, where the highest electrical leakage is possible, are consistent with the findings of histological studies by Fayad [8]: in 11 patients who underwent cochlear implant surgery, they found that almost all of the fibrosis and osteoneogenesis occurred in the basal turn. The authors stated that the period between the surgeries until CI-user death (range 0.9 to 12.9 years) had a negative correlation with the amount of fibrosis in the basal cochlear segment, while the bone tissue growth tended to have a positive correlation in that segment. This reported trend and our data lead us to hypothesise that for our study subjects (i.e. with up to one year of follow-up), fibrosis (and not osseous growth) could be the main attribute responsible for the changes we observed in the impedances measured.

For our patient group, the same cochleostomy approach was applied; therefore, the resultant high impedances in basal electrodes could be due to such an insertion technique compared to the round window route. Against this hypothesis, however, are the histological findings of Fayad [8] which in 5 round window surgeries compared to 5 cochleostomy technique cases, no significant differences were detected in the amount of fibrosis, bone growth or other characteristics in general of the newly formed tissue or in residual sensorineural cells. Nadol [33] report that in 12 of 21 (57%) of temporal bones in implanted patients, there was a cellular response of inflammatory type with mononuclear leukocytes, histiocytes and foreign-body giant cells revealing that these reactions are much more intensive proximal to the cochleostomy site, which means that the inflammatory cells may persist in the long term even after implantation.

In our results, there is a clear correlation between T-level, C- level and impedances in M1+2 up to t6 for apical, middle and basal segments. In CG mode, T and C correlates up to t3 for apical and middle segments, and up to t12 for basal electrodes.

Thus, the disappearance of correlation at t6 and t12 for cochlear apical and middle segments (Table II, no global T-level differences after t3) seems to suggest stabilisation of intracochlear fibrosis after this period in these regions. Different timing results were obtained for basal electrodes that show significant correlation from t0 up to t12, suggesting a stronger and/or prolonged importance of intra-cochlear factors in determining fitting parameters at this cochlear segment.

In conclusion, our results indicate an increase in absolute basal electrode impedances compared to middle and apical ones at different observation times. The higher proportion of newly formed tissue in the basal region, as reported in other studies, may explain this overall picture. There is a good linear correlation of impedance values with parameters of fitting that agrees with Ohm's law: higher IVs correspond to both lower T and C levels.

Conclusions

In conclusion, our results indicate an increase in absolute basal electrode impedances compared to middle and apical ones. The higher proportion of newly formed tissue in the basal region, as reported in other studies, may explain

this overall picture. The significant correlation between IVs and T and C values in the basal segment over time (up to t12) suggests to using more caution during fitting of basal electrodes.

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Otology

Conservative treatment of vestibular schwannoma: growth and Penn Acoustic Neuroma Quality of Life scale in French language

Trattamento conservativo degli schwannomi vestibolari: accrescimento e Penn Acoustic Quality of Life scale in lingua francese

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SUMMARY

The aim of this study was to determine the natural history of growth and quality of life (QoL) outcomes for vestibular schwannoma (VS) managed conservatively, and to validate the disease-specific Penn Acoustic Neuroma Quality-of-Life (PANQOL) scale in French language. We retrospectively studied 26 patients with VS managed conservatively. Patient characteristics and radiological findings were collected. Two scales were used to measure QoL: the Short Form-36 Health Survey (SF-36) and the PANQOL scale translated into French. Internal consistency and scores were compared with previous studies. The mean follow-up was 25 months (range 6-72). We observed tumour growth in 14 patients (53.8%), no growth in 12 patients (46.2%) and no case of tumour shrinkage. The mean tumour growth was 2.22 mm/year. No predictive factor of growth was found. Patients with vertigo or dizziness experienced a poorer QoL according to the SF-36 (Social Functioning and Emotional Role Limitation dimensions) and to the PANQOL scale (Balance and Energy dimensions). Our results were comparable with the literature using the SF-36. With the PANQOL scale, our scores were not statistically different with those from Dutch and North American studies except in the field of hearing (p = 0.019). Quality of life becomes essential in the management of VS. According to these results, we support a non-conservative strategy associated with vestibular rehabilitation for patients with dizziness or vertigo. The PANQOL is a validated specific scale for VS, which can be useful in French.

KEY WORDS: Vestibular schwannoma • Conservative treatment • Tumour growth • Quality of life • Short Form-36 Health Survey • Penn Acoustic Neuroma Quality-of-Life scale

RIASSUNTO

L'obiettivo di questo lavoro è stato di valutare la storia naturale di crescita degli schwannomi vestibolari (VS), la qualità di vita di quelli trattati in maniera conservativa e di validare una scala specifica per tale malattia in lingua francese, Penn Acoustic Neuroma Quality-of-Life (PANQOL). Sono stati studiati retrospettivamente 26 pazienti con VS trattato in maniera conservativa. Sono state raccolte le caratteristiche dei pazienti e i reperti radiologici, e sono state utilizzate due scale per validare valutare la qualità di vita: la Short Form-36 Health Survey (SF-36) e la PANQOL scale, tradotta in francese. I punteggi ottenuti sono stati comparati con gli studi precedenti. Il tempo medio di follow up è stato di 25 mesi (range 6-72). È stata osservato un accrescimento del tumore in 14 pazienti (53,8%), nessun accrescimento in 12 pazienti (46,2%), e non si è verificata nessuna riduzione. La crescita media del tumore è stata di 2,22 mm/anno, e non sono stati individuati fattori predittivi di crescita. I pazienti con vertigini e instabilità hanno riferito una più bassa qualità di vita, sia secondo la scala SF-36, sia secondo la scala PANQOL. Utilizzando la scala SF-36, i nostri risultati si sono rivelati paragonabili a quelli della letteratura. Utilizzando la scala PANQOL, i nostri punteggi non si sono rivelati statisticamente diversi da quelli derivanti da studi tedeschi e nordamericani, ad eccezione di quelli riguardanti l'udito (p=0,019). La qualità di vita diventa sempre più importante nella gestione dei VS. In linea con questi risultati, noi sosteniamo la strategia non conservativa associata ad una riabilitazione vestibolare per quei pazienti con vertigini ed instabilità. La scala PANQOL, disponibile in lingua francese, si è rivelata specifica per i VS.

PAROLE CHIAVE: *Schwannoma vestibolare • Trattamento conservativo • Accrescimento tumorale • Qualità di vita • Short Form-36 Health Survey •Penn Acoustic Neuroma Quality-of-Life scale*

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Introduction

Vestibular schwannomas (VS) are benign tumours that represent 6% of intracranial tumours and 85% of cerebellopontine angle (CPA) tumours [1]. Most grow slowly, but some do not and some regress [1 2]. Nowadays, there is the ability to diagnose very small VS increases thanks to the availability of magnetic resonance imaging (MRI).

The management strategy of VS is still controversial. Management options include microsurgery, stereotactic radiosurgery, a combination of both and observation by serial imaging. Invasive treatments by microsurgery or radiosurgery are associated with consequences for quality of life (QoL) [3]. Radiosurgery seems to provide better functional outcomes with less morbidity than microsurgery, but side effects are still present [3 4]. Since 1985, conservative management with serial observations by MRI has become more interesting, especially for small tumours and elderly patients [5]. Therapeutic strategy is often correlated to the tumour size, the tumour capacity to grow, patient age and hearing status. Several studies have focused on predictive factors of growth with no strong significance in meta-analysis except for tumour size at diagnosis [1 6].

At present, QoL has become more predominant in VS management, but the literature is still heterogeneous [7]. Most studies use the Short Form-36 Health Survey (SF-36), a non-specific questionnaire, to measure QoL and few are prospective, randomised trials. Recently, Shaffer et al. have developed the Penn Acoustic Neuroma Quality-of-Life scale (PANQOL) as a specific QoL scale for VS [8]. Validated in the Dutch language by Van Leeuwen et al., it seems to be more correlated with symptoms influencing QoL [9]. To our knowledge, no study has validated the PANQOL scale in French.

Based on our experience and a review of the literature, this study focused on the natural history of growth and QoL outcomes for VS managed conservatively. The first aim of this work was to validate the PANQOL scale translated into French language and comparing it with data of previous studies. The second endpoint was to determine predictive factors of tumour growth of VS managed conservatively and make correlations between tumour growth and QoL using the SF-36 and PANQOL scales.

Materials and methods

Patients

This work reports on a retrospective study of consecutive cases of VS treated conservatively in a university tertiary referral centre over 10 years (August 2002-September 2012). Patients with a sporadic unilateral VS first managed by a "wait-and-scan" strategy with repeated MRI (at least two MRI six months apart) were included. Cases with other CPA tumours as well as cases with neurofibromatosis type II were excluded. Patients who are unable to answer a written questionnaire in French language were also excluded. The medical ethics committee of our University Medical Centre approved our protocol before the beginning of the study.

Workup

Epidemiological data and clinical assessment were recorded from patients' clinical charts. Audiometric data were analysed as recommended by the Committee on Hearing and Equilibrium guidelines [10]. Class A was defined as normal hearing, Class B as moderate hearing loss and Classes C and D as severe hearing loss. Facial function was defined by the House Brackmann grading.[(11)] Tumours were classified as intracanalicular, extracanalicular grade 1 (≤ 10 mm), grade 2 (11-20 mm), grade 3 (21-30 mm), grade 4 (31-40 mm) and grade 5 (≥ 41 mm) according to the 2003 consensus meeting in Tokyo [12]. Tumour size was measured by MRI using the longest extracanalicular size and the antero-posterior size. Comparisons of these two measures on repeated MRI were performed to determine tumour growth (mm/year).

Patients were contacted by phone to take part in the study. They then received a package with two questionnaires (SF-36 and PANQOL scale) and an agreement form they were asked to send back by postage-paid envelope.

Questionnaires

The *Short Form-36 Health Survey (SF-36)* is a valid, generalist QoL scale. It consists of 36 multiple-choice questions that assess 8 dimensions: Physical Functioning (PF), Social functioning (SF), Physical Role Limitations (PR), Emotional Role Limitations (ER), Mental Health (MH), Vitality (VT), Bodily Pain (BP), and General Health (GH). Physical component score is calculated from PF, PR, BP and GH dimensions. The mental component score is provided by the SF, ER, MH and VT dimensions. The SF-36 scale ranges from 0 to 100, and a higher score indicates a status of better health. The SF-36 has already been validated in French [13 14].

The *Penn Acoustic Neuroma Quality of Life (PANQOL) scale* is a specific questionnaire consisting of 26 questions that assess 7 dimensions: Hearing, Balance, Face, Anxiety, Energy, Pain, General Health. The PANQOL scale ranges from 0 to 100, and a higher score indicates better health status. The PANQOL questionnaire was translated into French according to the accepted rules of forward-backward translation as presented in Appendix 1 [15]. No divergence between the original and translated items was found.

Statistical analysis

Statistical analysis was performed using SPSS software (version 20. for Windows). Means, medians and standard deviations of demographic and clinical data were calcu-

lated and analysed using the student's T-test. The Pearson correlation coefficient was used to analyse predictive factors of tumour growth and relationships between tumour growth and QoL scores (SF-36 and PANQOL). Results were considered significant when the p value was < 0.05. Internal consistency of the French PANQOL scale dimensions was measured using Cronbach's alpha, which is an exploratory factor analysis used to describe the reliability of questionnaire items. The value of alpha is an indication of the extent to which a number of items in a test measure the same concept. A commonly accepted interpretation of Cronbach's alpha (between 0 and 1) is excellent (≥ 0.9), good (0.8-0.9), acceptable (0.7-0.8), questionable (0.6-0.7), poor (0.5-0.6), or unacceptable (≤ 0.5). The SF-36 scores and the PANQOL scores in our sample were compared with the PANQOL scores of Van Leeuwen et al. and Shaffer et al. studies using the student's T-test [8 9].

Results

Population and tumour growth

Over 10 years (August 2002-September 2012), 327 patients were diagnosed with VS. Twenty-six patients (8%) initially managed by conservative strategy were included in our study. Nine patients were males (34.6%) and 17 were females (65.4%), i.e. a sex ratio of 0.5. The mean age at diagnosis was 55.73 years (range 40-81 years). Half of the patients had useful hearing (class A or B) at diagnosis and 6 (23%) had severe hearing loss (class C or D). Hearing levels were not reported in 7 patients (27%). Tinnitus was presented at diagnosis in 9 patients (34.6%) and dizziness or vertigo in 2 patients. No facial palsy was presented.

Main tumours were small to medium size. There were 13 intracanalicular VS, 3 tumours of grade 1, 9 tumours of grade 2 and 1 tumour of grade 3. The mean and median tumour size at diagnosis were 11.65 mm and 11 mm, respectively.

Mean and median follow-up were 25.8 and 20.5 months respectively (range 6-40). Tumour growth was observed in 14 patients (53.8%), no growth in 12 patients (46.2%) and none cases presented shrinkage. Mean tumour growth was 2.22 mm/year (range 1-5 mm/year). All patients ended their conservative treatment by microsurgical procedure for following reasons: tumour growth, hearing loss, vertigo, or dizziness.

Predictive factors of tumour growth

Prognostic impact of patient characteristics (epidemiological data, clinical assessment, tumour size at diagnosis) on tumour growth were analysed. No significant predictive factor of tumour growth was revealed (Table I).

Quality of life

Twenty patients completed and returned the questionnaires (76.9%). Patient characteristics of non-responders were not significantly different from responding patients. The SF-36 scores are reported in Table II. These results were consistent with previous studies [9 16 17]. The SF-36 showed a poorer QoL in mental component score than in physical component score, 44.8% and 51.6%, respectively. We reported a significant decrease in Social Functioning ($p = 0.042$) and Emotional Role Limitations ($p = 0.033$)

Table I. Analyses of the prognostic impact of patient characteristics (epidemiological data, clinical assessment, tumour size at diagnosis) on tumour growth.

Patient characteristics	Patients (N = 26)	Prognostic impact on tumour growth (longest extracanalicular size) p	Prognostic impact on tumour growth (antero-posterior size) p
Mean age at diagnosis (year) (range)	55.73 (40-81)	0.247	0.453
Gender M/F	9/17	0.240	0.412
Mean follow-up (month) (range)	25.81 (6-72)	0.248	0.537
Tumour size at diagnosis, No. of patients (%)		0.797	0.423
Intracanalicular	13 (50)		
Grade 1	3 (11.5)		
Grade 2	9 (34.6)		
Grade 3	1 (3.9)		
Hearing levels at diagnosis, No. of patients (%)		0.233	0.391
Class A (normal hearing)	8 (30.8)		
Class B (moderate hearing loss)	5 (19.2)		
Class C or D (severe hearing loss)	6 (23)		
Not reported	7 (27)		
Vertigo or dizziness, No. of patients (%)	2 (7.7)	NA	NA
Tinnitus, No. of patients (%)	9 (34.6)	0.214	0.949
Facial palsy, No. of patients (%)	0 (0)	NA	NA

(NA: not applicable)

Table II. SF-36 scores and correlation coefficient with tumour growth.

Patients (N = 20)	Mean (SD)	Correlation coefficient with tumour growth	
		Longest extracanalicular size (p)	Antero-posterior size (p)
Physical Functioning (PF)	84.1 (22.7)	-0.379 (0.281)	-0.159 (0.622)
Social functioning (SF)	70.0 (34.2)	-0.227 (0.529)	-0.514 (0.087)
Physical Role Limitations (PR)	71.8 (38.5)	-0.627 (0.096)	-0.511 (0.131)
Emotional Role Limitations (ER)	75.0 (41.2)	-0.48 (0.228)	-0.583 (0.077)
Mental Health (MH)	64.3 (26.1)	-0.326 (0.357)	-0.46 (0.132)
Vitality (VT)	58.0 (22.8)	-0.405 (0.246)	-0.441 (0.151)
Bodily Pain (BP)	86.1 (26.6)	-0.435 (0.208)	-0.244 (0.455)
General Health (GH)	67.4 (12.4)	-0.153 (0.673)	-0.115 (0.722)
Physical component score	51.6 (10.4)	-0.274 (0.512)	-0.021 (0.954)
Mental component score	44.8 (14.3)	-0,378 (0.355)	-0.634 (0.049)

(SD: Standard Deviation; in bold: $p < 0.05$)

dimensions in patients presenting dizziness or vertigo. The mental component score was significantly lower in patients with hearing loss ($p = 0.040$). No significant relationship was found between QoL and tinnitus or facial palsy. Furthermore, a significant negative correlation was found between tumour growth measured on the antero-posterior size and mental component score ($p = 0.049$) using the SF-36. Although its subscales showed a negative correlation, none were statistically significant.

