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

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Review

Facial pain: sinus or not?

Algie cranio facciali: dolore di origine sinusale?

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SUMMARY

Facial pain remains a diagnostic and therapeutic challenge for both clinicians and patients. In clinical practice, patients suffering from facial pain generally undergo multiple repeated consultations with different specialists and receive various treatments, including surgery. Many patients, as well as their primary care physicians, mistakenly attribute their pain as being due to rhinosinusitis when this is not the case. It is important to exclude non-sinus-related causes of facial pain before considering sinus surgery to avoid inappropriate treatment. Unfortunately, a significant proportion of patients have persistent facial pain after endoscopic sinus surgery (ESS) due to erroneous considerations on aetiology of facial pain by physicians. It should be taken into account that neurological and sinus diseases may share overlapping symptoms, but they frequently co-exist as comorbidities. The aim of this review was to clarify the diagnostic criteria of facial pain in order to improve discrimination between sinogenic and non-sinogenic facial pain and provide some clinical and diagnostic criteria that may help clinicians in addressing differential diagnosis.

KEY WORDS: Facial pain • Headache • Migraine • Cranial neuralgia • Rhinogenic • Non-rhinogenic

RIASSUNTO

Le algie cranio-facciali rappresentano una sfida sia dal punto di vista diagnostico che terapeutico. Nella pratica clinica, è frequente che i pazienti affetti da tale condizione si sottopongano a più valutazioni da parte di specialisti diversi, ricevendo trattamenti medici e chirurgici eterogenei e inappropriati, che non portano al beneficio clinico. Questo purtroppo accade perché la sintomatologia algica cranio facciale viene spesso attribuita erroneamente alla rinosinusite. È importante, invece, escludere le cause di dolore facciale di origine diversa dall'eziologia nasosinusale, prima di prendere in considerare l'eventualità di un trattamento chirurgico che potrebbe rivelarsi inutile e inappropriato. Per tali motivi sfortunatamente, una significativa percentuale di pazienti trattati chirurgicamente per le algie cranio facciali continua a lamentare dolore persistente anche dopo la chirurgia endoscopica nasosinusale. È necessario tenere in considerazione che le patologie neurologiche possono presentare sintomi sovrapponibili a quelli delle patologie nasosinusali e che le due entità possono in alcuni casi coesistere come comorbidità. L'obiettivo del seguente lavoro è quello di chiarire i criteri diagnostici delle algie cranio-facciali allo scopo di migliorare la diagnosi differenziale tra dolore dovuto a patologie nasosinusali e quello dovuto ad altre cause, fornendo al contempo criteri clinici che possano essere d'aiuto ai curanti, indirizzandoli verso la corretta diagnosi e l'appropriato iter terapeutico.

PAROLE CHIAVE: *Algia cranio facciale • Cefalea • Emicrania • Nevralgia cranica • Rinogeno • Non rinogeno*

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Introduction

Facial pain is associated with significant morbidity and high levels of health care utilisation, and remains a diagnostic and therapeutic challenge for both clinicians and patients; these conditions are often regarded as diagnoses of exclusion. The diagnostic criteria for facial pain can be found in both the International Association for the Study of Pain classification (IASP) and the International Headache Classification (ICHD-III) [1]. According to the IASP, pain is an unpleasant emotional and sensory experience associated or not with real or potential injury; neuropathic pain occurs due to neural dysfunction [2 3]. In the group of patients who are referred to an otolaryngologist with a presumptive diagnosis of rhinosinusitis as the cause of facial pain, only a few cases are found to have pain attributable to sinus diseases [4]. Furthermore, studies selecting pa-

tients with facial pain with negative nasal endoscopy (NE) and computed tomography (CT) found that migraine was the most common cause of pain. Finally, clinical observations suggest that rhinosinusitis is an uncommon cause of facial pain:

- more than 80% of patients with purulent secretions visible at nasal endoscopy have no facial pain [4];
- most patients with nasal polyposis do not have facial pain [5 6];
- children who have rhinosinusitis rarely complain facial pain, even in the presence of florid purulent secretions [7];
- a significant proportion of patients who are candidate for endoscopic sinus surgery for facial pain have symptoms that persist post-operatively [4 8 9].

The management of patients with sinus pressure, pain, fullness, or headache is of utmost importance in the field of otolaryngology and rather challenging. From a merely clinical point of view, it is crucial distinguishing "sinogenic" from "non-sinogenic" facial pain to avoid erroneous treatment. Migraines are commonly misdiagnosed as sinus headache in approximately 42% of patients [10] due to sharing overlapping symptoms (facial pain-fullness, nasal congestion and rhinorrhoea), precipitating triggers (weather changes, allergies and environmental irritants) and common locations with chronic rhinosinusitis (CRS) [11]. Furthermore, sinonasal and migrainous disorders may frequently co-exist as comorbidities; in fact, chronic rhinosinusitis (CRS) may increase migraine-associated morbidity and frequency through irritation of trigeminal nerve receptors. Although American Academy of Otolaryngology-Head & Neck Surgery (AAO-HNS) criteria mandate objective confirmation by either NE or CT, non-otolaryngologists do not usually perform nasal endoscopy and the use of CT scan is limited due to radiation exposure and costs.

The aim of this work was to clarify the diagnostic criteria of sinogenic facial pain and to study differential diagnosis between sinogenic and non-sinogenic facial pain, as well as diagnostic-related strategies in patients presenting to an otolaryngologist for facial pain or headache [12].

Epidemiological data

Several epidemiological reports have been published regarding the relationship between sinus inflammatory disorders and headache, reaching different results. The clinical picture may be confounding due to overlapping symptoms. Runny nose, congestion and ocular symptoms may also be associated with neurological conditions. Migraine patients, for example, feel significantly bothered by nasal symptoms: a study on 46 patients diagnosed with primary headache disorder (PHD) showed high sino-nasal outcome test (SNOT-22) scores in almost all patients in whom CRS had been excluded by objective criteria [12]. Accordingly, Barbanti et al. [13] demonstrated that migraine patients may experience unilateral nasal and/or ocular symptoms. Ocular and nasal symptoms have been hypothesised to arise from activation of the trigeminal-autonomic reflex, which is mediated by a circuit of trigeminal afferents and parasympathetic efferents innervating the lacrimal glands and the nasal mucosa.

Several authors have demonstrated that the most common cause of self-diagnosed or primary physician-diagnosed "sinus headaches" in primary care scenarios is migraine. Schreiber et al. [14] observed, in a very large series of 3000 patients with a self-diagnosis of "sinus headache", that 88% of cases had migraine. Accordingly Eross et al. [15] demonstrated that 86% of patients with a self-diagnosis and/or physician diagnosis of "sinus headache" have a migraine; Mehle et al. [16] observed, finally, in a cohort of 35 patients affected by self-referred "sinus headache" that 74.3% satisfied International Headaches Society (IHS) criteria for migraine.

Several studies selecting otorhinolaryngological patients with negative NE and CT also found migraine to be the most common cause of sinus headaches. Perry et al. [17], for instance, observed that 58% of patients referring for self-diagnosed "sinus headache" in a tertiary rhinology practice, with negative NE or CT, were more properly diagnosed as migraine after referral to a neurologist.

Conversely, in studies from non-otorhinolaryngological settings, migraine is frequently misdiagnosed as sinusitis [18]. Lee [19] observed that 28.7% of 1,235 patients diagnosed with primary headache and treated by neurologists in the emergency room showed radiological signs of rhinosinusitis, intranasal contact point, septal spur, concha bullosa, isolated sphenoid lesion or osteoma.

Several epidemiological studies have confirmed that CRS and migraine may also be frequently comorbid, due to the high incidence of both disorders in the general population. Aaseth [20] showed a strong association between headache and CRS in a cohort of 30,000 individuals, aged 30-44 years: patients with CRS had a 9-fold increased risk of having chronic headache; rhinitis and CRS are also believed to increase migraine-associated morbidity. Moreover, a study conducted on 100 headache patients demonstrated that 54% of those with IHS-defined migraine reported allergic rhinitis and 76% had at least one episode of prior acute sinusitis [15].

"Sinogenic" facial pain

The term "sinogenic" facial pain is routinely used to

suggest a pathogenic relationship between rhinological disorders and facial pain, and several physiopathological theories have been postulated [21]. A "convergence hypothesis" has been elaborated, suggesting that headache might be a rebound mechanism that occurs when the central nervous system is stimulated by a headache-provoking environmental trigger. Sinus headache may be the result of trigeminal afferents in the nasal and sinus territory that activate the trigemino-vascular system. Peripheral trigger would occur with immunologic activation from allergies or infection or from stimulation derived from abnormal anatomic features culminating in facial pain [11]. In addition, the creation of a pressure differential across obstructed sinus ostia, presence of inflammation and bacterial toxins and underlying osteitis may influence sensory nerve function and contribute to the aetiology of headache.

Rhinosinusitis and facial pain

Acute rhinosinusitis (ARS) usually follows an acute upper respiratory tract infection. Pain related to ARS is often unilateral, severe and associated with fever in 50% of cases and with nasal obstruction. Unilateral facial and dental pain are predictors of maxillary infection as validated in studies using maxillary sinus aspiration [22]. Acute frontal ARS is often characterised by pyrexia and tenderness on the medial side of the orbital floor under the supraorbital ridge, where the frontal sinus is thinnest. Endoscopic examination is mandatory and usually shows hyperemia of the sinonasal mucosa, and purulent secretions. Acute sphenoiditis is uncommon, causing pain at the vertex of the head, although pain can be referred to the temporal region or the whole head.

In the CRS there is a poor correlation between the site of facial pain and evidence of sinus pathology. Indeed, CRS is usually painless, although the pain may occur during acute exacerbations. The relationship between facial pain/pressure, headache and chronic rhinosinusitis has long been debated and the most recent guidelines endorse the presence of pain in CRS [23]. Several studies, however, suggested that facial pain is a very rare symptom in CRS [24]. Hirsch et al. [25] suggested that only 9.1% of patients affected by CRS refer facial pressure/pain as prevalent symptoms. CRS patients most commonly have other clinical manifestations of rhinosinusitis, such as purulent nasal discharge and respiratory obstruction [14 26], with pain occurring usually, as mentioned above, only during an acute exacerbation [9]. Furthermore, more than 80% of patients with purulent secretions visible at nasal endoscopy have no facial pain [4].

CRS patients with facial pain and/or pressure have a higher risk of migraine compared to the patients without these symptoms. CRS may increase migraine-associated morbidity and migraine frequency through irritation of trigeminal nerve receptors. Additionally, the age- and sex-specific prevalence of CRS with pain and pressure mirror those of migraine (middle age, women) [20].

Diagnostic criteria for headache attributed to rhinosinusitis are listed in Table I.

Rhinogenic headache

There has been a growing level of interest shown in rhinogenic headache (RH) within the literature over the last two decades. Despite this, the sum of knowledge on RH remains low. Whilst the IHS does accept such a condition, the society has remarked on the paucity of evidence for RH as

Table I. Diagnostic criteria for headache attributed to rhinosinusitis. Headache Classification Committee of the International Headache Society (IHS) [1].