We kept the initial 7-dimensions structure of the PANQOL as published by Shaffer et al. after exploratory factor analysis [8]. Means, standard deviations and Cronbach's alphas of our PANQOL scale are compared on Table III with the American and Dutch scores [8 9]. Our results were consistent with these previous studies, as shown in Figure 1, except for Hearing dimension ($p = 0.019$) of Van Leeuwen et al. [9]. The lowest scores were found in Hearing dimension (57.23), Balance dimension (62.7) and General Health (59.72). Patients presenting vertigo or dizziness experienced a poorer QoL in Balance dimension ($p = 0.015$) and Energy dimension ($p = 0.047$). There was no significant relationship between tumour growth and QoL evaluated by the PANQOL.

Discussion

In the management strategy of VS, conservative management with repeated MRI and monitoring of tumour growth has become of increasing interest for small tumours and elderly patients. We aimed to determine the predictive factors of tumour growth and to analyse QoL using the SF-36 scale, a generalist QoL scale, and the PANQOL scale translated into French language, a specific scale for patients with VS. We retrospectively studied 26 cases of VS that were initially managed by conservative strategy. Twenty patients were evaluated by QoL scales. No significant predictive factor of tumour growth was revealed in our study. To the best of our knowledge, our study is the first using PANQOL scale in French language. Our results are comparable to the North American and Dutch version studies. The major finding of this work is that patients presenting vertigo or dizziness experienced a significantly poorer QoL.

Tumour growth analysis is consistent with the literature

Our study followed tumour growth for more than half of patients (53.8%) of an average of 2.22 mm/year. These results are consistent with the literature [16 17]. Nikolopoulos

Table III. Means, standard deviations and internal consistency (Cronbach's alpha) of PANQOL scale in current and previous studies.

PANQOL dimensions	Our study (N = 20)		Van Leeuwen et al. (N = 119)		Shaffer et al. (N = 143)	
	Mean (SD)	Alpha	Mean (SD)	Alpha	Mean (SD)	Alpha
Hearing	57.2 (25.3)	0.68	41.3 (27.3)	0.75	63.8 (22.2)	0.77
Balance	62.8 (28.2)	0.90	66.0 (29.4)	0.94	72.9 (20.5)	0.87
Face	84.2 (15.4)	0.46	83.6 (21.3)	0.65	85.4 (18.9)	0.71
Anxiety	72.4 (23.2)	0.72	71.3 (25.2)	0.88	73.5 (20.4)	0.81
Energy	69.3 (25.7)	0.89	66.2 (28.9)	0.91	67.6 (23.0)	0.88
Pain	78.9 (32.6)	NA	70.4 (35.9)	NA	77.7 (28.7)	NA
General Health	59.7 (19.9)	0.25	60.4 (22.1)	0.31	68.3 (21.3)	0.73

Means, standard deviations and internal consistency (Cronbach's alpha) of PANQOL scale in current and previous studies
(SD: Standard deviation; NA indicates not applicable because only one item is included in this dimension; in bold: $p < 0.05$)

et al. found in a meta-analysis that tumour growth was between 18 and 73% of an average of 2 to 4 mm/year and the absence of growth between 9 and 75% of cases depending on the study [1]. We did not find any case of tumour regression, although it is found in usually less than 10% of cases [1 24].

Although some authors relate mainly tumour growth in the first year after diagnosis, other tumours may begin to grow later [18 21 22]. Moreover, the absence of tumour growth after 5 years of follow-up has already been described, but even longer tumour growth as well [2 18 21]. Thus, among the various monitoring protocols proposed in the literature, those advising close monitoring during the first 5 years and then ongoing monitoring beyond seems to be the most suitable for monitoring patients with VS [2 18 23].

No significant predictive factor of tumour growth was revealed

Several studies failed to find a predictive factor, but Smouha et al. in a meta-analysis observed a significant relationship between tumour growth in the first year and future growth [1 6 18 20]. However, this result was not confirmed by a recent meta-analysis, emphasising the need to follow VS in the longer term [1]. Artz et al. reported unsteadiness/vertigo, no sudden onset of hearing loss and short duration of hearing loss as predictive factors of tumour growth and proposed a tumour growth risk (High Risk/Low Risk) according to these factors [19]. High Risk VS had a greater probability to grow than Low Risk VS during the first (36.9% vs. 2.5%) and second (64.6% vs. 12.7%) years. The absence of a significant predictive factor is probably related to the heterogeneity of methods and results in the literature as well as to some biases present in our study.

The SF-36 is most widely used in QoL studies on VS but it is a generalist scale

QoL has become decisive in the management of VS in the last decade. However, we note the difficulty to compare studies because of the different scales used to measure QoL [7]. Moreover, theses scales are unspecific to symptoms experienced by patients who suffer from VS.

We used the SF-36 as a generalist scale because it is most widely used in studies on VS. We found a greater deterioration of the mental component score than the physical component score in contrast to Lloyd et al. [25]. Our study suffers from a selection bias because we sent our questionnaires retrospectively to operated patients who follow a conservative strategy first. QoL seems to be worse in patients who complain with dizziness, especially in the social dimension. Previous studies already reported a similar result [7 25 26]. Thus, our results support ì that non-conservative management and vestibular rehabilitation should be proposed to dizzy patients.

The effect of hearing loss on QoL is still controversial [7]. Several studies have underlined the importance of hearing loss with QoL, although Godefroy et al. reported no association between hearing loss and SF-36 scores [17 27].On the contrary, we observed a significant relationship between hearing loss and the mental component score, but none of these subscales were significantly related to hearing loss. The reason is probably the low statistical power of our results.

A slightly significant negative correlation was found between tumour growth measured on the antero-posterior size and mental component score, but it was not significantly related in its subscales. Furthermore, we did not find such a correlation using the longest extracanalicular size or with the PANQOL scale. According to Godefroy et al., QoL measured with the SF-36 was not decreased by tumour growth [17]. However, this result underlines the need for psychological support in patients with VS managed conservatively.

Finally, according to Vogel et al., the perceived QoL of VS patients was significantly lower than the QoL of patients with head and neck cancer, benign prostate hypertrophy, or chronic obstructive pulmonary disease [16]. Poor illness perception can be explained by the lack of social support, underlying the need to measure the QoL of patients with VS following a conservative strategy and to provide psychological support.

The PANQOL scale is a specific QoL scale and requires a French version

Created by Shaffer et al., the PANQOL scale is a more specific QoL scale on symptoms experienced by VS patients [8]. Recently validated in Dutch language by Van Leeuwen et al., we used a French translated version in our study [9]. We decided to keep the initial 7-dimensions design proposed by Shaffer et al. and we obtained an acceptable reliability for four dimensions: Anxiety ($\alpha = 0.72$), Balance ($\alpha = 0.90$), Energy ($\alpha = 0.89$) and Hearing ($\alpha = 0.68$) [8]. Face dimension was unacceptable ($\alpha = 0.46$) probably because of a different interpretation of "face expression" in French language (question 10). The poor reliability obtained for General Health dimension ($\alpha = 0.25$) can be explained by the fact that there are only 2 questions that compose it. The pain dimension consists of only one question and internal consistency measured using Cronbach's alpha was not applicable; that is also a drawback of the PANQOL.

Despite the differences in internal consistency, our results are comparable to the North American and Dutch scores as shown in Figure 1. Van Leeuwen et al. obtained a significant difference in the Hearing dimension probably because they changed the initial 7-dimensions structure, as noted by them [9].

We again found a significant relationship between dizziness and a worse QoL in two dimensions of the PANQOL scale. The consequences of dizziness on QoL have already been explored by Shaffer et al. and Van Leeuwen et al. using the PANQOL scale [28 29]. Thus, conservative management of VS would not be appropriate for dizzy patients.

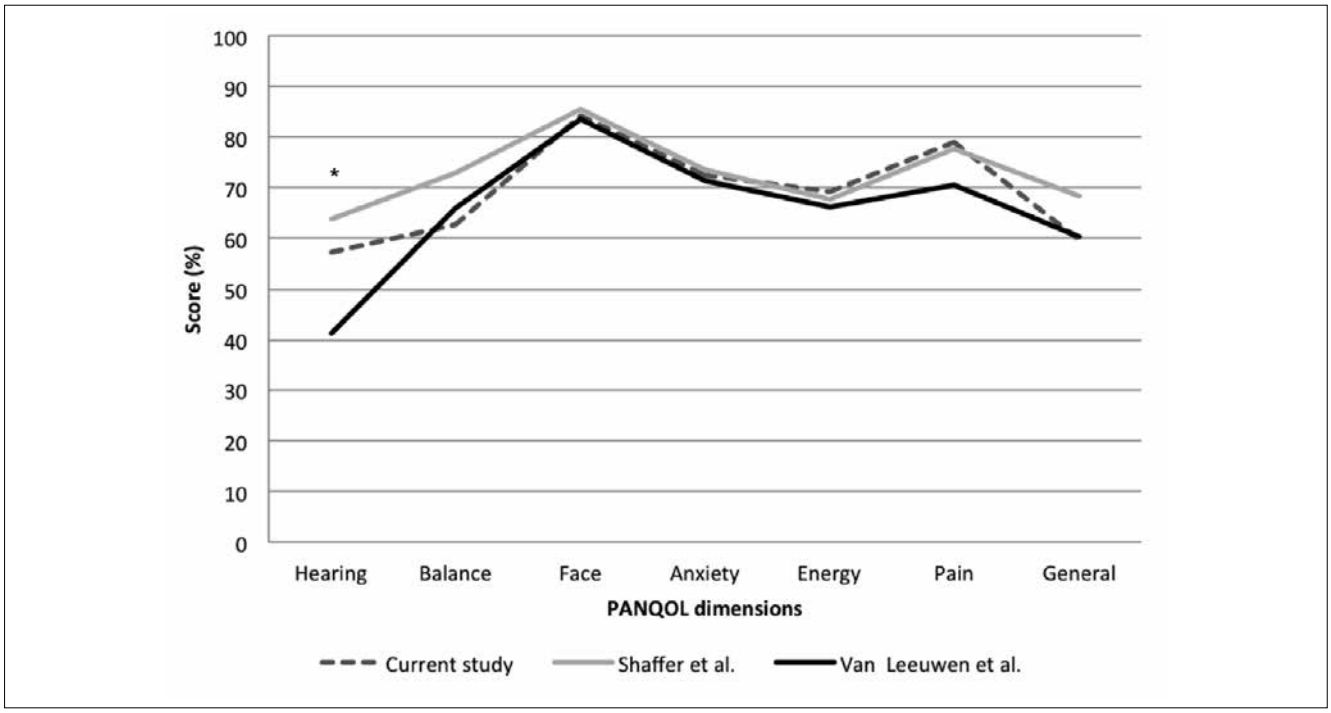

Fig. 1. Comparison of PANQOL scores in current and previous studies.

Some recent studies have reported no difference in QoL between invasive and conservative treatments after long-term follow-up. According to Robinett et al., there was no difference in QoL scores between microsurgery, stereotactic radiosurgery and observation by serial imaging after 5 years of follow-up, whereas radiosurgery was associated with significantly better QoL from 0 to 5 years [30]. The multicentric study of Carlson et al. found very small differences in long-term QoL between management groups using non-specific (SF-36, Glasgow Benefit Inventory) and specific (PANQOL) scales [31]. A better total PANQOL score and higher PANQOL subdomain scores (facial, balance and pain) were observed in patients with stereotactic radiosurgery or observation management in comparison with microsurgery. QoL might be deteriorated by a diagnosis of VS rather than its treatment. These results underlined the benefit of conservative treatment on VS. Invasive treatments should be reserved for fast-growing or symptomatic tumours.

Limitations and perspectives

We conducted a retrospective study to initiate the validation of the PANQOL scale in French language. Our results are consistent with the literature about tumour growth, but we failed to find any predictive factors of tumour growth probably because of the low power of our study. We are conscious of possible bias because of our population (recruitment bias) and the retrospective nature of our questionnaires. Concerning the PANQOL scale in French Language, our results are encouraging despite certain weaknesses in internal consistency. Furthermore, we did not compare the PANQOL scores to the SF-36 scores as Shaffer et al. and Van Leeuwen et al. did. This is why further studies must be applied to validate the French version of the PANQOL scale [8 9].

The study is divided in two different topics, the natural history of tumour growth and QoL of patients, but this investigation assessed correlations between tumour growth and QoL scores, which justified the decision to join these two aspects in the same study. In a population with a short mean follow up, difference in sizes and locations of tumours represented a bias in our study. In fact, the retrospective nature over a long period of data collection suffers recording and recollection bias amongst many other limitations of these types of study.

Conclusions

Nowadays, conservative management of VS seems to be dependent on QoL. QoL is significantly deteriorated by dizziness, suggesting the benefit of vestibular rehabilitation and non-conservative treatments in patient presenting incapacitating dizziness or vertigo. Finally, this first PANQOL in French language is a validated measure of QoL that needs to be confirmed by further explorations.

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Appendix 1. The French version of the Penn Acoustic Neuroma Quality-Of-Life scale (PANQOL-FR)

	Pas du tout d'accord	Pas d'accord	Indifférent	D'accord	Tout à fait d'accord
1. Ma surdité a affecté mes relations personnelles.	1	2	3	4	5
2. J'ai des difficultés à suivre une conversation à cause de ma surdité.	1	2	3	4	5
3. J'ai des difficultés de concentration à cause de sifflements, de bourdonnements, ou d'autres bruits dans mes oreilles.	1	2	3	4	5
4. J'ai des difficultés sérieuses à cause de mon instabilité.	1	2	3	4	5
5. Je me sens instable ou déséquilibré.	1	2	3	4	5
6. Je me sens tourner ou tomber quand je me lève ou quand je marche.	1	2	3	4	5
7. J'ai des difficultés à changer de direction quand je marche à cause de mon instabilité.	1	2	3	4	5
8. J'ai des difficultés à me déplacer dans le noir.	1	2	3	4	5
9. A cause de mes problèmes d'équilibre, j'ai peur que l'on me croit drogué ou saoul.	1	2	3	4	5
10. Je me comporte différemment avec les gens à cause de mes problèmes d'expression faciale.	1	2	3	4	5
11. Je ressens une gène, des démangeaisons ou un larmoiement à l'un de mes yeux.	1	2	3	4	5
12. J'ai du mal à parler car mon visage est déformé.	1	2	3	4	5
13. Le diagnostic de neurinome de l'acoustique a modifié mes activités quotidiennes.	1	2	3	4	5
14. Je ressens des maux de tête du coté de mon neurinome de l'acoustique.	1	2	3	4	5
15. Je ressens un sentiment d'inquiétude comme si quelque chose de grave allait arriver.	1	2	3	4	5
16. Je suis angoissé.	1	2	3	4	5
17. J'ai l'impression de vivre au ralenti.	1	2	3	4	5
18. J'ai le sentiment d'avoir l'estomac noué.	1	2	3	4	5
19. J'ai des attaques de panique.	1	2	3	4	5
20. Je me sens isolé à cause de mon diagnostic de neurinome de l'acoustique.	1	2	3	4	5
21. J'ai du mal à rester concentré sur une tâche (lire le journal, regarder la télévision).	1	2	3	4	5
22. Je suis devenu plus impatient.	1	2	3	4	5
23. Je me sens épuisé.	1	2	3	4	5
24. J'ai des pertes de mémoires.	1	2	3	4	5
25. Ma santé est excellente.	1	2	3	4	5
26. Je m'attends à ce que ma santé se détériore dans l'année à venir.	1	2	3	4	5

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Vestibology

Italian survey on benign paroxysmal positional vertigo

Survey italiana sulla vertigine parossistica posizionale

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SUMMARY

Benign paroxysmal positional vertigo (BPPV) is the most common type of peripheral vertigo. BPPV often relapses after the first episode, with a recurrence rate between 15% and 50%. To date both the aetiopathogenetic processes that lead to otoconia detachment and the factors that make BPPV a relapsing disease are still unclear, but recent epidemiological studies have shown a possible association with cardiovascular risk factors. The aim of the present study (Sesto Senso Survey) was to evaluate in the Italian population through an observational survey, the main demographic and clinical characteristics of patients with BPPV (first episode or recurrent) with particular focus on the potential cardiovascular risk factors. The survey was conducted in 158 vestibology centres across Italy on 2,682 patients (mean age 59.3 ± 15.0 years; 39.1% males and 60.9% females) suffering from BPPV, from January 2013 to December 2014. The results showed a high prevalence of cardiovascular risk factors such as high blood pressure (55.8%), hypercholesterolaemia (38.6%) and diabetes (17.7%), as well as a family history of cardiovascular disease (49.4%). A high percentage of patients also had hearing loss (42.9%), tinnitus (41.2%), or both (26.8%). The presence of hypertension, dyslipidaemia and pre-existing cardiovascular comorbidities were significantly related to recurrent BPPV episodes (OR range between 1.84 and 2.31). In addition, the association with diabetes and thyroid/autoimmune disease (OR range between 1.73 and 1.89) was relevant. The survey results confirm the significant association between cardiovascular comorbidities and recurrent BPPV and identify them as a potential important risk factor for recurrence of BPPV in the Italian population, paving the way for the evaluation of new therapeutic strategies in the treatment of this disease.