Attributed to acute rhinosinusitis	Attributed to chronic or recurring rhinosinusitis
A. Any headache fulfilling criterion C	A. Any headache fulfilling criterion C
B. Clinical, nasal endoscopic, and/or imaging evidence of acute rhinosinusitis	B. Clinical, nasal endoscopic, and/or imaging evidence of current or past infection or other inflammatory process within the paranasal sinuses
C. Evidence of causation demonstrated by at least 2 of the following: 1. headache as developed in temporal relation to the onset of rhinosinusitis; 2. either or both of the following: a. headache as significantly worsened in parallel with worsening of the rhinosinusitis, b. headache as significantly improved or resolved in parallel with improvement in or resolution of the rhinosinusitis; 3. headache is exacerbated by pressure applied over the paranasal sinuses; 4. in the case of unilateral rhinosinusitis, headache is localised and ipsilateral to it.	C. Evidence of causation demonstrated by at least 2 of the following: 1. headache as developed in temporal relation to the onset of chronic rhinosinusitis; 2. headache waxes and wanes in parallel with the degree of sinus congestion and other symptoms of the chronic rhinosinusitis; 3. headache is exacerbated by pressure applied over the paranasal sinuses; 4. in the case of unilateral rhinosinusitis, headache is localised and ipsilateral to it.
D. Not better accounted for/by another ICHD-III diagnosis	D. Not better accounted for/by another ICHD-III diagnosis

a nosological entity. RH is defined as a headache, or a pain syndrome affecting the face, caused by mucosal surfaces impinging on each other within the nose and sinuses and lacking evidence of inflammation, hyperplasia of mucosal surfaces, pus-filled discharge, polyposis within the nose or sinuses, or existence of a mass [27]. Normally, symptoms affect the area surrounding the orbit, the canthus medially and superiorly, or the zygomatic-temporal region and are one-sided, even if both sides may be affected in some cases. There is frequent recurrence of pain, the duration of which may be hours, interspersed with pain-free intervals. Where the mucosae impinge on each other, a "trigger point" may occur, with a resulting paroxysm of pain in the face area. Variations in anatomy can lead to impingement of structures on the nasal epithelium, the most frequently seen being a pneumatised middle turbinate (alternatively termed concha bullosa), which is a consequence of the way the ethmoidal sinus cells develop. Likewise, the middle turbinate may impinge painfully on the septum of the nose or the lateral wall, a situation Morgenstein [28] called "middle turbinate headache syndrome". Excising a portion of the middle turbinate in this group has an apparent benefit in relieving headache [29]. On the balance of probability, as assessed through reviewing published case histories [9], most such patients with aberrant anatomy obtain only partial relief or of short duration by surgery. Greenfield [30] has proposed the theory that cutaneous branches of the nasal afferents of cranial nerve V synapse in the cerebral cortex, thus accounting for the perception of nasal stimulation as pain. Since the cortex is unable to localise these afferent impulses, they are perceived as referred facial pain [31]. Stammberger and Wolf [32] suggest that anatomical aberrations may cause mucous pooling, with infection occurring with resultant facial pain. They hypothesise that impingement of mucosae may trigger discharge of the neurotransmitter peptide substance P, which is known to have a role in pain transmission, but do not offer further experimental corroboration of their theory.

To hypothesise a rhinogenic headache, three features must be present: an area of mucosal impingement, confirmed endoscopically or radiologically; infiltrating the suspicious area with local anaesthesia should abolish nociception for 5 minutes; the pain should disappear within a week [1]. In contrast, a recent publication observed that most individuals with an area of impingement do not perceive pain nor, where there is pain, does obliteration of the contact point usually cause facial pain to disappear completely [33]. Additionally, points of mucosal contact were discovered to occur with identical frequency in both symptomatic and asymptomatic individuals. Even more revealing, where individuals had one-sided pain that could be linked to a mucosal impingement, such lesions were also present asymptomatically in 50% of cases [34].

Impact of functional endoscopic sinus surgery (FESS) on facial pain

The way FESS influences headache has been under investigation for a lengthy period, and such research may help to provide information on the putative links between sinonasal inflammation and facial pain. Lal [12] stated that 66 of 211 patients (31.28%) undergoing endoscopic sinus surgery experienced pain relief. However, the population studied consisted of a mixture of cases referred from both ENT and neurology departments for sinus pressure or pain. The obstruction relinquished most often where the patient had received neurological input, either previously or concurrently. Indeed, 36% of cases, which had failed to improve on surgical intervention, were then given a primary diagnosis of headache disorder when reviewed by a neurologist. From research with more stringent inclusion criteria (including only genuine sinusitis and facial pain), the FESS success rate increases to 75-91.9% [4 9 20 35 36]. A study with a follow-up period of 7 to 8 years noted that 47% of the 51 cases included remained without headache throughout follow-up [37].

Some studies have looked at cases where FESS was carried out despite no endoscopic or CT confirmation of sinus pathology or anatomical anomaly. Boonchoo [38] carried out FESS in 16 cases where headache existed, but CT findings demonstrated no anomaly. Ten of these ended up completely pain-free, while the remaining 6 had some degree of alleviation. In a similar vein, Cook et al. [39] observed that 12 of 18 cases undergoing the procedure found it of benefit, although none saw their symptoms disappear completely.

If an individual experiences abrupt changes in pressure, for example while diving, flying, or skiing, regardless of whether they suffer from rhinosinusitis or not, they may have short lived facial pain, which, however, abates within hours thanks to increasing vascular perfusion over time. Such individuals frequently find surgical interventions that increase ostial patency to be of benefit [23]. By contrast, longer lasting ostial blockage is rarely the cause of uninterrupted facial pain. Silent sinus syndrome exemplifies this fact, in which an occluded sinus resorbs its contents, and the maxillary sinus is weakened to the extent that the orbit may prolapse into it. Despite this, the condition is painless. A similar effect may be responsible when intraoperative damage to afferents leading to the trigeminal nucleus causes the threshold for spontaneous discharge to be reset briefly [32].

Other rhinologic disorders occasioning sinogenic facial pain
Sinus mucocoeles, which expand gradually in a cystic fashion are among other diseases treated by a rhinologist that may cause facial pain. When the mucocele attains sufficient magnitude to impinge on the osteous wall of the sinus, pain results. A mucocoele of the maxillary sinus may occlude the ostiomeatus, resulting in sinusitis. The most significant lesion from a clinical viewpoint is a fronto-ethmoidal mucocoele, since it provokes frontal headaches and pain in the orbit. Pain over the occiput, the vertex, or deep nasal region may be the result of a spheno-ethmoidal mucocoele [40 41].
Where pain does not vary and has been worsening, other worrying features or neural signs are present, a neoplasm should be suspected, even if facial pain is seldom a presenting feature. A pus-filled, sanguineous discharge occurring on one side of the nose and blockage of the nose are more usual. Pain usually occurs at an advanced stage. Para-aesthetic sensation below the orbit, loosened dentition, dentures that no longer fit, proptosis, malar deformity and watering eyes are possible, less common signs. Radiological imaging is essential.

"Non-sinogenic" facial pain

The worldwide prevalence of some form of headache is 46%. Amongst non-sinogenic causes there are primary headache syndromes such as migraine and related disorders, tension headache and trigeminal autonomic cephalalgias (TACs). Somewhat seldom are headaches secondary to another condition, e.g. infection, vascular pathology, substance misuse, psychiatric illness and lesions or injuries of the cranial nerves, according to ICHD-III. The latter are often included in potential causes when assessing cases of facial pain thought to be sinogenic.
Diagnostic criteria for the most frequent types of primary headache are listed in Table II.

Table II. Diagnostic criteria for most frequent primary headaches. Headache Classification Committee of the International Headache Society (IHS) [1].

Migraine without aura	Migraine with aura	Frequent episodic tension type	Cluster headache
A. At least 5 attacks fulfilling criteria B-D	A. At least 2 attacks fulfilling criteria B-C	A. At least 10 episodes occurring on 1 to 14 d/mo on average for > 3 mos (> 12 and < 180 d/y) and fulfilling criteria B-D	A. At least 5 attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 h (untreated or unsuccessfully treated)	B. 1 or more of the following fully reversible aura symptoms: 1. visual; 2. sensory; 3. speech and/or language; 4. motor; 5. brainstem; 6. retinal.	B. Headache lasting 30 min-7 d	B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 min (when untreated)
C. Headache has at least 2 of the following characteristics: 1. unilateral location; 2. pulsating quality; 3. moderate or severe pain intensity; 4. aggravation by/or causing avoidance of routine physical activity (e.g. walking or climbing stairs).	C. Headache has at least 3 of the following characteristics: 1. at least 1 aura symptom spreads gradually over ≥ 5 min; 2. two or more aura symptoms occur in succession; 3. each individual aura symptom lasts ≥ 5 and ≤ 60 min; 4. at least 1 aura symptom is unilateral; 5. at least 1 aura symptom is positive; 6. the aura is accompanied, or followed within 60 min, by headache.	C. Headache has at least 2 of the following characteristics: 1. bilateral location; 2. pressing/tightening (nonpulsating) quality; 3. mild or moderate intensity of pain; 4. not aggravated by routine physical activity (e.g., walking or climbing stairs).	C. Either or both of the following: 1. at least one of the following symptoms or signs, ipsilateral to headache: a. conjunctival injection and/or lacrimation; b. nasal congestion and/or rhinorrhea; c. eyelid oedema; d. forehead and facial sweating; e. miosis and/or ptosis. 2. sense of restlessness or agitation
D. During headache, at least 1 of the following: 1. nausea and/or vomiting; 2. photophobia and phonophobia.	D. Not better accounted for/by another ICHD-III diagnosis	D. Both of the following: 1. no nausea or vomiting; 2. no more than 1 of photophobia or phonophobia.	D. Occurring with frequency between 1 every other day and 8 per day
E. Not better accounted for/by another ICHD-III diagnosis		E. Not better accounted for/by another ICHD-III diagnosis	E. Not better accounted for/by another ICHD-III diagnosis

** d: day; mos: months; y: year; h: hours; min: minutes*

Primary headaches

Migraine

Migraines are frequently seen as a common cause of infirmity, they contribute significantly to absence from work, reduce employee productivity and cause reduced quality of life that can be readily shown [42]. Worldwide, 11% of adults are sufferers [43], with a female to male ratio of 3:1, with the bias being attributed to hormonal changes. Children and elderly people are less commonly affected. The daily incidence in the general population is 3,000 in 1,000,000 [44].

The symptomatology of migraine shares common features with other headache types: tension, cluster and "sinus". The IHS defines migraine as of 4-72 hours duration when untreated coupled with particular features, i.e. pulsating pain on one side (40% are two-sided, however), affecting the face plus head. In a small number of cases pain is localised to the orbit alone and even more unusually, just the cheek and nose; there is often a prodrome, with 20-30% of sufferers describing an aura that may often affect vision. There are two principal variants: migraine minus aura (which used to be referred to as common migraine and affects around 75% of sufferers) and migraine plus aura (also known as classic migraine, affecting around 25%). Females have 3 times the likelihood of the condition and family history is common [45].