KEY WORDS: Benign paroxysmal positional vertigo • Risk factors • Cardiovascular diseases • Therapy

RIASSUNTO

La vertigine parossistica posizionale benigna (VPPB) è il tipo più comune di vertigine periferica. Frequentemente dopo il primo episodio la VPPB presenta recidive, con un tasso di ricorrenza tra il 15% ed il 50%. Ad oggi non vi è chiarezza sui processi eziopatogenetici che portano al distacco degli otoconi né su quali siano i fattori che rendono la VPPB una patologia recidivante, ma recenti studi epidemiologici hanno evidenziato una possibile associazione con fattori di rischio cardiovascolari. Lo scopo del presente studio (Sesto Senso Survey) è stato quello di valutare nella popolazione italiana, attraverso un'indagine osservazionale, le principali caratteristiche demografiche e cliniche dei pazienti con VPPB (primo episodio o ricorrente), con particolare attenzione ai potenziali fattori di rischio cardiovascolare. L'indagine è stata condotta in 158 centri di Vestibologia in tutta Italia su 2.682 pazienti (età media 59,3 ± 15,0 anni; 39,1 maschi e 60,9% femmine) affetti da VPPB, da gennaio 2013 a dicembre 2014. I risultati hanno mostrato in questi pazienti l'alta prevalenza di fattori di rischio cardiovascolari come ipertensione arteriosa (55,8%), ipercolesterolemia (38,6%) e diabete (17,7%), oltre ad una elevata familiarità per malattie cardiovascolari (49,4%). In un'elevata percentuale di pazienti si è inoltre registrata la presenza di ipoacusia (42,9%), acufeni (41,2%) o entrambi (26,8%). Significativamente correlata agli episodi di recidiva di VPPB è risultata la presenza di ipertensione arteriosa, dislipidemia e comorbidità cardiovascolare accertata (range OR tra 1,84 e 2,31). Rilevanti anche le associazioni con diabete e patologie tiroidee e autoimmuni (range OR tra 1,73 e 1,89). I risultati dell'indagine confermano la significativa associazione tra comorbidità cardiovascolari e VPPB recidivanti e le identificano come importante potenziale fattore di rischio per le recidive di VPPB nella popolazione italiana, aprendo la strada alla valutazione di nuove strategie terapeutiche nel trattamento di questa patologia.

PAROLE CHIAVE: *Vertigine parossistica posizionale benigna • Fattori di rischio • Patologie cardiovascolari • Terapia*

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Introduction

Benign paroxysmal positional vertigo (BPPV) is a clinical syndrome characterised by brief recurrent episodes of vertigo, triggered by changes in head position with respect to gravity and due to abnormal stimulation of the cupula of one of the three semicircular canals, most frequently the posterior one. The excitatory response of the cupula is generated by otoliths that detach from the macula of the utricle and move into the lumen of the semicircular canal in response to movements of the head; otoliths then reach the cupula that is stimulated abnormally by the small crystals, thus causing vertigo and nystagmus. Otoliths, which have been observed during surgery, may in some cases adhere to the cupula, generating a form of BPPV called cupulolithiasis [1 2]. The characteristic signs of BPPV are evoked when the subject's head is positioned so that the plane of the semicircular canal is aligned with gravity, generating nystagmus and vertigo. The duration, frequency and intensity of symptoms can vary. Autonomic manifestations (nausea, vomiting) or a persistent residual dizziness can be also present [1 2].

BPPV is the most common type of peripheral vertigo, with a reported prevalence of 11 to 64 cases per 100,000 persons, with a peak in the 50-70 age group; a higher prevalence is reported among women [1 3].

BPPV often relapses after the first episode, with a recurrence rate of between 15% and 50%, and the episode usually reoccurs within a few months [1 4].

To date both the aetiopathogenetic processes that lead to otoconia detachment and the factors that make BPPV a recurrent disease are unclear. In recent years, various epidemiological studies have analysed family history data in order to highlight any comorbidities that might be related to recurrences of BPPV [3-6]. Between 2007 and 2009, the Revert international registry collected data from over 4000 consecutive cases of vertigo observed in 618 vestibology centres in 13 countries around the world [7]. This and other studies demonstrated an association between recurrent BPPV and arterial hypertension (present in 52% of cases), hyperlipidaemia (up to 55% of cases), thyroid dysfunction (up to 21.3% of cases) and a significant prevalence of diabetes in patients with BPPV compared with the general population [4 6 8]. In a recent observational study, hypertension and diabetes were shown to be significantly related to risk of recurrent BPPV, with increased risk if both comorbidities were present at the same time [5]. The Revert registry showed that 46.3% of BPPV subjects had cardio-vascular comorbidities, and 17.2% hormonal dysfunctions [7]. This is consistent with the hypothesis that both arterial hypertension and hyperlipidaemia can cause vascular damage in the inner ear. Furthermore, it is known that BPPV may follow an ischaemic event around the anterior vestibular artery which would facilitate otoconia detachment from the utricle. Additionally, vertebrobasilar ischaemia has been suggested as a predisposing factor for BPPV and some data sustain a correlation between BPPV and stroke [4]. A recent retrospective nationwide population study in Taiwan examined data from the National Health Research Institute (NHRI) to assess cerebrovascular risk in patients with BPPV compared with a control group. Over a period of 9 years, the risk of stroke in BPPV subjects was 1.4-fold higher than the risk in subjects without BPPV ($p = 0.001$) [9].

The aim of the present study was to evaluate in the Italian population, through an observational survey, the main demographic and clinical characteristics of patients with BPPV (first episode or recurrent) with particular focus on potential cardiovascular risk factors.

Materials and methods

Our investigation is a multicentric observational study. We collected patient history and diagnostic and clinical assessments on 2,682 patients who had referred to 158 Italian vestibology out-patient clinics belonging to the "Sesto Senso Study Group" from January 2013 to December 2014. The inclusion criterion was a diagnosis of BPPV, either initial episode or recurrence. We considered recurrent BPPV the new clinical manifestation of vertigo signs and symptoms after the resolution of the previous episode, diagnosed according to the standard practice of each centre.

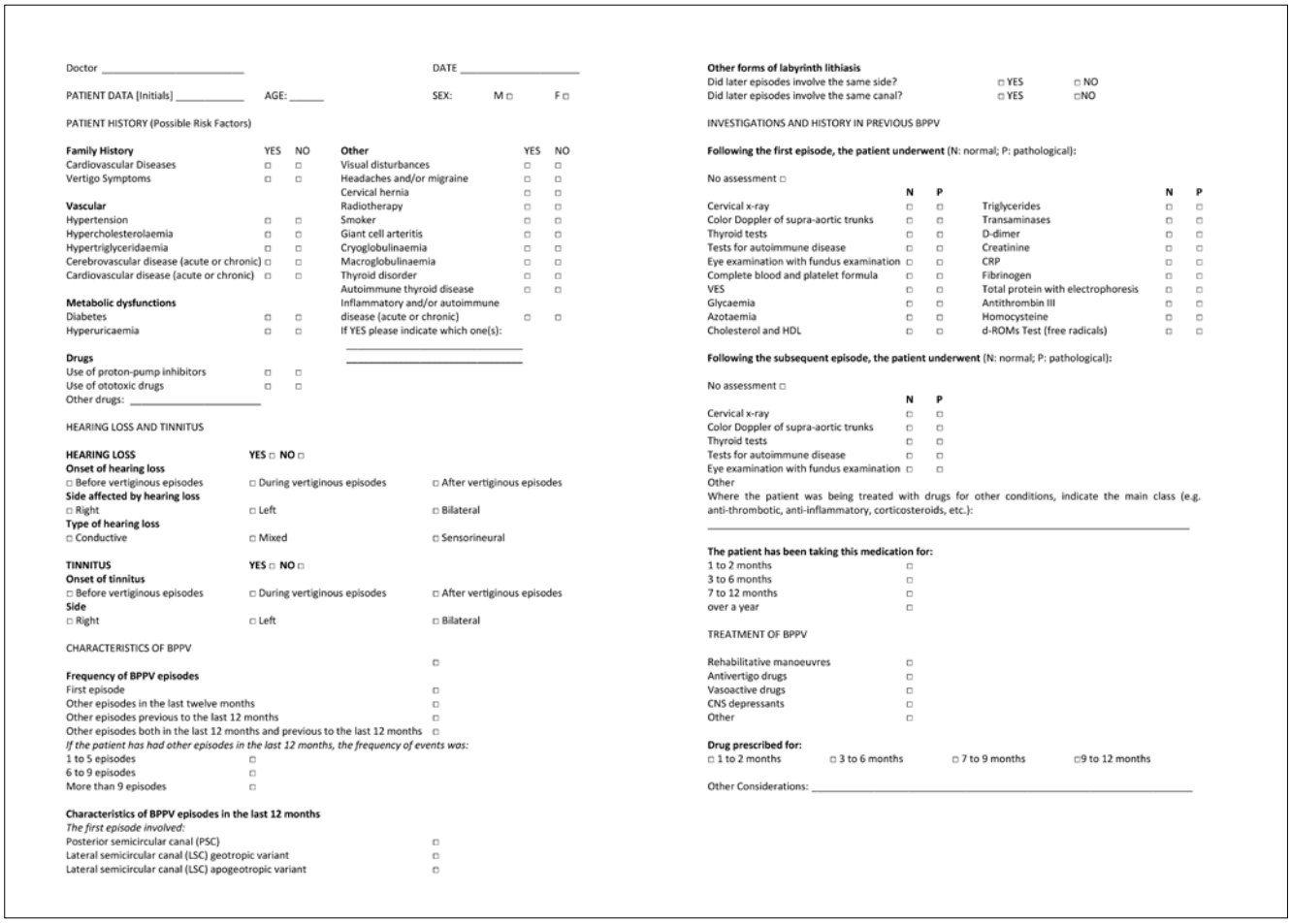
The data were registered using a form divided into four sections (Fig. 1):

1. Patient history (possible risk factors): family history of vertigo and cardiovascular disease, vascular and metabolic risk factors (hypertension, hypercholesterolaemia, hypertriglyceridaemia, acute or chronic cerebrovascular disease, acute or chronic cardiovascular disease, diabetes, hyperuricaemia), use of drugs and/or other comorbidities.
2. Hearing loss and tinnitus: reported audiological symptoms associated with episodes of BPPV.
3. Characteristics of BPPV, first episode or recurrence: number and frequency of episodes, canal involved.
4. Treatment of first BPPV episode and any subsequent episodes: description of the treatment used; in the event of pharmacological treatment, duration of therapy.

The demographic and clinical data were summarised in frequency tables or central tendency and dispersion tables, using the most suitable indicators for the variables (mean, standard deviation).

The discrete data were summarised as absolute frequencies and relative frequency percentages. Missing values were not considered for calculation of the relative frequency percentages.

The analysis of the association between recurrence and possible risk factors was performed through the χ^2 test and the odds ratios (OR) with 95% confidence intervals.



Doctor _____ DATE _____

PATIENT DATA [Initials] _____ AGE: _____ SEX: M □ F □

PATIENT HISTORY (Possible Risk Factors)

Family History	YES	NO	Other	YES	NO
Cardiovascular Diseases	□	□	Visual disturbances	□	□
Vertigo Symptoms	□	□	Headaches and/or migraine	□	□
			Cervical hernia	□	□
Vascular			Radiotherapy	□	□
Hypertension	□	□	Smoker	□	□
Hypercholesterolaemia	□	□	Giant cell arteritis	□	□
Hypertriglyceridaemia	□	□	Cryoglobulinaemia	□	□
Cerebrovascular disease (acute or chronic)	□	□	Macroglobulinaemia	□	□
Cardiovascular disease (acute or chronic)	□	□	Thyroid disorder	□	□
			Autoimmune thyroid disease	□	□
Metabolic dysfunctions			Inflammatory and/or autoimmune		
Diabetes	□	□	disease (acute or chronic)	□	□
Hyperuricaemia	□	□	If YES please indicate which one(s):		
			_____		
Drugs			_____		
Use of proton-pump inhibitors	□	□			
Use of ototoxic drugs	□	□			
Other drugs: _____					

HEARING LOSS AND TINNITUS

HEARING LOSS **YES □ NO □**

Onset of hearing loss
□ Before vertiginous episodes □ During vertiginous episodes □ After vertiginous episodes

Side affected by hearing loss
□ Right □ Left □ Bilateral

Type of hearing loss
□ Conductive □ Mixed □ Sensorineural

TINNITUS **YES □ NO □**

Onset of tinnitus
□ Before vertiginous episodes □ During vertiginous episodes □ After vertiginous episodes

Side
□ Right □ Left □ Bilateral

CHARACTERISTICS OF BPPV

□

Frequency of BPPV episodes
First episode □
Other episodes in the last twelve months □
Other episodes previous to the last 12 months □
Other episodes both in the last 12 months and previous to the last 12 months □
If the patient has had other episodes in the last 12 months, the frequency of events was:
1 to 5 episodes □
6 to 9 episodes □
More than 9 episodes □

Characteristics of BPPV episodes in the last 12 months
The first episode involved:
Posterior semicircular canal (PSC) □
Lateral semicircular canal (LSC) geotropic variant □
Lateral semicircular canal (LSC) apogeotropic variant □

Other forms of labyrinth lithiasis
Did later episodes involve the same side? □ YES □ NO
Did later episodes involve the same canal? □ YES □NO

INVESTIGATIONS AND HISTORY IN PREVIOUS BPPV

Following the first episode, the patient underwent (N: normal; P: pathological):

No assessment □

	N	P		N	P
Cervical x-ray	□	□	Triglycerides	□	□
Color Doppler of supra-aortic trunks	□	□	Transaminases	□	□
Thyroid tests	□	□	D-dimer	□	□
Tests for autoimmune disease	□	□	Creatinine	□	□
Eye examination with fundus examination	□	□	CRP	□	□
Complete blood and platelet formula	□	□	Fibrinogen	□	□
VES	□	□	Total protein with electrophoresis	□	□
Glycaemia	□	□	Antithrombin III	□	□
Azotaemia	□	□	Homocysteine	□	□
Cholesterol and HDL	□	□	d-ROMs Test (free radicals)	□	□

Following the subsequent episode, the patient underwent (N: normal; P: pathological):

No assessment □

	N	P
Cervical x-ray	□	□
Color Doppler of supra-aortic trunks	□	□
Thyroid tests	□	□
Tests for autoimmune disease	□	□
Eye examination with fundus examination	□	□

Other
Where the patient was being treated with drugs for other conditions, indicate the main class (e.g. anti-thrombotic, anti-inflammatory, corticosteroids, etc.):
_____

The patient has been taking this medication for:
1 to 2 months □
3 to 6 months □
7 to 12 months □
over a year □

TREATMENT OF BPPV

Rehabilitative manoeuvres □
Antivertigo drugs □
Vasoactive drugs □
CNS depressants □
Other □

Drug prescribed for:
□ 1 to 2 months □ 3 to 6 months □ 7 to 9 months □9 to 12 months

Other Considerations: _____

Fig. 1. Data collection form.

Statistical analysis was performed using SPSS Statistical Package, ver. 16.0.
In the event of missing data, no replacement approach was applied.

Results

Demographic data

A total of 2,682 valid forms were collected for statistical processing (Table I).
Most patients were women (60.9%). The mean age at diagnosis was 59.3 years (SD ± 15.0), with a percentage of over 65 of 38.3%. The 60-69 age group was the most frequent (26.6%), while only 0.2% were under 18 years of age.

Medical history and comorbidities

The possible risk factors are shown in Table II. 55.8% of patients had high blood pressure and nearly half (49.4%) had a family history of cardiovascular disease. Hypercholesterolaemia and hypertriglyceridaemia were found, respectively, in 38.6% and 21.1% of patients, and diabetes in 17.7%. At anamnesis, 12.3% of the sample reported a previous diagnosis of cardiovascular disease and 12.6% a cerebrovascular disease. The frequency of thyroid pa-

Table I. Demographic data.

Patients	**N = 2,682**
Gender (n = 2,579) *	**n (%)**
Males	1008 (39.1%)
Females	1571 (60.9%)
Age (n = 2621)†	**n (%)**
Mean (± SD)	59.3 ± 15.0
Over 65	1004 (38.3%)
Age groups	
< 18	6 (0.2%)
18-29	84 (3.2%)
30-39	204 (7.8%)
40-49	418 (15.9%)
50-59	486 (18.5%)
60-69	698 (26.6%)
70-79	535 (20.4%)
≥ 80	190 (7.2%)

**103 missing data on gender.*
† 61 missing data on age.

Table II. Medical history and possible risk factors.

Family history	n / N (%)
Cardiovascular diseases	1253 / 2538 (49.4%)
Vertigo symptoms	401 / 2318 (17.3%)
Risk factors and vascular disorders	
Hypertension	1416 / 2537 (55.8%)
Hypercholesterolaemia	917 / 2377 (38.6%)
Hypertriglyceridaemia	477 / 2266 (21.1%)
Cerebrovascular disease (acute or chronic)	277 / 2196 (12.6%)
Cardiovascular disease	268 / 2185 (12.3%)
Metabolic disorders	
Diabetes	419 / 2363 (17.7%)
Hyperuricaemia	72 / 2193 (3.3%)
Drugs	
Use of proton-pump inhibitors (PPI)	638 / 2279 (28.0%)
Use of ototoxic drugs	193 / 2122 (9.1%)
Other	
Headaches and/or migraine	668 / 2202 (30.3%)
Smoker	665 / 2216 (30.0%)
Visual disturbances	473 / 2163 (22.0%)
Cervical hernia	311 / 2111 (14.7%)
Thyroid dysfunction	298 / 2102 (14.2%)
Autoimmune disease	100 / 2024 (4.9%)
Inflammatory and/or autoimmune disease (acute or chronic)	79 / 1958 (4.0%)
Radiotherapy	71 / 2066 (3.4%)
Giant cell arteritis	37 / 2046 (1.8%)
Macroglobulinaemia	19 / 2022 (0.9%)
Cryoglobulinaemia	8 / 2031 (0.4%)
HEARING LOSS	**1131 / 2637 (42.9%)**
Onset	
Before episode of BPPV	811 / 1010 (80.3%)
During episode of BPPV	115 / 1010 (11.4%)
After episode of BPPV	81 / 1010 (8.0%)
Side	
Right side	121 / 1020 (11.9%)
Left side	107 / 1020 (10.5%)
Bilateral	792 / 1020 (77.6%)
Type	
Conductive	24 / 929 (2.6%)
Mixed	112 / 929 (12.1%)
Sensorineural	793 / 929 (85.4%)
TINNITUS	**1027 / 2494 (41.2%)**
Onset	
Before episode of BPPV	631 / 902 (69.9%)
During episode of BPPV	156 / 902(17.3%)
After episode of BPPV	115 / 902(12.8%)
Side	
Right side	221 / 848 (26.1%)
Left side	184 / 848 (21.7%)
Bilateral	443 / 848 (52.2%)
HEARING LOSS and TINNITUS *	**719 (26.8%)**

** We considered all patients (n=2682), counting those who answered "Yes" to "Hearing loss" and "Tinnitus".*

thology was 14.2%; 28% of patients used proton-pump inhibitors and 30% were smokers.

Hearing loss and tinnitus

In most cases, BPPV was associated with audiological symptoms (Table II). 42.9% of patients presented hearing loss, 80.3% of whom reported onset before the episode of BPPV and 85.4% of cases were of a sensorineural nature. 41.2% of patients had tinnitus, 69.9% of whom reported onset before the episode of BPPV and in 52.2% of cases this was bilateral. 26.8% of the sample presented hearing loss and tinnitus simultaneously. The patients who had hearing loss were older ($p < 0.001$). In particular, the average age of the patients with hearing loss (n = 1131) was of 66.4 years (SD 12.4), while the average age of patients without hearing loss (n = 1506) was 53.8 years (SD 14.4).

Characteristics of BPPV

The clinical features of BPPV episodes are shown in Table III. A near-uniform distribution was recorded between the first episode of BPPV (47.5%) and recurrent BPPV (52.5%). In terms of the frequency of recurring episodes, 1-5 episodes per year was the most commonly reported range (84.3%), while 15.7% reported 6 or more episodes per year. The canal most commonly involved in the first episode of BPPV was the posterior semicircular canal (57.4%), and most relapses involved the same canal (49.2%).

Treatment of vertigo

The treatment of BPPV, reported in Table IV, is based on rehabilitative manoeuvres (85.9%), followed by vasoactive drugs (35.9%). Use of antivertigo drugs was found in roughly one-third of the total sample (32.7%). Only in 4.4% of cases were central nervous system (CNS) depressants used.

In most cases, medical treatment lasted between 1 and 2 months (64.7%), while in about one-third of patients (30%) it was 3-6 months and only in 5.3% of cases did treatment continue for over 6 months.

Association between recurrence and comorbidities

In addition to the descriptive research, statistical processing of the data was performed in order to analyse the association between recurrent BPPV and possible risk factors (Table V, Fig. 2). The following significant correlations were found: family history of vertigo associated with cardiovascular disease (OR = 1.5, $p < 0.001$ and OR = 1.46, $p < 0.005$), hypertension (OR = 2.05, $p < 0.001$), hypercholesterolaemia (OR = 1.84, $p < 0.001$), hypertriglyceridaemia (OR = 2.11, $p < 0.001$), cerebrovascular disease (OR = 1.88, $p < 0.001$) and cardiovascular disease (OR = 2.31, $p < 0.001$). In addition, the association with diabetes was significant (OR = 1.73, $p < 0.001$). Finally, a correlation with the use of proton-pump inhibitors and

Table III. Characteristics of BPPV episodes.

	No. (%)
Patients - BPPV*	**2638**
First Episode	1252 (47.5%)
Recurrences	1386 (52.5%)
Other episodes in the last twelve months (< 12 months)	781 (56.4%)
Other episodes prior to the last 12 months (> 12 months)	326 (23.5%)
Other episodes both in the last 12 months and prior to the last 12 months	279 (20.1%)
Frequency of BPPV recurrence in the last 12 months†	
1 to 5 episodes	840 (84.3%)
6 to 9 episodes	101 (10.1%)
More than 9 episodes	56 (5.6%)
Canal affected in the first episode of BPPV‡	
The posterior semicircular canal (PSC)	1356 (57.4%)
The lateral semicircular canal (LSC) geotropic variant	681 (28.8%)
The lateral semicircular canal (LSC) apogeotropic variant	214 (9.1%)
Other forms of labyrinth lithiasis	112 (4.7%)
Canal affected in subsequent BPPV episodes	
Same canal	682 / 1386 (49.2%)

** 44 missing data for BPPV features.*
† 63 missing data for number of BPPV episodes in the 1060 (781 + 279) patients who reported episodes in the last twelve months.
‡ 319 missing data for canal affected in the first episode of BPPV

Table IV. Treatment of BPPV.

	No. (%)
Treatment used for BPPV episodes	
Rehabilitative manoeuvres	2305 (85.9%)
Antivertigo drugs	878 (32.7%)
Vasoactive drugs	964 (35.9%)
CNS depressants	118 (4.4%)
Total patients treated with drugs*	**1571 (58.6%)**
Duration of drug therapy†	
1 to 2 months	841 (64.7%)
3 to 6 months	390 (30.0%)
7 to 9 months	26 (2.0%)
9 to 12 months	43 (3.3%)

** 365 out of 1,571 (23.2%) patients used more than one drug.*
† Of the 1,571 patients with prescribed medications, 271 had missing data for "Duration of drug therapy."

with the use of ototoxic drugs was also found (OR 1.81, $p < 0.001$ and OR 1.96, $p < 0.001$, respectively).

Discussion

To date it is still unclear what is the aetiopathogenetic mechanism of BPPV and whether there are any other diseases related to the recurrence of BPPV. Recent epidemiological studies have shown a possible association with cardiovascular risk factors [3 5-7 9].

In the present observational study, cardiovascular history was assessed for 2,682 patients diagnosed with BPPV, both

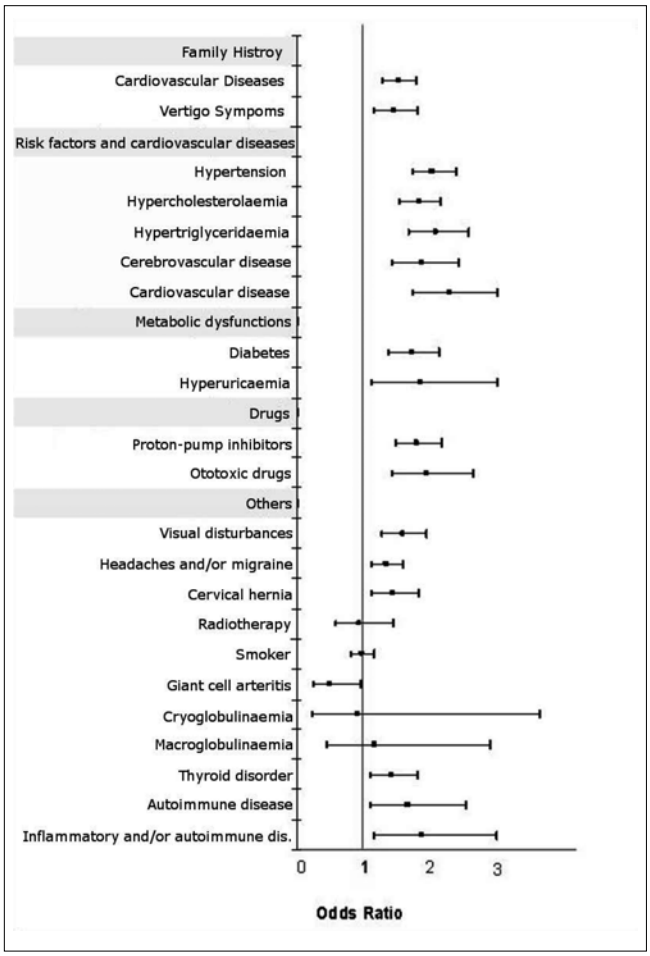


Fig. 2. Association between recurrent BPPV and comorbidities, medications, lifestyles: Crude OR and 95% Confidence Intervals.

Table V. Association between the first episode of BPPV or recurrent BPPV and comorbidities, drugs and lifestyles.

	BPPV				
	Patients at first episode	Patients with recurrences	Crude OR	CI 95%	p (*)
Family history					
Cardiovascular diseases	526 (44.1%)	715 (54.7%)	1.54	1.31-1.80	< 0.001
Dizziness symptoms	159 (14.6%)	239 (20.0%)	1.46	1.17-1.82	< 0.005
Risk factors and vascular disorders					
Hypertension	557 (46.9%)	844 (64.4%)	2.05	1.75-2.41	< 0.001
Hypercholesterolaemia	348 (31.2%)	558 (45.5%)	1.84	1.55-2.18	< 0.001
Hypertriglyceridaemia	157 (14.8%)	314 (26.8%)	2.11	1.70-2.61	< 0.001
Cerebrovascular disease (acute or chronic)	96 (9.2%)	178 (15.9%)	1.88	1.44-2.45	< 0.001
Cardiovascular disease	82 (7.9%)	183 (16.5%)	2.31	1.76-3.05	< 0.001
Metabolic disorders					
Diabetes	152 (13.6%)	261 (21.5%)	1.73	1.39-2.16	< 0.001
Hyperuricaemia	24 (2.3%)	47 (4.2%)	1.86	1.13-3.06	< 0.05
Drugs					
Use of proton-pump inhibitors (PPI)	234 (21.9%)	396 (33.7%)	1.81	1.50-2.19	< 0.001
Use of ototoxic drugs	63 (6.2%)	124 (11.5%)	1.96	1.43-2.69	< 0.001
Other					
Visual disturbances	180 (17.9%)	288 (25.6%)	1.59	1.29-1.96	< 0.001
Headaches and/or migraine	279 (27.0%)	377 (33.1%)	1.34	1.12-1.61	< 0.01
Cervical hernia	122 (12.4%)	187 (17.0%)	1.44	1.13-1.84	< 0.025
Radiotherapy	35 (3.6%)	36 (3.4%)	0.93	0.58-1.45	ns
Smoker	316 (30.3%)	338 (29.6%)	0.97	0.81-1.16	ns
Giant cell arteritis	24 (2.5%)	13 (1.2%)	0.49	0.25-0.97	< 0.05
Cryoglobulinaemia	4 (0.4%)	4 (0.4%)	0.92	0.23-3.69	ns
Macroglobulinaemia	8 (0.8%)	10 (1.0%)	1.17	0.45-2.94	ns
Thyroid disfunction	118 (11.9%)	174 (16.1%)	1.42	1.10-1.82	< 0.025
Autoimmune disease	35 (3.7%)	63 (6.0%)	1.68	1.10-2.57	< 0.05
Inflammatory and/or autoimmune disease (acute or chronic)	26 (2.8%)	52 (5.2%)	1.89	1.17-3.04	< 0.05

Crude Odds Ratio (OR) and 95% Confidence Intervals (95%) and their p-values.
**χ2 Test.*

initial episodes and recurrences, who had referred to 158 Italian vestibology out-patient clinics from January 2013 to December 2014. Most patients were over 40 years old (88.6%), with a prevalence of women (60.9%) and a BPPV recurrence rate of 52.5%, in line with data reported in literature [1 3]. With regards to the prevalence of recurrent BPPV, only the Ogun et al. survey conducted in the United States has until now registered a higher frequency (76.3%), but this, as reported by the authors, may be due to the survey procedures used which favoured selection of patients with recurrent BPPV [6].

Our survey showed a high prevalence of cardiovascular risk factors such as high blood pressure (55.8%), hypercholesterolaemia (38.6%) and diabetes (17.7%), as well as family history of cardiovascular disease (49.4%). A comparison of the relative frequencies of these risk factors in the study sample with the data available for the general population highlighted the higher prevalence of these parameters in patients with BPPV vs. the general population (Fig. 3) [10].

A high proportion of patients had hearing loss and/or tinnitus (up to 42.9%), a result consistent with Ogun et al. study in which 41.9% of subjects displayed hearing loss, suggesting that audiological symptoms in BPPV patients are potential markers of vascular pathophysiology in the inner ear that should be validated [11].

Analysis of correlations also suggests that cardiovascular risk factors expose the BPPV subject to a risk of relapse with OR values that sometimes are higher than 2. Specifically, the presence of arterial hypertension, dyslipidaemia and established cardiovascular comorbidities (OR range between 1.84 and 2.31) would seem to be significantly related to episodes of recurrent BPPV, and association with diabetes and thyroid/autoimmune disease (OR range between 1.42 and 1.89) would seem to be relevant.

These results support the hypothesis of a vascular role in

	Survey Data	General population data*
Family History Of Cardiovascular Diseases	49.4%	40%
Hypertension	55.8%	32%
Hypercholesterolaemia	38.6%	23%
Hypertriglyceridaemia	21.1%	24%
Diabetes	17.70%	8%

** From Guidetti G. La terapia della vertigine vascolare nella pratica ambulatoriale: esperienza multicentrica (VascVert Study). Otorinolaringol. 2005;55:237-46*

Fig. 3. Prevalence of vascular risk factors in the study sample and the general population.

the aetiopathogenesis of BPPV and its recurrence. Moreover, the link between inflammation and vascular pathophysiology of the inner ear and audio-vestibular disorders has already been pointed out [10-13]. As is known, the blood supply to the inner ear is a terminal circulation and given the lack of collateral circulation, any even partial occlusion of the AICA (anterior inferior cerebellar artery) or VBA (vertebrobasilar artery) can cause an ischaemic event in the inner ear [11]. Recently, patients with idiopathic sudden hearing loss were shown to have significantly lower flow-mediated dilation of the brachial artery than controls (5.6 ± 1.6 vs. 7.7 ± 3.7; $p < 0.01$) [14], significantly lower levels ($p = 0.018$) of endothelial progenitor cells [15] and increased plasma levels of adhesion molecules, which is an early sign of endothelial dysfunction [16].

The data have also suggested an unexpected correlation between the recurrence of BPPV and use of proton-pump inhibitors, and confirmed a possible correlation between recurrence of BPPV and the use of ototoxic drugs. These data stimulate further specific studies.

Finally, it is interesting to note that in our sample more than 80% of patients reported hearing loss or tinnitus prior to the episode of BPPV. At the same time, it should also be underlined the fact that patients with hearing loss were significantly older. For these reasons, and given the importance of the issue, to evaluate the possible correlation between hearing loss and BPPV it would be necessary in the future perform a specific study, which evaluates in detail the various characteristics of the hearing loss in BPPV for classes of age and comparing such data with an adequate sample of subjects not suffering from BPPV.