The onset of an aura is 5-20 minutes and typically finishes within an hour. Headaches then typically commence less than 60 minutes after the aura has stopped, albeit on occasion the headache may not begin for several hours, and there may be sporadic absence of pain. 64% of attacks have no preceding migraine and this is the most usual type [46].

Migraines trigger action from the trigemino-vascular afferent nerves, leading to greater vascular perfusion of the dura mater [47]. The pain may occur in tandem with photophobia, acoustic hyperresponsivity and gut symptoms, e.g. nausea and vomiting.

Tension-type headaches (TTHs)

More than 70% of some populations describe having headaches of episodic tension-type, making it the most common of all headaches. However, the exact annual prevalence seemingly differs, being, on average, 42% amongst adults, with females more commonly affected than males. The chronic form has a prevalence of 1-3% [43]. TTH occurs bilaterally, tends to recur, has a duration of between minutes and weeks and is accompanied by a feeling of pressure or constriction that ranges from mildly to moderately severe. Usually none of the features that characterise migraine, such as nausea and vomiting, are present. However, excessive sensitivity to sounds or light may occur [48]. Frequently, no identifiable worsening or relieving factors are identified, even if sufferers may notice that bending forward worsens the situation, which may then lead to incorrectly ascribing the symptoms to pathology of the sinuses. The soft tissues may become sensitive to touch in TTH and may extend over the whole skull, with muscles being acutely tender and certain points, when touched, producing the sensation of pain. Notably, pressing for a long time on one point may result in pain referred elsewhere.

To diagnose TTH, the clinician must take a meticulous history, since the diagnosis hinges on identifying how long pain lasts, what type it is and how marked, alongside demonstrating clearly that concurrent symptomatology e.g. nausea and vomiting is absent. Asking what sets off or worsens an attack is valuable since TTH is both precipitated and aggravated by psychological pressure, lack of sleep and eating inadequately. It also helps when counselling patients about changing their lifestyle to cut down on the number of headaches and their severity when they do occur [49].

Trigeminal autonomic cephalalgias (TACs)

a) Cluster headache

Cluster headache is rather rare, but severe. It is a primary headache and typically consists of one-sided headaches that recur and classically interrupt sleep. Generally, the same side is affected each time and the pain is exceptionally severe at certain times. The episodes last from 15 min to 3 hours and affect the area behind the orbit or the mid-orbit. There is an accompanying autonomic neuropathy on the same side leading to nasal discharge, tearing and inability to sweat (due to parasympathetic activity), coupled with tiny pupils and ptosis (resulting from sympathetic outflow). It is periodic (which may reflect a circadian rhythm) and the attacks are present for 8 to 10 weeks a year, although there should be an entirely asymptomatic interlude of no less than a fortnight between attacks. Around 15 to 20% of sufferers with cluster headaches of a chronic type do not have asymptomatic interludes. They do not experience prodromal symptoms nor aura [50]. Alcoholic drinks such as red wine or nitroglycerin may set off an episode during times when patients are symptomatic, or for those with a chronic form of the disorder. The classical presentation is in a male aged 20 to 40. Males are, in fact, six times more likely to have the disorder than females [51].

b) Paroxysmal hemicrania

Paroxysmal hemicrania causes extreme one-sided pain,

generally around the eyes and the forehead, which lasts between 2 and 45 minutes. While the usual presentation is unilateral, bilateral attacks also occur. The mean age at first episode is within the fourth decade of life, but the age range affected encompasses 6 to 81. The episodic variant affects younger patients and typically causes attacks to happen frequently, generally 5 times daily. Remission may be between three months and three years. At least one feature of autonomic dysfunction must be observed: blocked nose, nasal discharge, tearing, bloodshot eyes, ptosis, swollen eyelid, altered cardiac rhythm (brady- or tachy-cardic, extrasystole), localised epiphora, saliva production and flushing of the face [52].

c) Hemicrania continua

This condition shares the feature with chronic paroxysmal hemicrania of being a one-sided headache that shows definite responsivity to indomethacin. Its severity is moderate, does not switch sides and the pain is unswerving, albeit allowing for variations in intensity and peak intensity brought about by autonomic dysfunction (bloodshot eyes, tearing and avoiding bright light on the side involved) [53].

d) Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome

SUNCT comprises a syndrome of headaches of unknown aetiology, which is distinguished by pain over the trigeminal distribution, especially around and within the orbit, and has associated autonomic features (bloodshot eyes and lacrimation). The duration of attacks is 15 seconds to 1 minute and happens anywhere between 5 and 30 times each hour. The action of chewing and eating sour-tasting foods can trigger episodes [54].

Secondary headaches, involving cranial nerves

Trigeminal neuralgia

The abrupt onset of sharp, stab-like pains that endure from a matter of seconds to under 2 minutes and recur several times during a brief interval, where such pains are brought on by a sensory or mechanical stimulus, supports a diagnosis of cranial neuralgia. The majority of facial neuralgias follow a similar pattern [55]. By far the most common of these is trigeminal neuralgia. It is well known that extreme stabbing pains occur in waves following stimulation of a particular trigger point. While both maxillary and mandibular branches are affected in many cases (CNV2 and CNV3), one in five trigeminal neuralgias involves only the maxillary branch. Only 4% of trigeminal neuralgias are confined to the ophthalmic branch (CNV1) [56].

Trigeminal neuralgia may occur without any trigger or may come about through sensation originating in specific facial regions (cheek, chin, lips or tongue). Such origins generally correspond to where the pain is. The usual triggers are touch to the face, washing, shaving, cleaning teeth, or mastication. Facial flushing may be observed. During its natural history, the frequency of painful attacks increases, and the asymptomatic intervals shorten. While it is frequent for the disease to remit, it may also worsen. If the sufferer is young, MRI evaluation is necessary to exclude other conditions such as widespread sclerosis or neoplasms (e.g. meningioma or neuroma) of the posterior fossa.

Other nerve-related conditions

Glossopharyngeal neuralgia is a seldom-encountered condition in which pain occurs in sudden flare-ups, and affects the pharynx, lingual base, velum and tonsillar fossae, potentially extending to the lower jaw angle or, unusually, the external acoustic meatus [57]. Frequently, deglutition, mastication, speech, laughter or coughing. Occipital neuralgia, nervus intermedius (geniculate) and supraorbital neuralgia are much less frequently seen conditions. Charlin's neuralgia and Sluder's neuralgia generally affect the medial ocular angle. In most cases, the pain goes towards the superciliary, orbital or nasal and mandibular regions. Tearing, bloodshot eyes, blocked nose, sternutation and frontal erythema are characteristic signs/symptoms [58 59]. This pattern is, therefore, hard to disentangle from the separate cluster headache phenomenon.

Persistent idiopathic facial pain

The other term for this condition, atypical facial pain, is preferred by the IHS. The pain is unremitting, deeply felt and frequently only affects one side. Patients frequently give an unclear and changeable account of their symptoms, describing pain that affects multiple areas including the face and other regions of the head and neck. Many times, they have already had sinus operations or dental treatment and may be displeased about the outcome. A somewhat frequent situation is a history of traumatic injury to the nose. Numerous sufferers from atypical facial pain have noticeable psychological difficulties or have had depression and the pain interferes with their normal functioning. Most often the patient is a female aged above 40 years. Detailed physical assessment, encompassing nasal endoscopy, is mandatory, and an MRI would be a worthwhile precaution before settling on atypical pain as a final diagnosis.

Differential diagnosis

The history must include information on what the patient recalls about previous pain episodes if the diagnosis is to

accurately reflect an origin in the sinuses or not. More specifically, there must be recollection of: time course (when it started, how long it lasts and how frequently it occurs); site and where it spreads to (e.g. does it follow the distribution of a nerve?); type of pain and how marked; how it responds to pharmacological intervention; what helps and what makes it worse (such as eating hot, cold or sweet items, chewing a long time, swallowing, cleaning teeth, facial touch, weather conditions, doing particular things, posture, being stressed or tired); other factors (effect on taste, amount of saliva, clenching or grinding teeth, TMJ problems, changed sensation, symptoms affecting the nose, eyes or ears); effect on sleep, mood, ability to focus, tiredness level, associated thoughts and general life quality.

Just as with other chronic pain syndromes, mental status, family and social history and important life happenings all merit consideration. Physical examination may reveal different colouration, oedema and cutaneous lesions. Cranial nerves should be assessed. Since pain is a subjective phenomenon, the use of special questionnaires may help. The Brief Pain Inventory, Beck Depression Inventory, Hospital Anxiety and Depression Scale and McGill Pain Questionnaire have adequate sensitivity and validation [60 61]. Other than when assessing cranial arteritis or auto-immune pathologies, such as Sjögren's syndrome, in vitro and pathological tests are of no help [62].

The AAO-HNS advises that rhinosinusitis diagnosis depends critically on the use of nasal endoscopy and radiology. For instance, there are reports of disease mimicry occurring due to other conditions [63]. Hyperaemic mucosae and pus-containing secretions are frequent findings at endoscopy. In situations where the patient has no symptoms and endoscopy reveals no abnormality, a repeated endoscopy during a symptomatic period is of value. Nevertheless, it is worth bearing in mind that migraine attacks have also been shown to be associated with oedema of the lining of the nose [11]. Endoscopy can also beneficially identify sites of mucosal impingement, although the existence of such contact points does not invariably correlate with an origin for pain in the sinuses [23], even where inflammation and infection are present.

Plain X-ray views of the sinuses may support a diagnosis of acute bacterial rhinosinusitis, but for chronic rhinosinusitis, they lack both sensitivity and specificity. For certain disorders, CT or MRI are indicated, but CT may give a misleading impression about the sinuses since approximately 30% of normal subjects have the appearance of thickened mucosae and the area of increased opacification on CT has no relation to where pain is actually felt. Hence, increased opacification need not mean the pain is sinogenic [61]. Evaluating CT scans using different methods of scoring (Harvard and Kennedy) failed to improve the correlation [64] and, indeed, only a weak association existed between CT appearances as scored using Lund-Mackay and the degree of chronic rhinosinusitis [65]. Mehle studied a group of individuals who referred themselves for a "sinus headache" and discovered that scores using Lund-Mackay criteria are not significantly different for the presence or absence of migraine.

Differences apparent clinically between sinus and non-sinus origin headache are outlined in Table III.

Conclusions

Individuals suffering from chronic facial pain experience significant changes in their lives and functioning. Identi-

Table III. Differences between sinogenic and non-sinogenic pain in term of clinical features.