The survey results also suggests some considerations regarding therapeutic strategies adopted in the treatment of BPPV. Standard treatment generally involves rehabilitation therapy based on liberatory or repositioning manoeuvres that are effective in resolving symptoms in up to 90% of cases within 24 hours [17]. However, the number of manoeuvres needed to achieve resolution can vary and the incidence of residual dizziness after treatment is high (60%) and long-term (13-16 days), thus complicating complete resolution of symptoms [18 19]. The use of vasoactive drugs could therefore be of help, especially to contrast any pathogenetic mechanism with a microcirculatory component. Specifically, treatment could include not only drugs to reduce the impact of known risk factors (antihypertensives, statins, antidiabetics) but also more specific vascular drugs to counteract "causal" damage generated on the endothelial wall in the inner ear, such as glycosaminoglycans (GAGs), which exert anti-inflammatory and antithrombotic actions on the endothelial wall [10 20-24]. In this regard, our study showed that antivertigo drugs were prescribed in almost 33% of cases and vasoactive drugs in about 36%, thus demonstrating that specialists are aware of vascular risk factors.

Our study has some limitations. For example, many parameters have not been evaluated, including brain MRI, post-traumatic vertigo and psychiatric disorders. Furthermore, the study did not have an appropriate control of the population without BPPV. Finally, the observational nature of the study, obviously, did not allow definitive answers about the investigated correlations, which require appropriate studies, but that nonetheless gave, albeit partial, a significant picture of the Italian real-life situation on BPPV helping to increase knowledge about the comorbidity in BPPV also investigated recently in other studies [25-27].

Conclusions

In conclusion, the present study investigated the demographic and clinical characteristics of 2,682 Italian patients with BPPV. In particular, the results have highlighted a population of patients with 60 years on average, a prevalence of women (60.9%) and a high BPPV recurrence rate (52.5%). Finally, the study seems to confirm the prevalence of cardiovascular comorbidities in patients suffering from BPPV and identify them as potential important risk factors for recurrent BPPV in the Italian population, paving the way for the evaluation of new therapeutic strategies.

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VESTIBOLOGY

Sensitivity and specificity of vestibular bed-side examination in detecting VIII cranial nerve schwannoma with sensorineural sudden unilateral hearing loss as presenting symptom

Sensibilità e specificità della vestibular bed-side examination nell'individuare lo schwannoma dell'VIII nervo cranico con ipoacusia improvvisa come sintomo di esordio

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SUMMARY

The objectives of this study were to identify signs of vestibular nerve suffering through a bedside vestibular examination protocol in case of sudden sensorineural unilateral hearing loss without spontaneous signs of vestibular impairment and to propose a bed-side vestibular examination based protocol for the focused execution of gadolinium-enhanced magnetic resonance imaging (MRI) only if a vestibular schwannoma is suspected. 96 patients, 52 men, 44 women, mean age 57.73 +/- 12.85 years, suffering from sudden sensorineural unilateral hearing loss, which presented neither vertigo nor spontaneous nystagmus, were enrolled. Pure tone audiometry, tympanometry, measurement of acoustic reflexes and Anderson test to detect adaptation, bedside vestibular examination through head shaking test, vibration test, head impulse test, hyperventilation test and detection of nystagmus in supine and lateral decubitus to search for signs of vestibular impairment were performed. Patients with signs of vestibular impairment and pure tone audiometry threshold at high frequencies better than 70 dB nHL were subjected to auditory brainstem responses. Gadolinium enhanced MRI centred on internal acoustic canals was carried out in all patients with sudden sensorineural unilateral hearing loss. Main outcome measures were signs of vestibular impairment at vestibular bedside examination and presence of vestibular schwannoma on MRI. Signs of vestibular impairment were detected in 22/96 cases (22.9%); a vestibular schwannoma was detected by MRI in 5/96 cases (5.2%), always when vestibular impairment was present. In case of sudden sensorineural unilateral hearing loss, vestibular bedside examination seems to be useful to restrict the suspicion of a vestibular schwannoma to cases with signs of vestibular impairment, reducing the number of MRI exams, with considerable economic savings.

KEY WORDS: Vestibular Schwannoma • Sudden Sensorineural Hearing Loss • Vestibular bed-side examination

RIASSUNTO

Gli obiettivi dello studio sono stati: identificare segni di sofferenza vestibolare attraverso un protocollo di "bed-side examination" in caso di ipoacusia improvvisa monolaterale senza segni clinici di sofferenza vestibolare; proporre i risultati della bed side examination vestibolare come criterio per l'esecuzione mirata della RMN per i canali acustici interni in caso di sospetto di neurinoma dell' VIII nervo cranico. Sono stati valutati 96 pazienti, 52 uomini e 44 donne, con ipoacusia improvvisa neurosensoriale monolaterale che non presentavano né vertigine né nistagmo spontaneo. Sono stati eseguiti: esame audiometrico tonale, esame impedenzometrico con test di Anderson per la ricerca di adattamento, Head Shaking Test, Test Vibratorio, Head Impulse Test, Test di iperventilazione, ricerca del nistagmo posizionale in posizione supina e nei decubiti laterali; l'ABR è stato eseguito nei pazienti con segni di sofferenza vestibolare se con soglia tonale ai toni acuti migliore di 70 dB nHL; tutti i pazienti con ipoacusia improvvisa hanno eseguito RMN con gadolinio per i canali acustici interni. Segni di sofferenza vestibolare sono stati identificati in 22/96 pazienti (22.9%) e la RMN ha evidenziato la presenza di schwannoma dell' VIII nervo cranico in 5/96 casi (5.2%), tutti con segni di sofferenza vestibolare evidenziati alla "vestibular bed-side examination". I nostri dati hanno evidenziato che gli schwannomi dell' VIII nervo cranico sono stati individuati solo nei casi di ipoacusia improvvisa monolaterale con segni di deficit vestibolare omolaterale. L'indicazione alla RMN con gadolinio può quindi essere limitata solo a questi casi, con evidente beneficio organizzativo ed economico.

PAROLE CHIAVE: *Schwannoma vestibolare • Ipoacusia improvvisa • Valutazione vestibolare "bed-side"*

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Introduction

Vestibular schwannoma (VS) represents about 80% of cerebellopontine angle tumours, 90% of intra-cranial schwannomas and 5-10% of all intra-cranial tumours. Its most common origin is from the superior branch of the vestibular nerve, but some studies on the temporal bone have identified its origin from the cochlear branch of the 8th cranial nerve in 24% of the cases [1].

The incidence of VS seems to be increasing, both because of improvements in diagnostic techniques and the presence of supposed favouring factors, such as electromagnetic pollution [2]; there is no sex predilection and the peak of incidence is between 50 and 60 years old; it usually occurs in isolated forms, as opposed to the multiple lesions often observed in neurofibromatosis type 2, which is caused by mutations in the NF2 tumour suppressor gene on chromosome 22.

The most common symptoms of VS are progressive unilateral sensorineural hearing loss, tinnitus and postural instability. Sudden sensorineural unilateral hearing loss (SSUHL) can be the presenting symptom in 2%-10% of the cases, whereas it occurs in 20-25% of cases during the natural history of the tumour [3-10]. Sudden hearing loss is defined as "a rapid onset, occurring over a 72-hour period, of a subjective sensation of hearing impairment in one or both ears. The most frequent used audiometric criterion is a decrease in hearing of ≥ 30 decibels (dB) affecting at least 3 consecutive frequencies" [11].

SSUHL seems to be more common in intracanalicular tumours [3 7] and in young patients [4]; its complete resolution is possible [12 13] so that even in the case of a recovered SSUHL, magnetic resonance imaging (MRI), which is the diagnostic gold standard for VS, is recommended.

It is reasonable to think that suffering of the superior vestibular nerve could cause clinical signs of vestibular impairment, recognisable through a vestibular bedside examination protocol.

The objectives were: 1) to identify signs of vestibular nerve suffering through a bedside vestibular examination protocol-head shaking test (HST), vibration test (VT), head impulse test (HIT), hyperventilation test (HVT) and detection of nystagmus in supine and lateral decubitus;

2) to propose a clinical protocol for the focused execution of gadolinium-enhanced MRI only if a VS is clinically suspected.

Materials and methods

From January 2013 to December 2015 we observed 96 cases (52 men, 44 women, mean age 57.73 ± 12.85 years) of apparently idiopathic SSUHL, that presented neither vertigo nor spontaneous nystagmus in the sitting position. In particular, we investigated in the absence of barotrauma, acute acoustic trauma or other trauma as causes of SSUHL. Seven individuals referred a previous diagnosis of benign paroxysmal positional vertigo. Pure tone audiometry, tympanometry, measurement of acoustic reflexes and Anderson test were performed in all patients. Diagnosis of SSUHL was based on the criterion exposed in the previously reported guidelines [11].

In SSHUL patients and in a homogeneous control group of 20 individuals (11 men, 9 women, mean age 56.75±14.53 years ($p = 0.76$)) with no medical history of audiological, vestibular or neurological diseases, we searched for signs of vestibular impairment under infra-red binocular videonystagmoscopy: head shaking induced nystagmus (HSIN), vibration induced nystagmus (VIN), hyperventilation induced nystagmus (HVIN), and positional nystagmus in both the supine position and lateral decubitus, and compensatory saccades evoked through HIT. Patients with one or more signs of vestibular impairment performed ABR, if the tonal threshold in the range 2000-4000 Hz was better than 70 dB nHL. Criteria of suspect for VS were considered: absence of waves in relation to the pure tone audiometry data; lengthening of I-III and I-V interpeaks and lengthening of wave V absolute latency. All patients affected by SSUHL underwent gadolinium-enhanced MRI centred on internal auditory canals.

Main outcome measures

We considered: the presence of signs of vestibular impairment and the presence of VS on MRI.

Statistical analysis

Fisher's exact test was performed to compare: a) diagnosis of VS by MRI with vestibular bedside examination results; b) data on vestibular impairment in the VS group: one sign vs. at least two signs of vestibular suffering and both groups with vestibular impairment vs. the group without vestibular impairment; c) vestibular bedside examination results of the SSUHL group vs. the control group. An unpaired t test was used to compare the mean

Table I. Results of vestibular bed-side examination in cases with at least two positive tests.

	HSIN	VIN	HVIN	HIT	Supine position nystagmus	Schwannoma (MRI)
Case 1	Paretic	Paretic	Absent	No saccades	Absent	No
Case 2	Paretic	Paretic	Paretic	No saccades	Paretic	12 mm
Case 3	Paretic	Excitatory	Paretic	No saccades	Absent	13 mm
Case 4	Absent	Paretic	Excitatory	No saccades	Absent	8 mm

HSIN: Head Shaking Induced Nystagmus; VIN: Vibration Induced Nystagmus; HVIN: Hyperventilation Induced Nystagmus; HIT: Head Impulse Test; paretic: nystagmus with fast phases directed toward the healthy side; excitatory: nystagmus with fast phases directed toward the affected side (hearing loss); MRI: Magnetic Nuclear Imaging

age of the SSUHL group with the control group. In both tests, a P value < 0.05 was considered significant.

Results

Audiometric tests. A flat configuration hearing loss was observed in 50/96 patients (pure tone average from 250 to 8000 Hz: 54.3 ± 10.24 dB; range: 45-94.5 dB); a sloping configuration in 28/96 patients (pure tone average from 250 to 8000 Hz: 38.5 ± 15.64 dB; range: 28.5-56.3 dB); a rising configuration in 10/96 patients (pure tone average from 250 to 8000 Hz: 33.5 ± 9.40 dB; range: 25.5-50.3 dB); a "U" shaped configuration- greatest hearing loss in the mid-frequency range- in 8/96 patients (pure tone average from 250 to 8000 Hz: 36.5 ± 12.65 dB; range: 30.5-55.3 dB). In all cases, the criterion for a decrease in hearing of ≥ 30 decibels (dB) affecting at least 3 consecutive frequencies was respected [11]. At least two signs of vestibular impairment were found in 4/96 patients (4.2%) (Table I). Only one sign of vestibular impairment was found in 18/96 patients (18.8%) (Table II). On the whole, vestibular impairment was observed in 22/96 patients (22.9%). In the control group, no signs of vestibular impairment were observed, with a significant difference vs. the SSUHL group (p = 0.02).

ABR was performed on 16/22 patients with vestibular impairment. In 2/5 of the cases in which MRI demonstrated a VS, we observed the lengthening of I-III and I-V interpeak latencies, which are the most specific signs of suspicion for VS; in three cases we observed the lengthening of Wave V absolute latency, which is a less specific sign of neural suffering [13]; in fact, it was the most frequent finding in the 11 cases that were MRI-negative for VS. In these cases, when evaluable, I-III and I-V inter-latencies were normal.

MRI revealed the presence of VS in 3/4 cases in the group with at least two signs of vestibular impairment (Table I) and in 2/18 cases in the group with only one sign of vestibular impairment. VS was never found in the 74 cases without signs of vestibular impairment. Incidence of VS in the population affected by SSUHL was 5.2% (5/96 patients). The differences were statistically significant: $p < 0.001$ for the group with at least two signs of vestibular impairment vs. the group without vestibular impairment; $p = 0.03$ for the group with one sign of vestibular impairment vs. the group with no sign of vestibular impairment; $p = 0.02$ for the group with at least two signs vs. the group with one sign of vestibular impairment. A flat configuration hearing loss (pure tone average 250-8000 Hz: 54 dB and 50 dB) was observed in two cases MRI positive for VS, in three cases a sloping configuration (pure tone average: 35.5 dB, 37.5 dB, 40.5 dB). No significant difference was noted for the pure tone average vs. the cases MRI negative for VS. The Anderson test was positive in 4/5 cases MRI positive for VS, but it was also positive in six cases that were MRI negative for VS (sensitivity = 80%; specificity = 64.7%). In relation to the detection of VS, vestibular bedside examination presented a sensitivity of 60%, a specificity of 98.8% and a positive predictive value of 75% in the group with at least 2 signs of vestibular impairment (4/96 cases);

Table II. Results of vestibular bed-side examination in cases with one positive test.

	HSIN	VIN	HVIN	HTT	Supine position nystagmus	Schwannoma (MRI)
Case 1	Absent	Absent	Excitatory	No saccades	Absent	6 mm
Case 2	Paretic	Absent	Absent	No saccades	Absent	No
Case 3	Absent	Paretic	Absent	No saccades	Absent	12 mm
Case 4	Absent	Paretic	Absent	No saccades	Absent	No
Case 5	Paretic	Absent	Absent	No saccades	Absent	No
Case 6	Absent	Paretic	Absent	No saccades	Absent	No
Case 7	Absent	Paretic	Absent	No saccades	Absent	No
Case 8	Absent	Absent	Absent	No saccades	Paretic	No
Case 9	Paretic	Absent	Absent	No saccades	Absent	No
Case 10	Paretic	Absent	Absent	No saccades	Absent	No
Case 11	Absent	Absent	Absent	No saccades	Paretic	No
Case 12	Absent	Paretic	Absent	No saccades	Absent	No
Case 13	Paretic	Absent	Absent	No saccades	Absent	No
Case 14	Absent	Paretic	Absent	No saccades	Absent	No
Case 15	Absent	Paretic	Absent	No saccades	Absent	No
Case 16	Absent	Paretic	Absent	No saccades	Absent	No
Case 17	Absent	Paretic	Absent	No saccades	Absent	No
Case 18	Paretic	Absent	Absent	No saccades	Absent	No

HSIN: Head Shaking Induced Nystagmus; VIN: Vibration Induced Nystagmus; HVIN: Hyperventilation Induced Nystagmus; HIT: Head Thrust Test; paretic: nystagmus with fast phases directed toward the healthy side; excitatory: nystagmus with fast phases directed toward the affected side (hearing loss); MRI: Magnetic Resonance Imaging

a sensitivity of 100%, a specificity of 81.3% and a positive predictive value of 22.7% % in the group with at least one sign of vestibular impairment (22/96 cases).

Discussion

Diagnosis of VS is sometimes "elusive" because its symptoms can be slowly progressive, especially unilateral hearing loss and postural instability. VS can be suspected through standard audiological and vestibular functionality examinations, but the diagnostic gold standard is gadolinium-enhanced MRI which must be performed in all cases with both clinical and functional suspicion.

In a low percentage of cases, SSUHL was identified as a possible presenting symptom of a VS [8 10]; however, since SSUHL can occur in a higher percentage of VS cases-up to 20% during the natural history of the tumour, an MRI of the internal auditory canals is recommended in cases of apparently idiopathic SSUHL [11]. Notwithstanding, since SSUHL is a revealing symptom of VS in only a few cases, most MRIs do not reveal the suspected disease, with an obvious waste of economic resources.

For this reason, it would be useful to develop a diagnostic protocol able to identify a suspect VS, with high sensitivity and specificity, especially when SSUHL is the presenting symptom.