Features	Sinogenic pain	Non-sinogenic pain
Severity of pain	Mild/moderate	Moderate/severe
Quality of pain	Pressure/congestion	Pulsatile/tightening/excruciating
Duration	> 72 hours	< 72 hours
Location	Frequently unilateral and depending on the sinus of origin.	Unilateral/bilateral. Poor correlation between the site of facial pain and sinuses anatomy.
Triggers	Variations in atmospheric pressure (e.g. flying, skiing, diving)	Exercises, menstrual cycle, certain foods (e.g. chocolate, cheese)
Frequently associated features	Nasal blockage, congestion or discharge. Reduction/loss of smell	Nausea, vomiting, phono/photofobia, +/– aura, monolateral conjunctival injection
ENT examination	Nasal congestion, mucosal oedema and purulent nasal discharge	No abnormalities or nasal mucosal congestion
Nasal endoscopy	Purulent nasal discharge (anterior/ posterior), mucosal oedema, +/– polyps, occlusion of osteomeatal complex and/or spheno-etmhmoidal recess	No abnormalities or nasal mucosal congestion
CT scan	Sinuses opacification; osteomeatal complex and/or spheno-etmhmoidal recess occlusion	No abnormalities

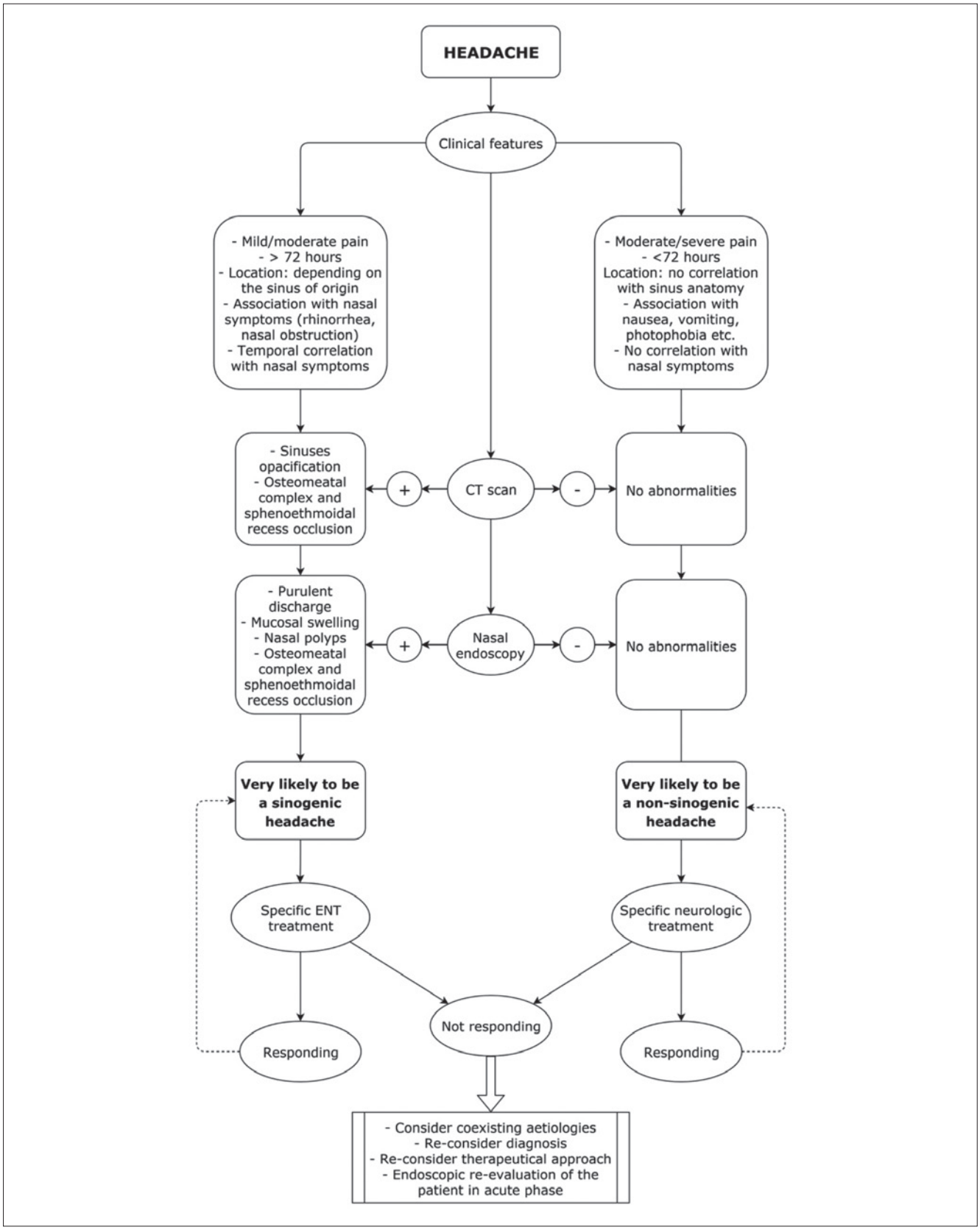

Fig. 1. Specific algorithm for thoroughly investigating the aetiology of facial pain.

fying the likely cause and treating appropriately may represent a clinical challenge and currently much remains to be discovered about the underlying pathology. Significant attempts have been made to separate different disorders on the basis of clinical features. The most usual way of classifying individuals is in terms of the underlying pathology. For a number of conditions, e.g. trigeminal neuralgia or cluster headache, clinical definitions are well established, despite the lack of confirmatory diagnostic investigations. One method of confirming the clinical impression is by observing the response to treatment. The current classification scheme suffers, however, from being inadequate for numerous cases that do not easily fit in one category, and for having a significant degree of overlap between syndromes.

The aim of this study is to highlight the optimal ways in ENT to diagnose facial pain arising from the sinuses. The published research indicates that nasal endoscopy is more specific than CT in the diagnosis of rhinosinusitis. Where nasal endoscopy is negative, the likelihood that pain in the face is sinogenic is very low. Pain originating in the sinuses is not likely to occur where the interior of the nose has neither pus-filled secretion nor swollen mucosae, and this is especially so where there is pain at the time of examination or in the recent past. A normal endoscopy on a symptom-free day may, however, need to be repeated during an episode of pain.

Facial pain or pressure, if unaccompanied by other clinical features pointing to nasal involvement, is rarely the result of sinus pathology. In any case, it is noteworthy that blockage of the nose with or without a clear nasal discharge may co-occur with facial pain elicited by vascular problems. Such a situation is, nonetheless, typically of short duration, seldom exceeding 72 hours.

For individuals experiencing unremitting pain of identical distribution bilaterally, midfacial segment pain is a diagnosis of exclusion. Where patients come with a history of recurrent acute rhinosinusitis but are asymptomatic at interview, they should return when symptoms recur. Given the rarity of bacterial rhinosinusitis, a vascular origin for their pain is a distinct possibility.

In this article, we have compared the differing features of sinogenic and non-sinogenic pain in a comprehensive way. Inappropriately classifying the reason for facial pain may explain treatment failures. Inappropriate diagnosis and consequent treatment appear to be common, from the epidemiological data we have gathered. Individuals having facial pain, but no corroborating sinus pathology at endoscopy, have a minimal chance of rhinosinusitis and thus are unlikely to benefit from operations or pharmacological interventions intended for sinus disease. Managing those with sinus pressure or fullness, facial pain, or headache can represent a clinical challenge, and this is best addressed using an approach that identifies the aetiology, whether rhinosinusitis, neurogenic or some other pathology. ENT practitioners are well-placed to assist in most cases of facial pain since their specialty is able to pinpoint the underlying aetiology, whether sinogenic or not. Figure 1 summarises our suggested clinical algorithm, which can help clinicians identify the underlying cause.

Conflict of interest statement

None declared.

References

1 Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders*. 3rd edition. Cephalalgia 2018;38:1-211.

2 Mertens E. *Modifying factors on perception and expression of pain.* Pflege Z 2007;60:312.

3 Lerman SF, Rudich Z, Brill S. *Longitudinal associations between depression, anxiety, pain, and pain-related disability in chronic pain patients.* Psychosom Med 2014;77:333-41.

4 West B, Jones NS. *Endoscopy-negative, computed tomography negative facial pain in a nasal clinic.* Laryngoscope 2001;111:581-6.

5 Fahy C, Jones NS. *Nasal polyposis and facial pain.* Clin Otolaryngol 2001;26:510-3.

6 Gelardi M, Iannuzzi L, De Giosa M, et al. *Non-surgical management of chronic rhinosinusitis with nasal polyps based on clinical-cytological grading: a precision medicine-based approach.* Acta Otorhinolaryngol Ital 2017;37:38-45.

7 Walliczek-Dworschak U, Diogo I, Strack L, et al. *Indication of cone beam CT in head and neck imaging in children.* Acta Otorhinolaryngol Ital 2017;37:270-5.

8 Tarabichi M. *Characteristics of sinus-related pain.* Otolaryngol Head Neck Surg 2000;122:84-7.

9 Jones NS, Cooney TR. *Facial pain and sinonasal surgery*. Rhinology 2003;41:193-200.

10 Graff-Radford SB. *Facial pain.* Curr Opin Neurol 2000;13:291-6.

11 Cady RK, Schreiber CP. *Sinus headache: a clinical conundrum.* Otolaryngol Clin North Am 2004;37:267-88.

12 Lal D, Rounds A, Dodick DW. *Comprehensive management of patients presenting to the otolaryngologist for sinus pressure, pain, or headache.* Laryngoscope 2015;125:303-10.

13 Barbanti P, Fabbrini G, Pesare M, et al. *Unilateral cranial autonomic symptoms in migraine.* Cephalalgia 2002;22:256-9.

14 Schreiber CP, Hutchinson S, Webster CJ, et al. *Prevalence of migraine in patients with a history of self-reported or physician-diagnosed "sinus" headache.* Arch Intern Med 2004;164:1769-72.

[15] Eross E, Dodick D, Eross M. *The Sinus, Allergy and Migraine Study (SAMS)*. Headache 2007;47:213-24.

[16] Mehle ME, Kremer PS. *Sinus CT scan findings in "sinus headache" migraineurs*. Headache 2008;48:67-71.

[17] Perry BF, Login IS, KSE. *Nonrhinologic headache in a tertiary rhinology practice.* Otolaryngol Head Neck Surg 2004;130:449-52.

[18] Lipton RB, Manack Adams A, Buse DC, et al. *Migraine diagnosis and treatment: results from the American Migraine Study II*. Headache 2001;41:1280-9.

[19] Lee JH. *Underestimation of rhinogenic causes in patients presenting to the emergency department with acute headache.* Acta Neurol Taiwan 2015;24:37-42.

[20] Aaseth K, Grande RB, Kvaerner K, et al. *Chronic rhinosinusitis gives a ninefold increased risk of chronic headache. The Akershus study of chronic headache.* Cephalalgia 2010;30:152-60.

[21] Farri A, Enrico A, Farri F. *Headaches of otolaryngological interest: current status while awaiting revision of classification. Practical considerations and expectations.* Acta Otorhinolaryngol Ital 2012;32:77-86.

[22] Berg O, Carenfelt C. *Analysis of symptoms and clinical signs in the maxillary sinus empyema.* Acta Otolaryngol 1988;105:343-9.

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

[24] Clifton NJ, Jones NS. *Prevalence of facial pain in 108 consecutive patients with paranasal mucopurulent discharge at endoscopy.* J Laryngol Otol 2007;121:345-8.

[25] Hirsch AG, Stewart WF, Sundaresan AS, et al. *Nasal and sinus symptoms and chronic rhinosinusitis in a population-based sample.* Allergy 2017;72:274-81.

[26] Gamerra M, Cantone E, Sorrentino G, et al. *Mathematical model for preoperative identification of obstructed nasal subsites.* Acta Otorhinolaryngol Ital 2017;37:410-5.

[27] Gelardi M, De Candia N, Quaranta N, et al. *The relevance of counseling in patients with nasal polyps.* Acta Otorhinolaryngol Ital 2016;36:326-7.

[28] Morgenstein KM, Krieger MK. *Experiences in middle turbinectomy.* Laryngoscope 1980;90:1596-603.

[29] Anselmo-Lima WT, de Oliveira JA. *Middle turbinate headache syndrome.* Headache 1997;37:102-6.

[30] Greenfield DP. *Diagnosis and clinical management of headaches.* CNS Spectr 1999;4:32-47.

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

[32] Stammberger H, Wolf G. *Headaches and sinus disease: the endoscopic approach.* Ann Otol Rhinol Laryngol 1988;134:3-23.

[33] Harrison L, Jones NS. *Intranasal contact points as a cause of facial pain or headache: a systematic review.* Clin Otolaryngol 2013;38:8-22.

[34] Abu-Bakra M, Jones NS. *Prevalence of nasal mucosal contact points in patients with facial pain compared with patients without facial pain.* J Laryngol Otol 2001;115:629-32.

[35] Falco JJ, Thomas AJ, Quin X, et al. *Lack of correlation between patient reported location and severity of facial pain and radiographic burden of disease in chronic rhinosinusitis.* Int Forum Allergy Rhinol 2016;6:1173-81.

[36] Moretz WH, Kountakis SE. *Subjective headache before and after endoscopic sinus surgery.* Am J Rhinol 2006;20:305-7.

[37] Senior BA, Kennedy DW, Tanabodee J, et al. *Long-term results of functional endoscopic sinus surgery.* Laryngoscope 1998;108:151-7.

[38] Boonchoo R. *Functional endoscopic sinus surgery in patients with sinugenic headache.* J Med Assoc Thai 1997;80:521-6.

[39] Cook PR, Nishioka GJ, Davis WE, et al. *Functional endoscopic sinus surgery in patients with normal computed tomography scans.* Otolaryngol Head Neck Surg 1994;110:505-9.

[40] Cummings CW. *Otolaryngology: head and neck surgery*. 4th edition. Mosby; 2005.

[41] Yüce S, Akal A, Doğan M, et al. *Results of endoscopic endonasal dacryocystorhinostomy.* J Craniofac Surg 2013;24:e11-2.

[42] Lanteri-Minet M. *Economic burden and costs of chronic migraine.* Curr Pain Headache Rep 2014;18:385.

[43] Stovner LJ, Hagen K, Jensen R, et al. *The global burden of headache: a documentation of headache prevalence and disability worldwide.* Cephalalgia 2007;27:197-210.

[44] Steiner TJ, Scher AI, Stewart WF, et al. *The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity.* Cephalalgia 2003;23:519-27.

[45] Kelman L. *The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs.* Headache 2004;44:865-72.

[46] Truong T, Slavin L, Kashani R, et al. *Prevalence of migraine headaches in patients with congenital heart disease.* Am J Cardiol 2008;101:396-400.

[47] Pietrobon D, Moskowitz MA. *Pathophysiology of migraine.* Annu Rev Physiol 2013;75:365-91.

[48] Sahler K. *Epidemiology and cultural differences in tension-type headache.* Curr Pain Headache Rep 2012;16:525-32.

[49] Freitag F. *Managing and treating tension-type headache.* Med Clin North Am 2013;97:281-92.

[50] Bernstein JA, Fox RW, Martin VT, et al. *Headache and facial pain: differential diagnosis and treatment.* J Allergy Clin Immunol Pract 2013;1:242-51.

[51] Lanteri-Minet M. *Epidemiology, clinical presentation, diagnosis, natural history and screening of cluster headache.* Presse Med 2015;44:1176-9.

[52] Prakash S, Patell R. *Paroxysmal hemicrania: an update.* Curr Pain Headache Rep 2014;18:407.

[53] Viana M, Tassorelli C, Allena M, et al. *Diagnostic and therapeutic errors in trigeminal autonomic cephalalgias and hemicrania continua: a systematic review.* J Headache Pain 2013;14:14.

[54] Pomeroy JL, Nahas SJ. *SUNCT/SUNA: a review.* Curr Pain Headache Rep 2015;19:38.

[55] Cheshire WPJ. *Cranial neuralgias.* Continuum (Minneap Minn) 2015;21:1072-85.

[56] Maarbjerg S, Gozalov A, Olesen J, et al. *Trigeminal neuralgia: a prospective systematic study of clinical characteristics in 158 patients.* Headache 2014;54:1574-82.

[57] Reddy GD, Viswanathan A. *Trigeminal and glossopharyngeal neuralgia.* Neurol Clin 2014;32:539-52.

[58] Oomen KP, Van Wijck AJ, Hordijk GJ, et al. *Sluder's neuralgia: a trigeminal autonomic cephalalgia.* Cephalalgia 2010;30:360-4.

[59] Vinken PJ, Bruyn GW. *Charlin's neuralgia.* In: Rose FC, editor. *Headache: handbook of clinical neurology.* Amsterdam: Elsevier; 1986. p. 483-86.

[60] DeConde AS, Mace JC, Ashby S, et al. *Characterization of facial pain associated with chronic rhinosinusitis using validated pain evaluation instruments.* Int Forum Allergy Rhinol 2015;5:682-90.

[61] Smarr KL, Keefer AL. *Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS) and Patient Health Questionnaire-9 (PHQ-9).*Arthritis Care Res 2011;63:S454-66.

[62] Jones NS. *Sinogenic facial pain: diagnosis and management.* Otolaryngol Clin North Am 2005;38:1311-25.

[63] Batra PS, Setzen M, Li Y, et al. *Computed tomography imaging practice patterns in adult chronic rhinosinusitis: survey of the American Academy of Otolaryngology Head and Neck Surgery and American Rhinologic Society membership.* Int Forum Allergy Rhinol 2015;5:506-12.

[64] Shields G, Seikaly H, LeBoeuf M, et al. *Correlation between facial pain or headache and computed tomography in rhinosinusitis in Canadian and U.S. subjects.* Laryngoscope 2003;113:943-5.

[65] Hopkins C, Browne JP, Slack R, et al. *The Lund-Mackay staging system for chronic rhinosinusitis: how is it used and what does it predict?* Otolaryngol Head Neck Surg 2007;137:555-61.

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HEAD AND NECK

The supraclavicular artery island flap (SCAIF) in head and neck reconstruction: an Italian multi-institutional experience

Il lembo peduncolato sovraclaveare (SCAIF) nella ricostruzione del distretto testa-collo: esperienza multicentrica italiana

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SUMMARY

The supraclavicular artery island flap (SCAIF) is a thin and pliable pedicled flap that is easy and quick to harvest. Thanks to its particular features and high reliability, it is best indicated for the elderly or most fragile patients. SCAIF is very versatile, as it can be used for reconstruction of oral cavity, oropharynx, hypopharynx, facial and cervical skin and tracheostomal defects. We began using this flap in four Italian tertiary referral centres, with several indications, both as first treatment and as salvage surgery. The aim of the study was to demonstrate the easy reproducibility of the flap among four different centres. A series of 28 patients underwent head and neck reconstructions with SCAIF with no recorded complications during flap harvesting. After the very first cases, harvesting time was approximately 45 minutes; 24 patients had successful flap integration at the recipient site, while the remaining 4 suffered from partial flap necrosis, two of whom needed revision surgery. Other minor complications were reported at the recipient site, always at the most distal and most delicate portion of the flap. Donor site was always closed primarily, with only three cases of partial suture dehiscence. We only selected the most fragile patients for SCAIF reconstruction, such as the elderly or those with one or more comorbidities; for this reason, we reported some serious systemic complications and one intraoperative death. SCAIF is an easy reproducible flap, with multiple possible indications. Its use as an alternative to free flaps in the head and neck region is nowadays under discussion. Its use should be encouraged among head and neck surgeons thanks to its various advantages.

KEY WORDS: Supraclavicular flap • Head and neck reconstruction • Pedicled flap • Fragile patients

RIASSUNTO

Il lembo peduncolato sovraclaveare è un lembo sottile e malleabile, facile e veloce da scolpire. Grazie alle sue peculiari caratteristiche e alla sua alta affidabilità trova un'ottima possibilità di utilizzo nei pazienti più anziani o più compromessi. Si tratta di un lembo molto versatile, che può essere utilizzato per ricostruzioni del cavo orale, dell'orofaringe, dell'ipofaringe, della cute della regione della faccia e del collo e dei difetti del tracheostoma. Abbiamo iniziato ad utilizzare il lembo sovraclaveare in quattro centri italiani di riferimento, con diverse indicazioni, sia come prima scelta ricostruttiva, sia come terapia di salvataggio. Con il presente studio ci si propone di dimostrare la agevole riproducibilità del lembo nei quattro diversi centri. 28 pazienti sono stati trattati con ricostruzione del distretto testa-collo mediante lembo peduncolato sovraclaveare, senza evidenza di complicanze durante l'allestimento del lembo. Dopo i primissimi casi, il tempo di allestimento si è stabilizzato attorno ai 45 minuti. In 24 casi si è verificata un'ottima integrazione del lembo nel sito ricevente, mentre i restanti 4 pazienti hanno sofferto una parziale necrosi del lembo, e 2 di essi hanno necessitato di una revisione chirurgica. Altre complicanze minori sono state riscontrate a carico del sito ricevente, sempre a livello della porzione distale e più delicata del lembo. Il sito donatore è sempre stato chiuso mediante sutura diretta, con solo tre casi di parziale deiscenza della ferita. Sono stati selezionati per ricostruzione mediante lembo peduncolato sovraclaveare solo i pazienti più delicati, ovvero i più anziani o coloro che soffrivano di una o più comorbidità; per questo motivo abbiamo riportato alcune complicanze sistemiche severe e persino un caso di morte intraoperatoria. Il lembo peduncolato sovraclaveare è un lembo riproducibile, con multiple possibili indicazioni. Nonostante il suo utilizzo in alternativa ai lembi liberi nelle ricostruzioni del distretto testa-collo rimanga dibattuto, il lembo peduncolato sovraclaveare dispone di numerosi vantaggi e pertanto il suo impiego andrebbe incoraggiato tra i chirurghi che si occupano di chirurgia ricostruttiva.

PAROLE CHIAVE: *Lembo sovraclaveare • Ricostruzione testa-collo • Lembo peduncolato • Pazienti delicati*

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Introduction

The supraclavicular artery island flap (SCAIF) is a fasciocutaneous pedicled flap that is gaining an increased popularity over recent years, thanks to its high versatility, and has been proposed for reconstruction of many head and neck defects. The SCAIF is harvested from the supraclavicular and deltoid region and can be transferred to the head and neck region, thanks to an arc of rotation ranging up to 180°. This flap is a precious option for skin reconstruction due to similar colour and texture to the nearby skin, but at the same time it is useful for reconstructing all the defects of head and neck regions, because it can be de-epithelialised and tunnelled into the neck.