Since the preferential origin of the VS is from the superior branch of the vestibular nerve, it makes sense to seek dynamic, static and metabolic signs of vestibular imbalance through a vestibular bedside examination that can be performed in less than 10 minutes. Teggi et al.[15] showed that intracanalicular length and intracanalicular diameter seem to be the main parameters that correlate with vestibular function and that also in case of small intracanalar VS a vestibular impairment is possible; Niu [16] observed caloric hyporeflexia in 50% patients with SSUHL without vertigo. Our data suggested vestibular impairment in 22/96 patients (22.9%). The vestibular bedside examination tests showed results in line with our previous studies [17]; VT presented the most frequent number of positive cases associated with VS (4/5 cases), even if the significance of the data is limited by the small number of VS cases it was related to. HIT did not show any positivity. This is not unexpected, because the occurrence of compensatory saccades to HIT is related to the presence of a serious vestibular hyporeflexia [4], which is not necessarily present in the small tumours that are the object of the present study (6-13 mm), as highlighted by MRI. Furthermore, HIT was performed in its clinical form; video-HIT could possibly improve its diagnostic sensitivity. A possible bias is that the positivity of vestibular tests could be related to a previous suffering of the system. The bias can be minimised by careful medical history. However, such a situation would lower the specificity and not the sensitivity of the vestibular bedside examination. In other words, we would have detected all the VS, carrying out most MRI.

VS, identified through gadolinium-based MRI of internal auditory canals, presented an incidence of 5.2%-5/96 cases, all in the group of 22 patients with one or more signs of vestibular impairment, whereas VS was not found in patients with no sign of vestibular impairment ($p < 0.0001$). The above percentage is in agreement with previous studies that identified SSUHL as a rare VS revealing symptom [4 7 8 10 13]. Nevertheless, we must again consider that our results are limited by the low number of VS identified, even if their number is consistent with the predictable one.

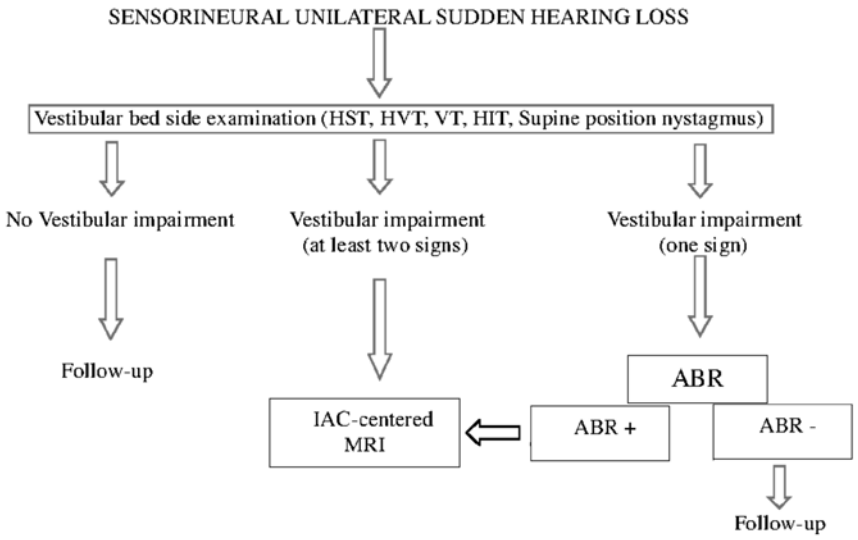

Fig. 1 Decision making flow-chart for sensorineural unilateral sudden hearing loss.

Conclusions

In case of unilateral sensorineural hearing loss it is mandatory to exclude VS as its cause. SSUHL is reported as the presenting symptom of VS in > 10% of the cases, but MRI is considered to be the gold standard test to exclude VS in case of SSUHL, too.

We propose to immediately perform MRI to detect a possible VS in case of SSUHL as presenting symptom only when a vestibular impairment is present; a cut-off value at two signs makes the protocol very specific (98.8%), but less sensitive (60%); nevertheless, a cut-off value at one sign decreases its specificity to 81.3%, whereas its sensitivity is increased to 100%. If a cut-off value at two signs is chosen, in cases with only one sign of vestibular impairment, to increase the sensitivity of our analysis, we recommend performing ABR before an MRI is carried out. In any case, even the decision to carry out MRI on all patients with at least one sign of vestibular asymmetry, would decrease significantly its number: according to our results, MRI would have been carried out only in 22/96 cases, with considerable economic savings. Audiometric and clinical follow-up will suggest MRI if new data eventually augment the suspect of the presence of VS.

In our opinion, for its simplicity of execution, sensitivity and specificity, vestibular bedside examination is indicated in all cases of apparently idiopathic SSUHL. A possible decisional flow-chart is represented in Figure 1.

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CASE SERIES AND REPORTS

Papillary squamous cell carcinoma of the palatine tonsil: a rare cancer of the head and neck

Carcinoma squamoso papillare della tonsilla palatina: un raro tumore della testa e del collo

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SUMMARY

Papillary squamous neoplasms of the upper respiratory tract are rare variants of squamous cell carcinomas. They are characterised by an exophytic, papillary growth and generally have favourable prognosis. The tumour has been described in the upper aerodigestive tract. In this context, most common sites of involvement are the larynx and hypopharynx, and rarely the oral cavity and oropharynx. The limited studies and small number of published cases of papillary squamous cell carcinoma of the palatine tonsil led us to make a complete analysis of this tumour by analysing the clinical, histological, radiological, virological and therapeutic aspects that are not always present in the literature. A case of papillary squamous cell carcinoma of the palatine tonsil is reported. The lesion (T2N0M0) was located into the left palatine tonsil that hung towards the oral cavity. Both HPV 16 DNA and E6/E7 mRNA were detected in the lesion. The clinicopathological profile of the neoplasm is presented and a comprehensive review of recent literature was made by analysing all aspects of interest of this neoplasm.

KEY WORDS: Squamous neoplasm • Human papillomavirus • Upper aerodigestive tract • Blot hybridization analysis

RIASSUNTO

Le neoplasie squamose papillari delle vie aeree digestive superiori sono una rara variante del carcinoma a cellule squamose. Sono caratterizzate da una crescita esofitica papillare e hanno una prognosi generalmente favorevole. Il tumore è già stato descritto a livello delle vie aeree digestive superiori. In tale contesto, le localizzazioni più frequenti sono la laringe e l'ipofaringe, mentre raramente sono interessati la cavità orale e l'ipofaringe. Gli studi limitati unitamente all'esiguo numero di casi pubblicati di carcinoma squamoso papillare a localizzazione tonsillare, ci hanno indotto a una completa analisi di questo tumore, analizzando gli aspetti clinici, istopatologici, radiologici, virologici e terapeutici, non sempre presenti in letteratura. Un case report di carcinoma squamoso papillare della tonsilla palatina è pertanto riportato. La lesione (T2N0M0), localizzata a livello della tonsilla palatina sinistra, si aggettava verso la cavità orale. HPV DNA 16 e mRNA E6/E7 erano rilevati nella lesione. Un profilo della neoplasia è pertanto presentato unitamente a una completa revisione della recente letteratura, analizzando tutti gli aspetti di interesse di tale neoplasia.

PAROLE CHIAVE: *Neoplasia squamosa • HPV • Vie aeree digestive superiori • Ibridizzazione blot*

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Introduction

Papillary squamous cell carcinoma (PSCC) is a variant of squamous cell carcinoma, recently identified and classified separately in the World Health Organization (WHO) classification [1]. It is characterised by an exophytic, papillary growth and has favourable prognosis [1].

PSCC occurs predominantly in males (male-female ratio of 2:1) and most patients are more than 50 years old [2-4].

The tumour has been described in the upper aerodigestive tract [3]. In this context, most common sites of involvement are the larynx and hypopharynx [1], and rarely the oral cavity and oropharynx [5]. Tonsil involvement, as in our case, is very uncommon, and only very few cases are reported in the literature [6 7].

Major predisposing factors of PSCC are smoking and alcohol abuse [1], and immunosuppression is believed to be a risk factor [8]. A subset of head and neck squamous cell carcinomas are caused by the human papillomavirus (HPV). This HPV related form of head and neck squamous cell carcinoma (HPV-HNSCC) has captured the attention of the oncology community for its rising incidence, its connection to non-traditional risk factors and its divergent clinical behaviour. This virus is associated with approximately 40% of head and neck squamous cell carcinomas, but the role played in the oncogenesis of papillary lesion

is unclear [7]. The presence or absence of stromal invasion is important for the diagnosis. It is not always easy in particularly in cases of biopsy considering the scarcity of the tissue, which is often superficial. If no stromal invasion is found, the lesion is called atypical papillary hyperplasia or PSCC *in situ* [1].

Case report

A 59-year-old man, afflicted with benign prostate hyperplasia, presented at the ENT Clinic of the Department of Medical Sciences, Surgical and Advanced Technologies "G.F. Ingrassia, University of Catania (Sicily, Italy), with the complaint of foreign body sensation in his throat for one month, with no aggravating and relieving factors.

The medical history of the patient was not significant and he did not report any history of alcohol or tobacco use and he was not immunosuppressed. Physical examination found no significant abnormalities.

Laboratory examination revealed an elevated erythrocyte count (6.21 x 10^6/μL) and RDW-CV (15.5%); the total count of white blood cells (WBC) was decreased (4.32×10^3/μL), as well as MCH (23.1 pg). Blood glucose was increased (134 mg/dL); other haematological and biochemical parameters were within normal limits.

The intra-oral examination and fiberoptic endoscopy revealed a papillomatous lesion of the left palatal tonsil that hung towards the oral cavity. Under the suspicion of malignancy, an incisional biopsy was performed.

Therefore, he underwent complete staging work up including dynamic contrast-enhanced computed tomography multidetector (CT) of the neck & chest, which showed a well-defined solid mass in the left part of the tongue (Figs. 1, 2). There was no radiological evidence of cervical metastasis, but only homolateral lymph nodes that were about 10 mm at the maximum dimension. There were no pulmonary lesions and no lymphadenopathy was seen in either hila. There were no pleural and pericardial effusions, but there were signs of vascular stasis in the dorsal segments of the lungs. The main airways were free.

In the present case, the presurgical staging of the tumour according to the TNM system proposed by the American Joint committee on Cancer (AJCC) was evaluated and was found to be stage I (T2N0M0).

After staging, the patient was hospitalised and underwent left tonsillectomy.

He received general anaesthesia by administration of propofol in TCI (4 mcg/ml), continuous infusion of remifentanil (0.2-0.5 mcg/kg/min) and rocuronium (0.6 mg/kg in bolus). Neuromuscular function was monitored using Train of Four (TOF) nerve stimulation and acceleromyography (TOF watch SX®) at the adductor thumb muscle, starting after the induction of anaesthesia. TOF and PTC (post-tetanic count) were assessed to evaluate the depth of the neuromuscular block. Four minutes after the beginning of drug infusion, laryngoscopy and tracheal intubation were performed using a videolaryngoscope (GlideScope®). The tonsil was removed along with part of the front pillar palatal adhering to it.

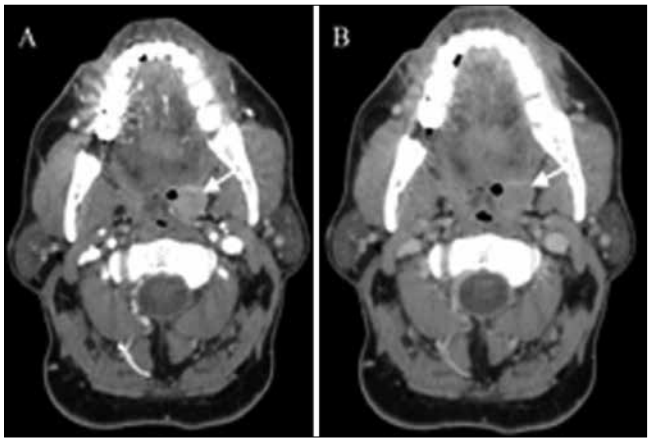

Fig. 1. Multidetector CT. Images A and B were acquired in different phases after contrast administration (arterial and venous phases respectively). A well-defined solid mass, oval in shape, is well depicted in the left tongue (white arrows).

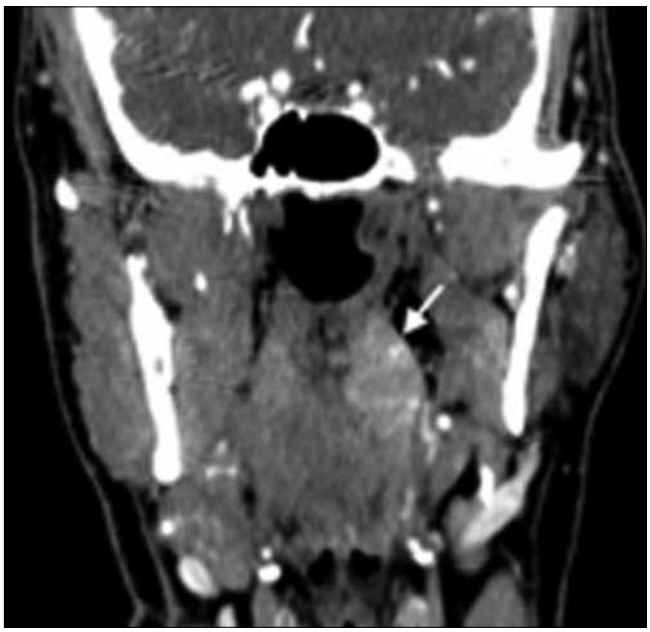

Fig. 2. Coronal reformatted MDCT image. Image clearly shows the lesion (white arrow), with moderate enhancement after contrast medium.

After completion of surgery, patient was extubated and admitted to recovery room for postoperative monitoring. Pain control was achieved by the intravenous administration of acetaminophen (15 mg/kg up to 1 g) and morphine (0.05 mg/kg).

The patient was vomiting blood in the immediate postoperative period. The intra-oral examination revealed bleeding from the left tonsil and thus he was sent back to the operating room for surgical revision. A rapid sequence in-

tubation, avoiding mask ventilation, was performed with propofol (2 mg/kg), fentanyl (2 mcg/kg) and rocuronium (1.2 mg/kg) in bolus. Anaesthesia was maintained with sevoflurane (2-2.5%). At the end of surgical haemostasis, neuromuscular block was still deep (TOF 0, PTC 3), so it was antagonised by the administration of sugammadex (4 mg/kg). A TOF ratio of 0.9 was reached in 160 sec. Thus the patient was extubated, monitored in recovery room for about 60 min and then moved to the ward. The patient was discharged, after two days, without any other post-operative complications.

At histopathological evaluation, the tonsil was about 3.6 x 2.5 x 1.3 cm in size and on gross examination presented an exuberant papillary outgrowth on the oropharynx face (Fig. 3). On the cut surface, the tumour was friable in its exophytic component. Histological features showed a proliferation of epithelial immature-basaloid cells around a fibrovascular axis, having the typical appearance of papillary growth pattern. The tumour cells showed high nuclear pleomorphisms with hyperchromasia, open and fine chromatin and numerous mitotic figures. Stromal invasion was evident with multiple nests of tumour cells and dense lymphoplasmacytic inflammation at the tumour-stromal interface (Figs. 4, 5).

Two 10 μm tissue sections paraffin wax embedded from palatine tonsil were sent to the Clinical Virology Unit of the Central Laboratory of the University Hospital "Policlinico-Vittorio Emanuele", Catania, for the detection of HPV DNA. The sections, after deparaffinisation steps, were processed using the Qiagen QIAmp DNA Mini kit (QIAGEN Gmbh, Hilden, Germany).

HPV DNA detection was accomplished by amplification of a target sequence within L1 ORF (HPV-HS Bio, AB Analitica s.r.l, Padua, Italy). HPV typing was performed with a reverse line blot hybridisation assay with specific probes for the most frequent HPV-genotypes (HPV-type, AB Analitica s.r.l., Padua, Italy). The genotype HPV 16 was detected. To evaluate the viral oncogenic activity, the HPV E6/E7 mRNA was performed by the NucliSENSE EasyQ HPV v1.1 (NASBA DIAGNOSTICS, bioMérieux bv, NL-5281 RM Boxtel). HPV 16 mRNA was also detected.

Based on clinical, radiographical, general and histopathological examination, a final diagnosis of palatal tonsil papillary squamous cell carcinoma was made with definite stage T2N0M0.

Acording to postoperative oncologic evaluation, no additional radiochemotherapy treatment was needed.

The clinical and radiological (MR ± CT) follow-up, performed at 5 years excluded local and regional recurrences (Fig. 6).