The flap is hairless, thin and pliable, and has been proposed as a valid alternative to free flaps [1], especially to the radial forearm free flap (RFFF). In fact, SCAIF is easy and quick to harvest, and as it is pedicled it does not require a dedicated team for microsutures. It has been proposed as a first choice flap for patients who would benefit from shorter and simpler procedures because of comorbidities [2].

The flap is known since the beginning of the 19th century, but was abandoned because of the high number of complications, probably caused by the scarce knowledge of the vascular anatomy of the shoulder. In the 1990s, Pallua [3 4] recovered this flap for facial and cervical skin reconstruction after burn injuries, and subsequently in 2009 Chiu [5] first used it for head and neck reconstruction after oncologic surgery. Since then, multiple reports about SCAIF appeared in the literature [6-10], and in a recent review it was proposed as a possible reconstructive option for the floor-of-mouth and hypopharynx [11].

The flap is based on the supraclavicular artery, a branch of the transverse cervical artery; the vessel diameter generally ranges between 1.1 and 1.5 mm. The venous drainage originates from venae comitantes running together with the artery and reaches the transverse cervical vein or the external jugular vein [4 5]. A major cutaneous nerve from the cervical plexus is found in most cases, located 1-2 cm anterior to the pedicle toward the clavicle [12].

The Italian experience in SCAIF application is limited, but recently consensus is increasing [2 13].

Popularity of the SCAIF use may be encouraged by its easy and quick harvesting and by its multiple possible applications. In this paper, we present the experience with SCAIF reconstruction from four Italian Head and Neck Surgery Departments. The present study aims at evaluating the reproducibility of the flap, and underlining indications, outcomes and complications, in order to increase awareness about the advantage of SCAIF as an alternative to free flaps for moderate to large defects of the head and neck region.

Materials and methods

Since October 2012 to April 2017, a series of 28 patients (53-95 years old, 16 males and 12 females) underwent reconstructions with SCAIF in 4 Italian tertiary referral hospitals ("San Raffaele" Hospital in Milan, "Policlinico San Matteo" in Pavia, "Ospedale Policlinico San Martino" in Genoa and University Hospital of Brescia). Table I shows demographic data.

All the patients were affected by locally advanced head and neck malignancies, recurrent cancers or failure of previous reconstruction, except a case of a pT1 hypopharyngeal retrocricoid carcinoma in a patient who was previously irradiated for a tongue base lymphoma.

As a general rule, the use of SCAIF as a first choice flap for head and neck reconstructions was preferred for older patients or for those with the most serious comorbidities. All of our patients were affected by one or more comorbidities. Most suffered from cardiovascular or metabolic comorbidities, and 43% of them were affected by multiple comorbidities.

The supraclavicular artery arises from the transverse cervical artery. It is mandatory to demonstrate the presence of the artery and to locate it preoperatively. If the patient previously underwent a neck dissection, an angio-CT scan was preferred to demonstrate the artery. Otherwise, the artery was located and marked with a pencil Doppler probe. When used for hypopharyngeal reconstruction, the supraclavicular artery was searched bilaterally, and the most convincing side was chosen, to maximise the chances of flap survival.

All four centres follow the flap harvesting technique described by Kokot [10]. The pedicle is found in a triangular region between the posterior edge of the sternocleidomastoid muscle, the external jugular vein and the clavicle. Size of the flap was designed according to the distance of the site of reconstruction and extension of the defect. Flap rising was conducted from distal to proximal, dissecting it in a subfascial plane. The pencil Doppler probe may help to locate the artery intraoperatively. The flap is dissected until its most proximal portion, where the supraclavicular artery arises from the transverse cervical artery; in this region, the pedicle is surrounded by fascia and connective tissues: it can be demonstrated with a Doppler probe, and can be dissected without the need to expose the supraclavicular artery. At the same time, no particular effort was made to locate and preserve the nervous pedicle of the flap.

After harvesting was completed (Fig. 1), the flap was rotated to reach the site of reconstruction and, in most cases, the intermediate portion of the flap was de-epithelialised

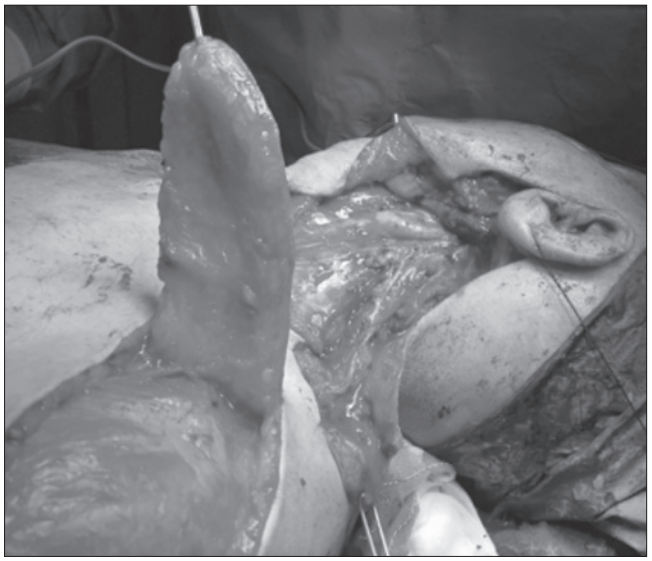

Fig. 1. SCAIF harvesting. The flap will be tunnelled and used for cervical skin reconstruction, with a 180° arc of rotation.

and the flap was tunnelled under the cervical skin. For facial and cervical skin reconstruction, the flap can be tunnelled or simply rotated to cover the defect (these latter cases are marked with an "*" in Table I). After simple rotation of the flap, the pedicle can be cut after at least 3 weeks to gain better aesthetic and functional outcomes.

Results

In Table II patient distribution between centres, indications and complications are shown. No intraoperative complications during flap harvesting were reported in any of the four institutions and none of our patients needed a postoperative ICU stay.

Harvesting time decreased from 55-60 minutes in the first cases to approximately 40-45 minutes in the latter ones.

24 of 28 (86%) patients had successful integration of the flap into the recipient site with closure of the defect (Fig. 2). The donor site was always sutured directly, avoiding a skin graft. Most of patients referred a sensation of great tension to the donor shoulder, which always disappeared within a few months.

When used for facial and cervical skin reconstruction, colour and texture of the flap were always very similar to those of the recipient site (Fig. 3).

Recipient site complications were always caused by desquamation or loss of the most distal portion of the flap. We reported one case of distal tip desquamation, which was managed with conservative treatment and healing by secondary intention. Partial flap loss occurred in 4 cases. It was treated conservatively in two cases, in which the SCAIF was used for cutaneous reconstructions. Revision surgery was needed for two patients who developed a pharyngocutaneous fistula, one after lateral oropharyngeal wall reconstruction and the other after revision surgery for a previous fistula after total pharyngolaryngectomy. None of the partial flap necrosis occurred to the 4 previously irradiated patients.

Considering the donor site, we observed three cases of dehiscence of the suture, which were all treated conservatively.

Table I. Patient demographics.

Mean age at surgery	72.6 years (range 53-95)
Sex	16 Male 12 Female
Site of the lesion	*Oral cavity* 3 SCC: - 1 pT2 pN2b – stage IV A - 2 pT4a pN0 – stage IV A
	Oropharynx 1 SCC: pT4a pN1 – stage IV A 1 AdCC: pT4a pN0 – stage IV A
	Hypopharynx 7 SCC: - 1 pT1 pN0 – stage I - 2 pT4a pN0 – stage IV A - 1 pT4a pN1 – stage IV A - 1 pT4a pN2a – stage IV A - 1 pT4a pN2b – stage IV A - 1 pT4a pN2c – stage IV A 5 Revision surgeries for pharyngocutaneous fistula
	Facial skin 1 Parotid Undifferentiated Carcinoma: pT4b pN2b – stage IV B * 5 Parotid SCC Metastases (1*)
	Cervical skin 3 SCC Metastases with skin invasion 2 SCC: - 1 pT3 pN0 – stage III * - 1 pT3 pN2b – stage IV *
Previous treatments	3 RT 1 CRT
Comorbidities	18 (64%) Cardiovascular – 12 HBP, 6 CAD, 6 arrhythmia (2 AF), 3 PAD, 1 CHF, 1 MI
	8 (29%) Metabolic – 7 Obesity, 2 Type 2 Diabetes
	4 (14%) Pulmonary – 4 COPD
	4 (14%) Neurologic – 2 stroke, 1 TIA, 1 Parkinson Disease
	4 (14%) Hepatic – 3 Chronic Hepatitis, 1 HCC
	2 (7%) Psychiatric – 2 MDD
	1 (4%) Autoimmune – SLE
	12 (43%) Multiple

*SCC: Squamous Cell Carcinoma; AdCC: Adenoid Cystic Carcinoma; HBP: High Blood Pressure; CAD: Coronary Artery Disease; AF: Atrial Fibrillation; PAD: Peripheral Artery Disease; CHF: Congestive Heart Failure; MI: Mitral Insufficiency; COPD: Chronic Obstructive Pulmonary Disease; TIA: Transient Ischaemic Attack; HCC: Hepatocellular Carcinoma; MDD: Major Depressive Disorder; SLE: Systemic Lupus Erythematous; *: cases in which the flap was simply rotated without tunnelling under cervical skin.*

Table II. Patient distribution between centres, indications and complications.

	Indications	Complications
Ospedale San Raffaele Milan	4 CCR 3 FCR 3 HPR 2 OCR 2 OPR	2 PFN 2 SSD 1 pulmonary embolism 1 peripheral artery thrombosis 1 intraoperative death
Policlinico San Matteo Pavia	1 HPR 1 CCR 3 R-HPR	1 PFN
Ospedale Policlinico San Martino Genoa	3 HPR 2 R-HPR 1 FCR	1 PFN 1 SSD 1 respiratory acidosis
University Hospital Brescia	2 FCR 1 OCR	1 sepsis

CCR: Cervical Cutaneous Reconstruction; FCR: Facial Cutaneous Reconstruction; OCR: Oral Cavity Reconstruction; OPR: Oropharyngeal Reconstruction; HPR: Hypopharyngeal Reconstruction; R-HPR: Revision surgery after previous Hypopharyngeal Reconstruction; PFN: Partial Flap Necrosis (< 50%); SSD: Shoulder Suture Dehiscence.

As we propose this flap preferentially for the elderly or for most fragile patients, we also report systemic complications. There was one case of intraoperative death at the end of a surgery for a lymph node metastasis with massive skin invasion from SCC of the helix. During SCAIF suturing the patient had a massive myocardial infarction and cardiac arrest.
4 of 28 (14%) patients reported serious postoperative systemic complications that were not related to the procedure itself, but to their general compromised conditions. Reported complications were sepsis, respiratory acidosis, pulmonary embolism and arterial thrombosis, but none of the patients died because of these complications.
Postoperative hospital stay was related to the site of reconstruction and presence of complications, being shorter after cutaneous reconstructions (5-15 days), and longer after oral cavity, oropharyngeal, or hypopharyngeal reconstructions (9-45 days).
SCAIF was used 11 times to cover a skin defect in the face or in the neck, and always demonstrated colour and texture that perfectly matched the site of reconstruction. Among these, the flap was simply rotated without tunnelling in 4 cases. In 2 patients, the pedicle was subsequently cut after at least 3 weeks; the remaining 2 patients refused cutting of the pedicle to maintain sensation on the skin flap.
Three patients (11%) reported some kind of sensation of the flap, which was referred as skin sensation after cutaneous reconstruction or wet sensation to the shoulder when drinking after hypopharyngeal reconstruction.

Discussion

The results of our initial experience with the SCAIF are similar to those reported in the literature [5-10]. This flap, although in our initial experience, was found to be safe and reliable in all four centres, with reproducible results.
The application of SCAIF in head and neck reconstructive surgery may offer a series of advantages. First, flap harvesting is easy and quick, and does not require microsurgical expertise. Vascular microsutures needed during free tissue transfer are time-consuming and expose the patient to eventual thrombotic complications of the anastomoses. In our experience, SCAIF harvesting time was quickly reduced after the very first cases, to approximately 45 minutes. Comparable harvesting times are reported in the literature [8 14 15]. The learning curve was very quick in all four centres, and no surgeon reported any difficulty in flap harvesting. Thanks to its reduced harvesting time, it is best indicated for the most fragile patients [2], who would benefit from simpler and shorter procedures.

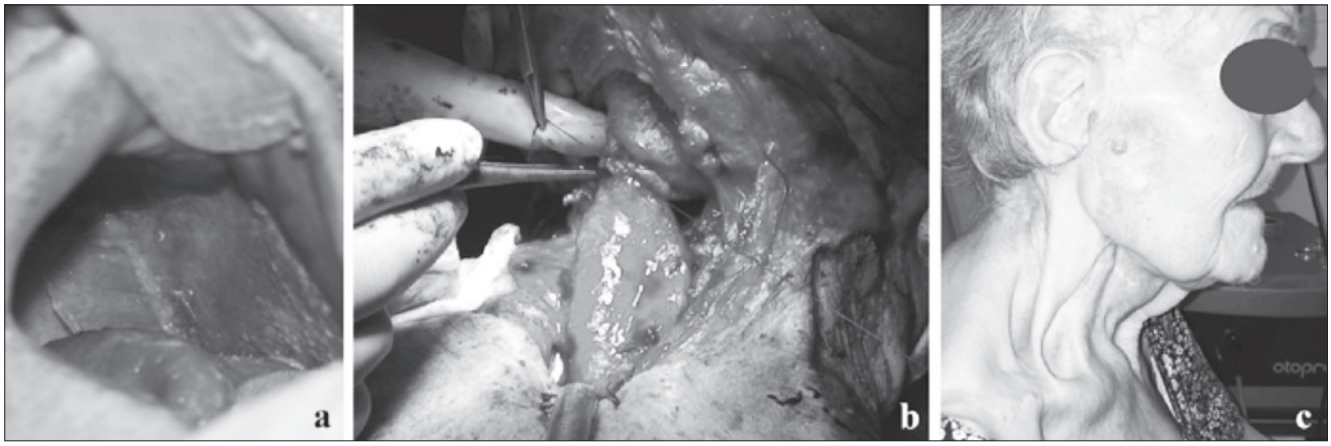

Fig. 2. Different indications to SCAIF reconstruction: oral cavity **(a)**, hypopharynx **(b)** and cervical skin **(c)**.

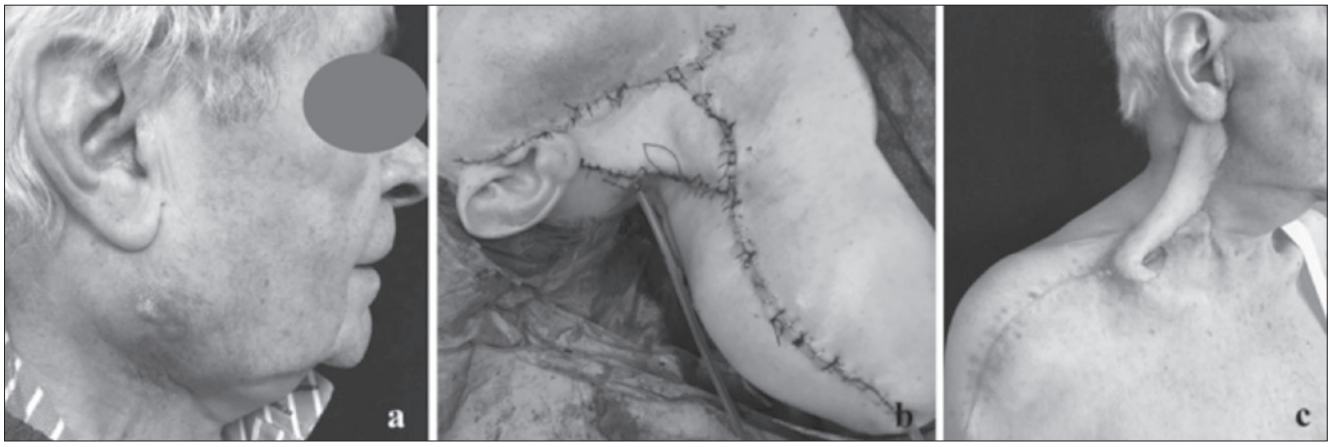

Fig. 3. Cervical skin reconstruction: preoperative appearance of a SCC lymph node metastasis involving cervical skin **(a)** and after tumour removal and SCAIF reconstruction **(b)**, demonstrating optimal colour and texture of the flap **(c)**.

Nonetheless, accurate preoperative assessment of flap feasibility is advisable. SCAIF is pedicled on the supraclavicular artery, a branch of the transverse cervical artery. The pencil Doppler probe is a very useful tool to locate the artery both preoperatively and intraoperatively [9 10]. However, in our experience it can sometimes be hard to draw the course of the artery preoperatively. If there is any doubt about the presence and location of the supraclavicular artery, angio-CT [16] can be a valuable resource to aid in safe flap harvesting. This is especially true for patients who already underwent previous surgeries on the neck, as the transverse cervical artery is encountered during dissection of the lower portion of Robbins level IV [17], where it can be damaged.

The second advantage of SCAIF is its high versatility. We used SCAIF for facial and cervical skin, oral cavity, oropharynx and hypopharynx, always with good results. Similar applications are described in the literature [5-10 12-15]. In particular, SCAIF seems to be very useful for hypopharyngeal reconstructions [18] for several reasons: the flap can be harvested bilaterally, giving to the surgeon the possibility to choose the side with the most convincing pedicle; the site of reconstruction is very close, so that a shorter flap can be harvested, reducing possible complications to the distal portion; SCAIF can be harvested both in men and in women; SCAIF may also be used as a pharyngeal interposition flap to protect the suture of the neopharynx in a previously irradiated patient [18], even if in our series this was never attempted. Tracheostomal defects reconstruction have also been described with good results [18-20].

In addition, facial and cervical skin reconstructions are very satisfactory [3 4 7]. In our patients, colour and texture always showed a good match to the recipient site. SCAIF is a valid alternative even in cases of skin recurrence on previously irradiated fields or after previous surgeries, as skin transferred from the shoulder do not suffer from previous treatments. In fact, previous radiation therapy on the neck is not a contraindication to flap harvesting.

SCAIF is thin, pliable and hairless, providing a valid alternative for reconstruction of oral and oropharyngeal defects [8 10 14 15 21 22]. In our experience, to reach these sites it is necessary to harvest longer flaps with more potential complications.

A third advantage, but not less remarkable, is the reproducibility of SCAIF. Following the technique described by Kokot [10], our results were consistent in all four centres, with a low complication rate. Such a small number of complications is reported in the literature [2]. Notably, in our series all complications to the recipient site occurred at the distal portion of the flap. We reported both simple tip desquamation and partial flap loss. When harvesting the flap, it is mandatory to carefully check for bleeding at the distal portion, and to eventually trim the flap back if there is any doubt [10]. In fact, the distal portion is the most delicate area, as it may suffer from reduced vascularisation, being the terminal portion of the angiosome [4]. For this reason, longer flaps are more prone to develop complications: 3 of the 4 recipient site complications in our series occurred when reconstructing the most distant sites. It is reported that most complications occur in flaps longer than 22 cm, and to stop harvesting 5 cm beyond the point where the artery can be located with the Doppler [10]. Preoperative Doppler drawing of the artery and intraoperative Doppler check are crucial, especially if a long flap is needed. If the flap is used for reconstructing the floor of mouth, oropharynx or hypopharynx, even a simple distal tip desquamation may produce salivary infiltration, resulting in partial flap loss and consequent fistula: this even-

tuality was faced in the two cases that needed revision surgery.

Eventual flap loss does not preclude the possibility of other reconstructive options, including free tissue transfer. We never observed recipient site infections. In fact, SCAIF has a relatively low incidence of surgical site infections, and even in the setting of a surgical site infection it usually remains viable. Clean-contaminated surgeries are associated with an increased risk of infection [23].

Complications to the donor site are not frequent [2], as the skin of the shoulder can be widely undermined to slide and cover the defect [10]. In our series we reported one intraoperative death, as well as some systemic complications. None of these complications were related to the choice of the flap, but rather to patient selection. In our series, SCAIF was used in most fragile patients: longer and more complicated procedures, as for example during free flap reconstruction, may have caused even worse outcomes.

To reconstruct cervical or facial skin defects, the flap can be tunnelled under the skin or simply rotated to cover the defect. It has to be noted that if the flap is simply rotated, it doesn't really match the definition of "island" flap [24]. However, harvesting technique and potential complications are exactly the same, and the flap still lives on its axial vascular pedicle. For this reason, these cases (marked in Table I) were still included in our report.

It is still under discussion if SCAIF can be an alternative to free tissue transfer in head and neck reconstruction. Results obtained with SCAIF and with free flaps have been compared in only a few papers [1 15 25]. All found comparable or better results with SCAIF than with free flaps in terms of operative time, ICU stay, complications, hospitalisation and costs. Granzow [1] and Welz [15] refer that in their institutions, SCAIF has largely supplanted free flaps reconstruction techniques. Notwithstanding, these are all retrospective studies, with possible selection biases. A perspective multicentre randomised study comparing SCAIF and free flaps (in particular RFFF) is needed.

Recently, Pallua et al. modified the supraclavicular flap by introducing the anterior supraclavicular perforator flap, which is based on the anterior branch of the transverse cervical artery. This new flap is harvested in the deltopectoral fossa; it is thinner, more pliable and with a superior colour match to the face and neck skin [26]. It can even be pre-expanded to considerably increase its size [27].

Conclusions

SCAIF is a reliable and versatile alternative for head and neck reconstructions. It is quick and easy to harvest and is best suited to the most fragile patients. Its easy reproducibility is another advantage that hasn't been assessed previously. We began using the SCAIF in four Head and Neck Surgery Departments, with excellent and consistent results in all four centres. The very short learning curve, high versatility and possibility to use it as an alternative to free flap in selected cases should encourage head and neck surgeons to start using the SCAIF.

Conflict of interest statement

None declared.

References

1 Granzow JW, Suliman A, Roostaeian J, et al. *Supraclavicular artery island flap (SCAIF) vs free fasciocutaneous flaps for head and neck reconstruction*. Otolaryngol Head Neck Surg 2013;148:941-8.