Discussion

PSCC has been accepted as a clinical pathological distinct

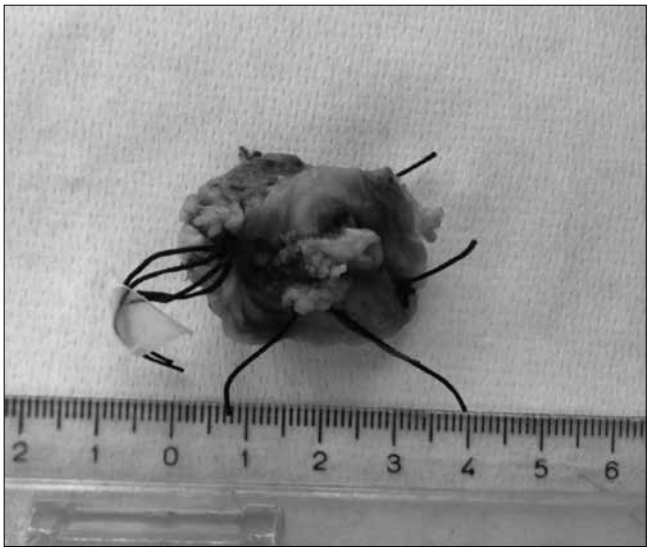

Fig. 3. At gross examination an exuberant papillary neoplastic outgrowth in the tonsil was evident.

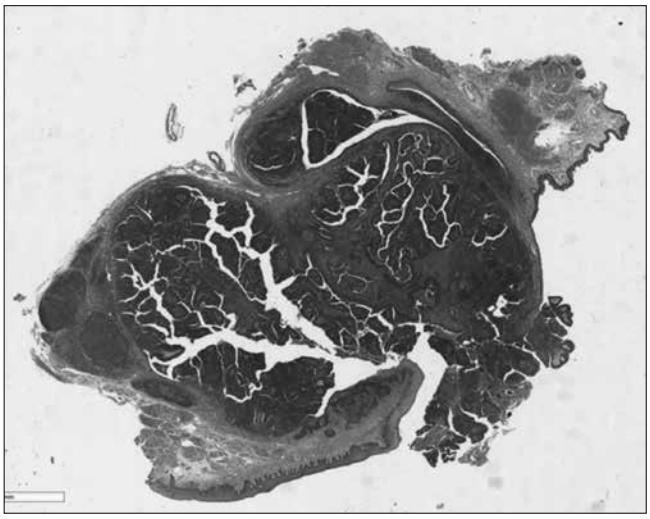

Fig. 4. At low magnification, a characteristic papillary finger-like pattern of growth was evident (H&E x 25).

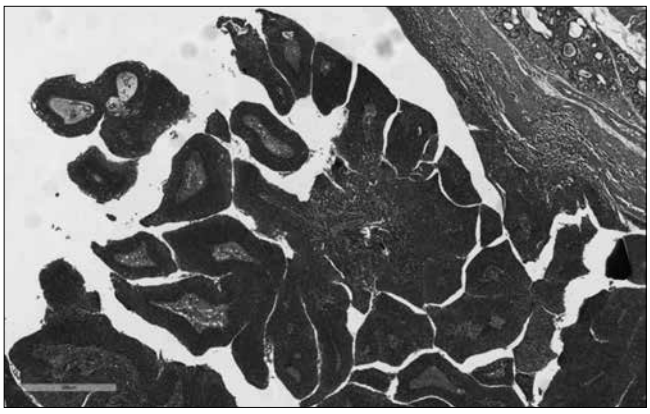

Fig. 5. At high magnification, papillary stalks in PSCC showed well visible fibro-vascular axis and markedly pleomorphic immature-basaloid neoplastic cells (H&E x 200).

neoplasm [3 9]; in the second edition of the World Health Organization (WHO), published in 1991, the term PSCC was applied to "invasive squamous cell carcinomas which have an exophytic papillary component" [10]. The differential diagnosis includes squamous papilloma and verrucous carcinoma. Squamous papilloma can be considered a precursor lesion of PSCC, cellular pleomorphism and mitotic activity allow differential diagnosis. Verrucous carcinoma lacks cytologic features of malignancy, has a well-differentiated squamous epithelium with marked keratinisation and invades the stroma with a pushing, rather than infiltrating border. The small number of documented cases have shown a strong male predilection from 50 to 70 years of age. The confirmation of the rare involvement of the tonsil by Cobo et al. [8] in a review, report data on the localization of the tumour and document higher involvement of the larynx and alveolar ridge. The other sites affected were buccal mucosa, sinonasal tract, nasopharynx and oropharynx [8]. The major predisposing factors are represented by smoking and alcohol abuse, although there is no significant evidence in the literature. In our case, the medical history of the patient was not significant and he did not report any history of alcohol or tobacco abuse and he was not immunosuppressed.

HPV infection is involved in the pathogenesis of PSCC in a manner similar to that of other squamous cell carcinomas of the head and neck mucosa by the viral oncogenes E6 and E7 that initiate carcinogenesis [11]. In the literature, there are several articles analysing the relationship of HPV with PSCC [2]. Cobo et al [8]. reported one case of PSCC associated with HPV infection. Jo et al. [7], reviewed 31 PSCCs of the upper aerodigestive tract and reported an identifiable high-risk HPV by *in situ* hybridisation in 68% of cases. The tumours related to HPV infection seem to have a better prognosis and for this reason, those authors propose reporting HPV status when these tumours are encountered [7 14 15].

In fact, even in the present case, HPV 16 was detected in palatal tonsil tissue. Moreover, the oncogenic activity of this virus was demonstrated by the detection of the E6/E7 HPV mRNA. A wider use of these molecular techniques, especially of mRNA tests, could be extremely useful in prevent the evolution of HPV-related lesions toward invasive carcinoma. This can be achieved by a close cooperation among the specialists involved. In relation to genotype, there is no homogeneity of results with respect to the techniques used for diagnosis. In spite of this, the 6/11 and 16/18 genotypes are mainly detected [2 12 13 15-17].

Suarez et al. [2], conducted a clinicopathologic and molecular study on PSCC of the upper aerodigestive tract, qualifying this tumour as an informative model for defining how viral oncogenes cooperate with other factors in genomic instability, carcinogenesis and tumour development.

PSCC may present as either *in situ* (non-invasive form) or invasive tumour. In the majority of reports, T2 lesions were most common. In our case, the exophytic neoplastic lesion was classified as the early invasive form with stage T2 without clinical radiological evidence of nodal involvement.

The treatment of choice is surgery to which possible neck dissection (generally selective neck dissection) is added, if necessary. Radiation therapy may follow surgery in cases of high-T or in cases where there are positive resection margins. The 5-year overall survival is satisfactory with complete resolution of the disease in over 80% of cases [8].

Conclusions

A recent review of the literature and the complete description of the clinical biological characteristics of this tumour, in case treated, enable clinicians to define this very rare cancer of the head and neck.

Acknowledgements

We wish to thank the Scientific Bureau of the University of Catania for language support.

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CASE SERIES AND REPORTS

A rare case of embryonal rhabdomyosarcoma of the parapharyngeal space

Un raro caso di rabdiomiosarcoma embrionario dello spazio parafaringeo

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SUMMARY

A 24-year-old man was admitted to our Otolaryngology Department following a head and neck CT scan performed for cranial trauma that showed a bulky neoformation in the right parapharyngeal space. Magnetic resonance imaging confirmed the presence of an oval formation with sharp margins and colliquative areas of necrosis involving the right parapharyngeal space. The mass was completely excised by a latero-cervical approach. Based on histological features and immunohistochemical analysis, a diagnosis of embryonal rhabdomyosarcoma of the parapharyngeal space was made. The incidental detection at this site of an embryonal rhabdomyosarcoma has never been reported in adult males.

KEY WORDS: Parapharyngeal mass • Embryonal rhabdomyosarcoma • Sarcomas • Head and neck malignant tumours

RIASSUNTO

Un uomo di 24 anni giunse al nostro Dipartimento di Otorinolaringoiatria poiché una TC testa-collo eseguita per un trauma cranico evidenziava una voluminosa neoformazione dello spazio parafaringeo di destra. La risonanza magnetica nucleare confermava la presenza di una formazione ovalare con margini netti e aree colliquative di necrosi, che interessava lo spazio parafaringeo di destra. La massa fu completamente escissa attraverso un approccio laterocervicale. Sulla base alle caratteristiche istologiche e dell'analisi immunoistochimica fu fatta la diagnosi di Rabdomiosarcoma Embrionario dello spazio parafaringeo. La diagnosi incidentale in questa sede di Rabdomiosarcomi Embrionari non è mai stata riportata in uomini adulti.

PAROLE CHIAVE: *Massa parafaringea • Rabdomiosarcoma Embrionario • Sarcomi • Tumori maligni della testa e del collo*

Acta Otorhinolaryngol Ital 2017;37:346-349

Case report

A 24-year-old man was admitted to our Department following for a CT scan of the head/neck without contrast medium, performed elsewhere following a cranial trauma, which showed the presence of a bulky mass in the right parapharyngeal space: it measured approximately 5 cm in the transversal diameter. The mass was indistinguishable from the surrounding head and neck structures due to the limitations of CT scan without contrast. A reduction in the hypopharyngeal space was just visible (Fig. 1).

The patient did not complain of any symptoms except for a slight right ear fullness. Oropharyngeal examination did not detect any pathological condition. Fibre optic endoscopy of the upper respiratory airways showed a slight bulging of the right lateral wall of the hypopharynx in the absence of laryngeal abnormalities. The mass was scarcely appreciable on head and neck palpation and no ipsilateral or contralateral cervical lymph nodes were present.

Contrast-enhanced magnetic resonance (MRI) with T1- and T2-weighted sequences was immediately performed. MRI (Fig. 2, 3) confirmed the presence of an oval mass, measuring 6, 4 and 3 cm in the craniocaudal, transversal and anteroposterior diameters, respectively. The mass involved the right parapharyngeal space upward as far as the skull base, showed low and high signal intensity on T1- and T2-weighted sequences respectively. Central areas of colliquative necrosis were visible.

We opted for surgical treatment, removing the mass by a laterocervical approach, without postoperative complications.

Histology of the excised mass demonstrated a highly cellular tumour composed of small-medium size undifferentiated cells with atypical and hyperchromatic, frequently nucleolated, nuclei and virtually indistinct cytoplasm (Fig. 4 a, b). Mitotic activity was prominent and necrosis was extensive. The neoplastic cells were immunoreactive for vimentin, desmin (Fig. 4 c), muscle specific antigen and, focally (rare cells), for myogenin (Fig. 4 d). Ki-67

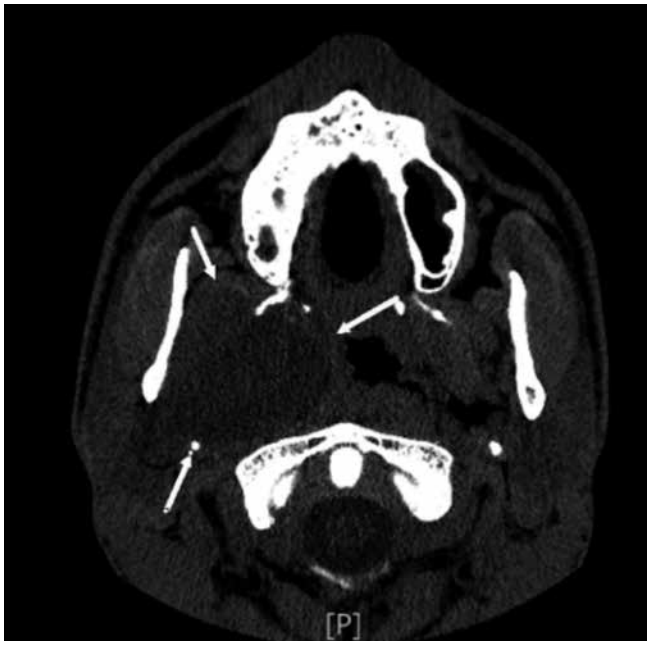

Fig. 1. Axial CT scan without medium contrast; Bulky neoformation in the right parapharyngeal space measured approximately 5 cm in the transversal diameter (arrows). The mass was indistinguishable from the surrounding head and neck structures. Reduction of the hypopharyngeal space is visible.

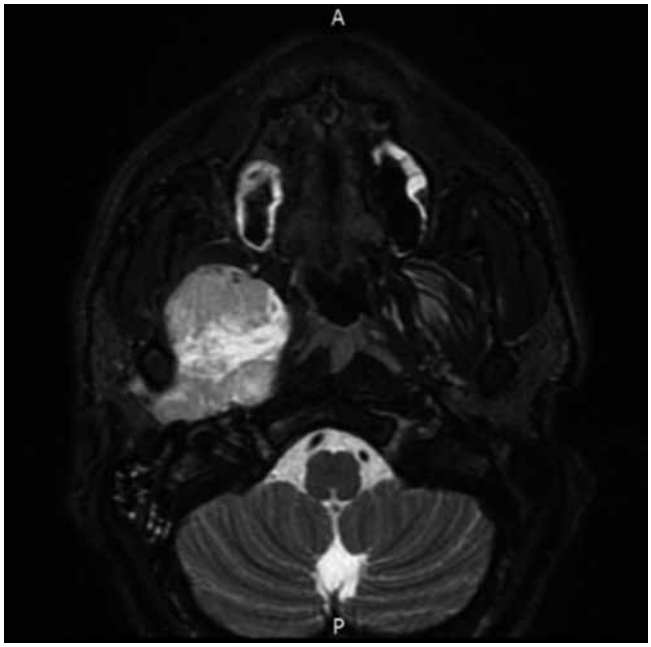

Fig. 2. Axial T2-weighed MRI with contrast medium; presence of high signal intensity neoformation with sharp margins occupant the right parapharyngeal space (4 x 3 cm). Presence of central areas of colliquative necrosis and reduction of the hypopharyngeal space is visible

immunostaining was 65%. Based on histological and immunohistochemical findings, a diagnosis of embryonal rhabdomyosarcoma was made. Small residues of the tumour (0.5 X 0.5 cm) were visible in the right parapharyngeal space at head and neck MRI and CT scan performed 30 days after surgery. According to the guidelines of the American Cancer Society[1], the embryonal rhabdomyosarcoma of our patient was classified as stage III.

At 3 months post-surgery the patient began adjuvant chemotherapy. Initially one cycle with adriamycin and cyclophosphamide was performed, following by four cycles of vincristine, adriamycin and ifosfamide. After this first oncological treatment, a partial reduction of the residual masses was observed in the follow-up MRI. Due to the partial response to first-line chemotherapy, the oncologist opted for a new chemotherapy with eight cycles of etoposide 450 mg / mq and isofosfamide 9000 mg/m^2. 30 cycles of radiotherapy (54Gy) were carried out after this last chemotherapy. At the last MRI performed (one year after surgery), substantial reduction of the disease residues was observed.

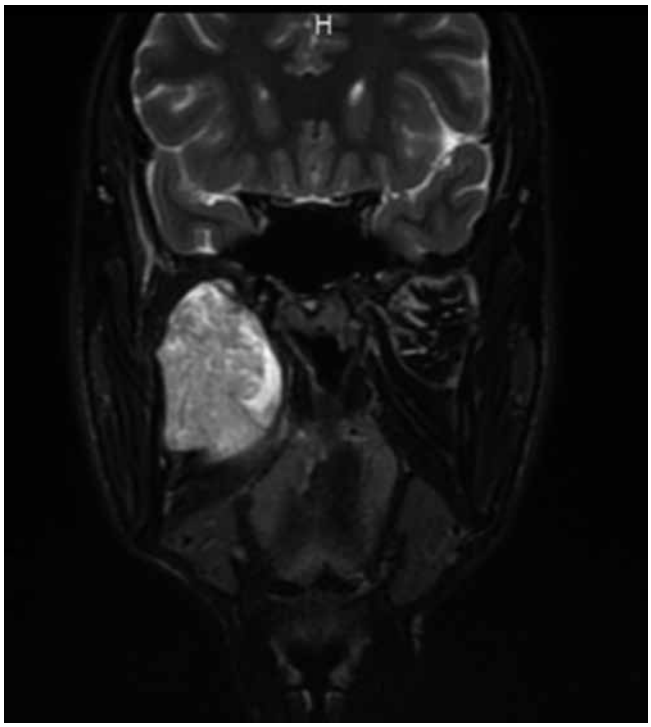

Fig. 3. Coronal T2-weighed MRI with contrast medium; presence of an oval formation (6 x 4 cm) with sharp margins extending in the right parapharyngeal space upward until the skull base.

Discussion

The main reason of interest of the case reported here is the incidental detection of a rare malignant mesenchymal tumour in the parapharyngeal space of a 24-year-old man. In fact, the tumour, which by histology and immunohistochemistry was an embryonal rhabdomyosarcoma, was incidentally detected by CT of the head and neck performed following cranial trauma. Even though incidental detection of benign and malignant tumours in the parapharyngeal space has been reported [2,3], to the best of

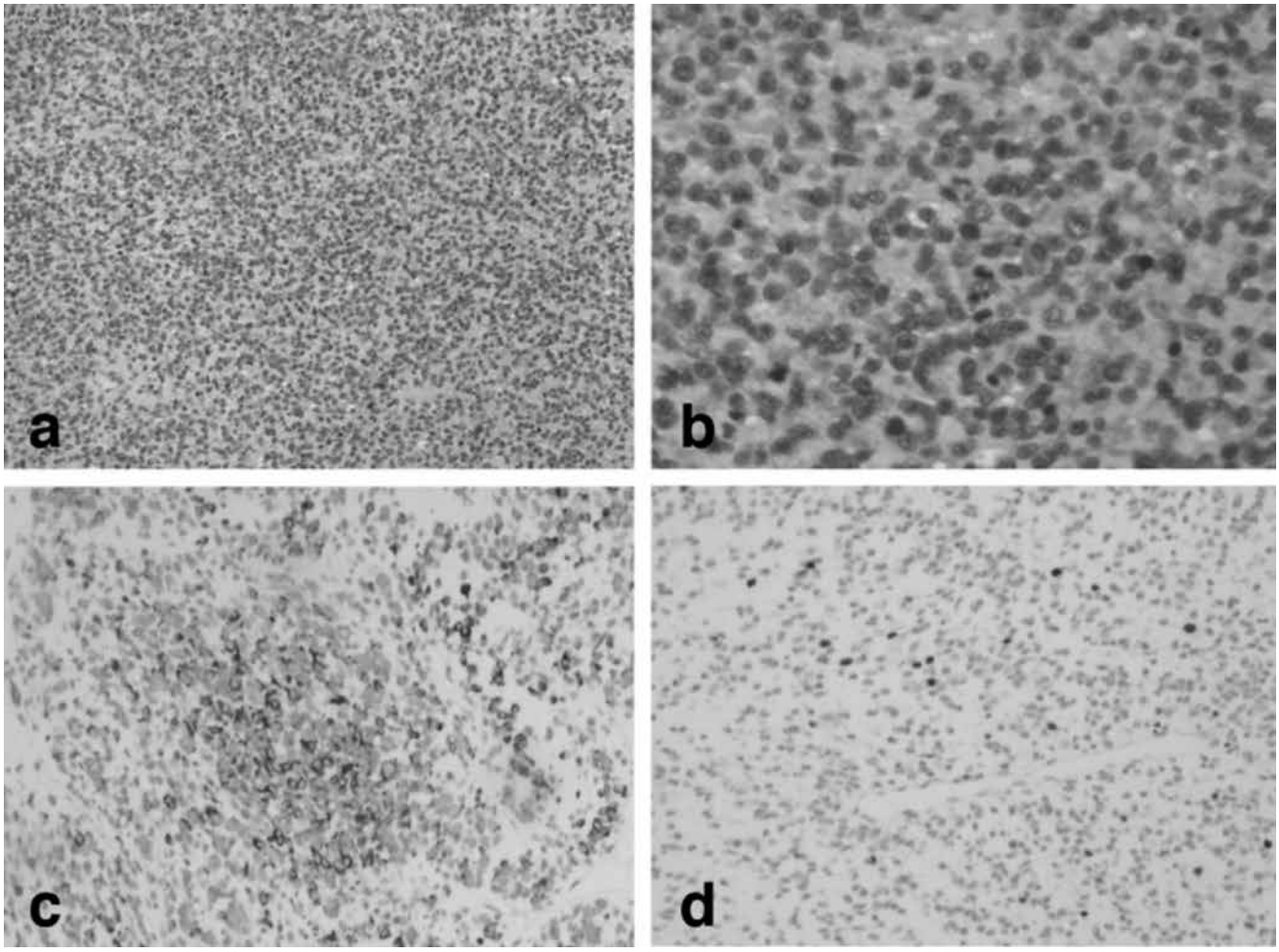

Fig.4. Low and high power magnification of the tumour are illustrated in a and b, respectively. The neoplastic cells are diffusely positive for desmin (c) and focally for myogenin (d).

our knowledge, the incidental detection at this site of an embryonal rhabdomyosarcoma has never been reported in adult males.

Rhabdomyosarcoma (RMS), one of the most common soft tissue sarcomas, is a malignant mesenchymal tumour composed of striated muscle myoblasts at different stages of differentiation [4]. It is considered the most common type of soft tissue sarcoma during the first two decades of life and accounts for 4.5% of all cases of childhood cancer. Additionally, it is the third most common extracranial solid tumour of childhood after Wilms' tumour and neuroblastoma [4 5].

Based on the histological pattern and degree of cell differentiation, different subtypes of RMS are distinguished [5]. Embryonal rhabdomyosarcoma (ERMS) is the most frequent, accounting for 50% - 60% of RMS cases [5 6]. The median age of RMS presentation is 6 years, although this disease follows a bimodal distribution with peak incidences between 2 and 6 years and again between 10 and 18 years of age. The bimodal distribution of RMS reflects the influence of the histologic subtypes. A diagnosis of ERMS is extremely rare in adults and usually involves children from 3 to 12 years [4 7]. In contrast, alveolar RMS peaks during childhood and adolescence then decreases up to 20 years of age [4 7]. MRI provides detailed imaging of soft tissue structures and is crucial for understanding the full extent of the RMS. In particular, MRI can be helpful for delineating invasion of the dura, involvement of orbital structures, perineural spread and bone marrow invasion. CT scan provides better detail of bony structures and can identify cortical erosion [4 8].

The best treatment options for ERMS include wide and complete resection of the primary tumour with a surrounding ''envelope'' of normal tissue whenever surgically possible. Adequate margins of 0.5 cm should be obtained circumferentially [4 5 9]. Obviously, such resection margins are more easily obtained in the extremities or trunk rather than head and neck tumours [4 7].

Adjuvant chemotherapy treatment must always considered if a diagnosis of ERMS is made [4 5 9]. Currently, standard therapeutic regimens consist of a combination of vincristine, actinomycin D, and cyclophosphamide (VAC) [3 4].

The overall prognosis for ERMS is good, with a 5-year survival rate of 60%, also in consideration of the fact that localisation to the head and neck region is a favourable prognostic factor [4]. However, local tumour recurrence and metastasis remain challenging [4 5 7]. Recent studies have shown that the recurrence rate may exceed 40% [2 4 5].
In conclusion, the possibility of an embryonal rhabdomyosarcoma should always be considered in case of a parapharyngeal mass, even in young adults.

Acknowledgments

We gratefully acknowledge Prof . Angelo P. Dei Tos (Department of Pathology, Treviso Regional Hospital, Treviso, Italy) who confirmed the histological diagnosis and performed FISH analysis which failed to detect FOXO1 gene rearrangement and Dr. Emanuela Pasqualitto (Department of Radiology, 'Sapienza' University, Rome, Italy) who carefully reviewed MRI images.

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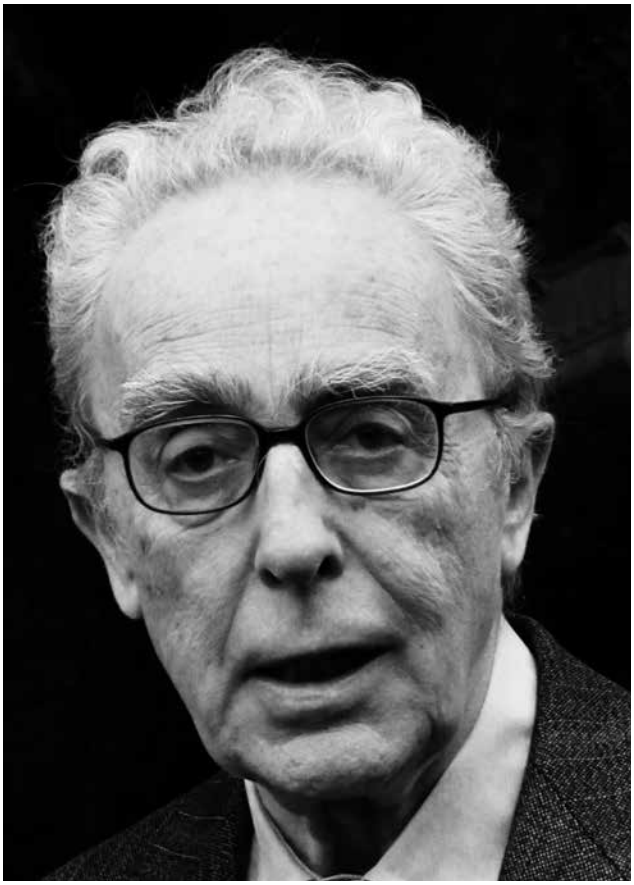
In Memoriam of Piero Miani

(1929 - 2017)



Another dear, close friend has left us. A colleague who profoundly influenced our lives and the Italian Society of Otorhinolaryngology, a person with untold charisma and rare human qualities.

The professional life of Piero Miani can be divided in two phases. The first was the university, from the mid-1950s to 1969, at Parma, at the school of Carlo Felice Porta. It was a promising career culminated in his position as professor of Audiology, which was interrupted as he felt more inclined to clinical practice, which for him was a sign of success and satisfaction. The second phase started in June 1969 as department head at Cremona that was perfected 8 years later with his return to Udine, the city of his roots, to direct the ORL Division of that prestigious hospital. The many scientific contributions by Piero remembered today during his long career may seem superfluous, but I cannot avoid mentioning at least two of the most significant ones, namely his work on cervical-facial lymphatic pathways and the basics of thyroid surgery. All of us colleagues learned something from him, and not only from a professional point of view, but even more from a human standpoint.

Our Scientific Society owes much to Piero Miani since he was the youngest of a group of exceptional colleagues who in 1976 were able to transform the old SILOR into SIOChCF, by radically reforming the older statutes. He became President of the new Society in 1993, and he always knew how to make meaningful contributions, and participated, until a few years ago, at all the Board of Director meetings with a commendable spirit of service.

Lastly, I would like to remember Piero as a person and recall his human qualities that always guaranteed him the esteem, respect and compassion of all colleagues and those who knew him. He had a special charisma and knew how to inspire immediate comradery thanks to his excellent sense of humour and his ready taste for good natured jokes. This, however, was only the outward appearance of his character, and having known him for over 50 years, I can say that Piero was the most serious and balanced person I was fortunate enough to know. Few have had his absolute dedication to fundamental values such as intellectual honesty, dedication to family and work and a deep sense of friendship.

In recent years, unfortunately, he suffered greatly for the loss of his wife, Giuliana, after a long and destructive illness. This event marked him irreparably, and in my opinion, also had a decisive influence on his health. Piero was morally changed and unhappy, but in spite of that, up until the very end in the frequent phone calls that we had, he never forgot to share a handful of lively jokes and the joy for life that he once had. Today, unfortunately, there is only room for the happy memories.

Giorgio Sperati

Notiziario SIO

CONSIGLIO DIRETTIVO SIO (2017/2018)

Cassandro E.	Presidente SIO	(Scad. Maggio 2018)
Vicini C.	Vice-Presidente	(Scad. Maggio 2018)
Bussi M.	Vice-Presidente	(Scad. Maggio 2019)
Succo G.	Segretario	(Scad. Maggio 2022)
Ruscito P.	Tesoriere	(Scad. Maggio 2022)
Ralli G.	Bibliotecario	(Scad. Maggio 2018)
Scarpa A.	Segretario del Presidente	(Scad. Maggio 2018)
Barillari U.	Consigliere	(Scad. Maggio 2018)
Benazzo M.	Consigliere	(Scad. Maggio 2018)
Croce A.	Consigliere	(Scad. Maggio 2018)
Cuda D.	Consigliere	(Scad. Maggio 2018)
Gianformaggio C.	Consigliere	(Scad. Maggio 2018)
Greco A.	Consigliere	(Scad. Maggio 2018)
Pisani P.	Consigliere	(Scad. Maggio 2018)
Santandrea L.	Consigliere	(Scad. Maggio 2018)
Tortoriello G.	Consigliere	(Scad. Maggio 2018)
Tirelli G.	Consigliere	(Scad. Maggio 2018)
Leone C.A	Past president	(Scad. Maggio 2018)
Paiano M.T.	Consigliere agg. LP	(Scad. Maggio 2018)

Comitato permanente per l'aggiornamento dello statuto e del regolamento

Cassandro E.	Presidente SIO	(Scad. Maggio 2018)
Lauriello M.	Segretario dell'AUORL	(Scad. Maggio 2019)
Rugiu M.G.	Segretario dell'AOOI	(Scad. Maggio 2018)
Succo G.	Segretario SIO	(Scad. Maggio 2022)
Bussi M., Iengo M. Quaranta N.	Colleghi nominati dall'AUORL	(Scad. Maggio 2019)
Della Vecchia L., Iemma M., Piemonte M.	Colleghi nominati dall'AOOI	(Scad. Maggio 2018)

Revisori dei conti SIO

Fiorella M.L.	(Scad. Maggio 2020)
Sessa M.	(Scad. Maggio 2020)

Collegio dei Proibiviri SIO

Chiesa F.	(Scad. Maggio 2018)
Conticello S.	(Scad. Maggio 2018)
De Benedetto M.	(Scad. Maggio 2018)
Fiorella R.	(Scad. Maggio 2018)
Passali D.	(Scad. Maggio 2018)

Coordinatore del Controllo di Qualità

Della Vecchia L.	(Scad. Maggio 2019)

Organo di consulenza SIO

Ansarin M., Camaioni A., Casolino D., Conticello S., Coppo L., Danesi G., De Benedetto M., De Campora E., Filipo R., Fiorella R., Laudadio P., Marcucci L., Maurizi M., Motta G., Ottaviani A., Pagella F., Passali D., Paludetti G., Piemonte M., Puxeddu P., Ralli G., Rinaldi Ceroni A., Sartoris A., Scasso F., Serra A., Sperati G., Spriano G., Zaoli G.

Delegati

EUFOS	Cuda D.	(Scad. Maggio 2018)
	Martini A.	(Scad Maggio 2019)
IFOS	Piemonte M.	(Scad. Maggio 2018)
	Galli J.	(Scad Maggio 2019)
UEMS	Cuda D.	(Scad. Maggio 2018)
	Motta Ga.	(Scad Maggio 2019)
EHNS	Spriano G.	(Scad. Maggio 2018)
	Motta Ga.	(Scad Maggio 2019)

CONSIGLIO DIRETTIVO AOOI

Danesi G.	Presidente	(Scad. Maggio 2018)
Barbara M.	Vice-Presidente	(Scad. Maggio 2018)
Della Vecchia L.	Vice-Presidente	(Scad. Maggio 2018)
Radici M.	Vice-Presidente	(Scad. Maggio 2018)
Rugiu M.G.	Segretario-tesoriere	(Scad. Maggio 2018)
Achilli V.	Consigliere	(Scad. Maggio 2018)
Boccuzzi S.	Consigliere	(Scad. Maggio 2018)
Caporale C.	Consigliere	(Scad. Maggio 2018)
De Campora L.	Consigliere	(Scad. Maggio 2018)
Miani C.	Consigliere	(Scad. Maggio 2018)
Napolitano A.	Consigliere	(Scad. Maggio 2018)
Panetti G.	Consigliere	(Scad. Maggio 2018)
Panu F.	Consigliere	(Scad. Maggio 2018)
Raso F.	Consigliere	(Scad. Maggio 2018)

Collegio dei probiviri AOOI

Barbieri F.	(Scad. Maggio 2020)
De Benedetto M.	(Scad. Maggio 2020)
Laudadio P.	(Scad. Maggio 2020)
Richichi M.	(Scad. Maggio 2020)
Villari G.	(Scad. Maggio 2020)

Delegati

IFOS	Piemonte M.	(Scad. Maggio 2018)
UEMS EUFOS	Cuda D.	(Scad. Maggio 2018)
EHNS	Spriano G.	(Scad. Maggio 2018)

CONSIGLIO DIRETTIVO AUORL (2017-2019)

Paludetti G.	Presidente
Lauriello M.	Segretario-tesoriere
Berrettini S.	Consigliere
Cassano M.	Consigliere
Martini A.	Consigliere
Motta G.	Consigliere
Nicolai P.	Consigliere
Presutti L.	Consigliere
Ricci G.	Consigliere
Tirelli G.	Consigliere
Turchetta R.	Consigliere
Bussi M.	Past-President

Collegio dei probiviri (2017-2019)

Cianfrone G.
Gaini R.
Iengo M.
Nuti D.
Pia F.

Revisori dei conti (2017-2021)

Cocuzza S.
Pelucchi S.

Comitato permanente per l'aggiornamento dello statuto e del regolamento (2017-2021)

Bussi M.
Iengo M.
Ricci G.

Temi scientifici 2018-2019

2018
Relazione ufficiale 2018
"Patologia infettiva emergente e riemergente in ORL" *a cura di: F. Scasso, G. Ferrari, G.C. De Vincentiis*

Tavola rotonda 2018
"Attualità delle problematiche medico-legali in ORL"*a cura di: A. Serra*

2019
Relazione ufficiale 2019
"La chirurgia della base cranica laterale – Lateral skull base surgery" *a cura di: A. Martini*