2 Giordano L, Di Santo D, Occhini A, et al. *Supraclavicular Artery Island Flap (SCAIF): a rising opportunity for head and neck reconstruction*. Eur Arch Otorhinolaringol 2016;273:4403-12.

3 Pallua N, Machens H, Rennekampff O, et al. *The fasciocutaneous supraclavicular artery island flap for releasing postburn mentosternal contractures*. Plast Reconstr Surg 1997;99:1878-84.

4 Pallua N, Noah EM. *The tunneled supraclavicular island flap: an optimized technique for head and neck reconstruction*. Plast Reconstr Surg 2000;105:842-51.

5 Chiu ES, Liu PH, Friedlander PL. *Supraclavicular artery island flap for head and neck oncologic reconstruction: indications, complications, and outcomes*. Plast Reconstr Surg 2009;124:115-23.

6 Kim RJT, Izzard ME, Patel RS. *Supraclavicular artery island flap for reconstructing defects in head and neck region*. Curr Opin Otolaryngol Head Neck Surg 2011;19:248-50.

7 Sandu K, Monnier P, Pasche P. *Supraclavicular flap in head and neck reconstruction: experience in 50 consecutive patients*. Eur Arch Otorhinolaryngol 2012;269:1261-7.

8 Alves HR, Ishida LC, Ishida LH, et al. *A clinical experience of the supraclavicular flap used to reconstruct head and neck defects in late-stage cancer patients*. J Plast Reconstr Aesthet Surg 2012;65:1350-6.

9 Granzow JW, Suliman A, Roostaeian J, et al. *The supraclavicular artery island flap (SCAIF) for head and neck reconstruction: surgical technique and refinements*. Otolaryngol Head Neck Surg 2013;148:933-40.

10 Kokot N, Mazhar K, Reder LS, et al. *The supraclavicular artery island flap in head and neck reconstruction. Applications and limitations.* JAMA Otolaryngol Head Neck Surg 2013;139:1247-55.

11 Hanasono MH, Matros E, Disa JJ. *Important aspects of head and neck reconstruction*. Plast Reconstr Surg 2014;134:968-80.

[12] Sands TT, Martin JB, Simms E, et al. *Supraclavicular artery island flap innervation: anatomical studies and clinical implications*. J Plast Reconstr Aesthet Surg 2012;65:68-71.

[13] Giordano L, Bondi S, Toma S, et al. *Versatility of the supraclavicular pedicle flap in head and neck reconstruction*. Acta Otorhinolaryngol Ital 2014;34:394-8.

[14] Anand AG, Tran EJ, Hasney CP, et al. *Oropharyngeal reconstruction using the supraclavicular artery island flap: a new flap alternative*. Plast Reconstr Surg 2012;129:438-41.

[15] Welz C, Canis M, Schwenk-Zieger S, et al. *Oral cancer reconstruction using the supraclavicular artery island flap: comparison to free radial forearm flap*. J Oral Maxillofac Surg 2017;75:2261-9.

[16] Adams AS, Wright MJ, Johnston S, et al. *The use of multislice CT angiography preoperative study for supraclavicular artery island flap harvesting*. Ann Plas Surg 2012;69:312-5.

[17] Robbins KT, Shaha AR, Medina JE, et al. *Consensus statement on the classification and terminology of neck dissection*. Arch Otolaryngol Head Neck Surg 2008;134:536-8.

[18] Emerick KS, Herr MA, Deschler DG. *Supraclavicular flap reconstruction following total laryngectomy*. Laryngoscope 2014;124:1777-82.

[19] Pallua N, Wolter TP. *Defect classification and reconstruction algorithm for patients with tracheostomy using the tunneled supraclavicular artery island flap*. Langenbecks Arch Surg 2010;395:1115-9.

[20] Chu MW, Levy JM, Friedlander PL, et al. *Tracheostoma reconstruction with the supraclavicular artery island flap*. Ann Plast Surg 2015;74:677-9.

[21] Chen WL, Zhang DM, Yang ZH, et al. *Extended supraclavicular fasciocutaneous island flap based on the transverse cervical artery for head and neck reconstruction after cancer ablation*. J Oral Maxillofac Surg 2010;68:2422-30.

[22] Wu H, Chen WL, Yang ZH. *Functional reconstruction with an extended supraclavicular fasciocutaneous island flap following ablation of advanced oropharyngeal cancer*. J Craniofac Surg 2012;23:1668-71.

[23] Goyal N, Emerick KS, Deschler DG, et al. *Risk factors for surgical site infection after supraclavicular flap reconstruction in patients undergoing major head and neck surgery*. Head Neck 2016;38:1615-20.

[24] Kimyai-Asadi A, Goldberg LH. *Island pedicle flap*. Dermatol Clin 2005;23:113-27.

[25] Kozin ED, Sethi RK, Herr M, et al. *Comparison of perioperative outcomes between the supraclavicular artery island flap and fasciocutaneous free flap*. Otolaryngol Head Neck Surg 2016;154:66-72.

[26] Pallua N, Wolter TP. *Moving forwards: the anterior supraclavicular artery perforator (a-SAP) flap: a new pedicled or free perforator flap based on the anterior supraclavicular vessels*. J Plast Recontr Aesthet Surg 2013;66:489-96.

[27] Pallua N, Kim BS. *Pre-expanded supraclavicular artery perforator flap*. Clin Plast Surg 2017;44:49-63.

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HEAD AND NECK

The prognostic significance of E-cadherin expression in laryngeal squamous-cell carcinoma: a systematic review

Il significato prognostico dell'espressione di E-caderina nel carcinoma a cellule squamose della laringe: una revisione sistematica

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SUMMARY

The aim of this study was to systematically review publications that investigated the prognostic role of E-cadherin immunostaining in patients affected by laryngeal squamous cell carcinoma. An appropriate string was run on PubMed to retrieve articles dealing with this topic. A double cross-check was performed on citations and full-text articles by two authors independently to analyse all manuscripts and perform a comprehensive quality assessment. Among 89 abstracts identified, 13 articles were included. These studies reported on 1,121 patients with histologically confirmed diagnosis of laryngeal squamous cell carcinoma. Overall, there were 10 studies that showed a significant correlation between E-cadherin immunohistochemical expression and at least one of the clinical and histopathological parameters considered by the authors. In particular E-cadherin expression was significantly associated with N stage (five studies), grading (four studies) and disease-free survival/disease-specific survival (six studies). In conclusion, the findings of our review appear similar to the results published by other authors on the putative role of E-cadherin in progression of malignancy. In fact, for laryngeal squamous cell carcinoma it seems that lower levels of E-cadherin correlate with increased tumoural aggressiveness and worse prognosis. Nevertheless, further high-quality prospective studies should be carried out to clarify if E-cadherin expression may be considered as an independent prognostic factor for patients affected by laryngeal cancer.

KEY WORDS: Laryngeal squamous carcinoma • Immunohistochemistry • E-cadherin • Prognostic factors

RIASSUNTO

L'obiettivo di questo studio è stato di revisionare in modo sistematico gli articoli che indagavano il ruolo prognostico dell'espressione immunoistochimica di E-caderina nei pazienti affetti da carcinoma laringeo a cellule squamose. Una stringa di parole chiave è stata utilizzata per trovare su PubMed gli articoli pubblicati riguardo a questo argomento. Una doppia scansione incrociata è stata poi eseguita da due degli autori sulle citazioni e sui testi degli articoli per analizzare tutti i lavori e ottenere una piena verifica della qualità di ricerca. Su un totale di 89 articoli identificati sono stati inclusi 13 studi. Questi studi riportavano 1.121 pazienti con diagnosi confermata di carcinoma laringeo a cellule squamose. Complessivamente 10 studi hanno mostrato una correlazione significativa tra l'espressione immunoistochimica di E-caderina con almeno uno dei parametri clinico-patologici presi in esame dagli autori. In particolare l'espressione di E-caderina è risultata statisticamente connessa allo stadio linfonodale (cinque studi), al grading istologico (quattro studi), alla sopravvivenza libera da malattia (sei studi). In conclusione i dati osservati nella nostra revisione appaiono simili ai risultati pubblicati da altri autori riguardo il possibile ruolo di E-caderina nella progressione di varie neoplasie maligne. Infatti anche per il carcinoma a cellule squamose della laringe sembra che livelli più bassi di E-caderina siano correlati ad un aumento dell'aggressività tumorale e ad un peggioramento della prognosi finale. Tuttavia ulteriori studi prospettici di alta qualità dovrebbero essere compiuti per poter considerare l'espressione di E-caderina come un fattore indipendente di prognosi nei pazienti affetti da carcinoma laringeo a cellule squamose.

PAROLE CHIAVE: *Carcinoma laringeo a cellule squamose • Immunoistochimica • E-caderina • Fattori prognostici*

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Introduction

Head and neck squamous cell carcinoma (SCC) is the sixth most common type of cancer in the world, accounting for more than 540,000 new cases and 271,000 mortalities each year. Laryngeal SCC represents the second most common malignancy of the head and neck region in adults accounting for about 1.5% of all cancers [1].

Known prognostic factors for survival and prognosis in laryngeal SCC are histopathological grading, involved subsite and tumour stage according to the TNM classification. Of these, the TNM system is the most sufficient, but its weakness in terms of prognostic accuracy is well recognised and patients with identical clinicopathologic features can show different clinical course or response to the same therapy [2].

For subjects affected by laryngeal SCC, poor survival can be mainly attributed to the high frequency of local recurrence. In fact, the presence of lymph node metastases represents the most important adverse independent prognostic factor in this malignancy and decreases overall survival by more than 50% if extracapsular expansion exists [3].

On the basis of the primary laryngeal subsite involved, for subjects with a clinically negative neck (cN0) there are two main strategies, which include elective neck dissection and "watchful waiting". Currently, the National Cancer Comprehensive Network's practice guidelines recommend to perform elective neck dissection for clinical N0 supraglottic SCC [4]. However, personalised management of the cN0 neck, especially in patients with early laryngeal SCC would benefit greatly from staging techniques that increase the accuracy of assessment of nodal disease.

For these reasons, clinical staging should be supplemented by other factors that would increase our knowledge about the biologic behaviour of this tumuor, and biological markers capable of distinguishing patients with good prognosis from those with poor prognosis are thus required [5].

An important step in the process of tumour metastases is the detachment of malignant cells from their original site. In normal epithelial tissues, cell-cell adhesion is mediated by a large number of cell adhesion molecules [6]. Cadherins are a family of transmembrane glycoproteins with a highly conserved cytoplasmic tail, which interacts with the cytoskeleton via the intracellular proteins a, b and g catenins. The cadherin family contains several members, depending on their tissue distribution, including E-cadherin, which forms the key functional component of adherens junctions between epithelial cells [7]. E-cadherin is involved not only in cell adhesion and morphogenesis, but also in cellular signal transduction. In a variety of epithelial neoplasms, loss or reduction of E-cadherin expression has been associated with advanced stages of tumour growth, increased metastatic potential, shortened disease-free period and lowered overall survival, with a concomitant poor prognosis [8-12].

The aim of our review was to systematically summarise published studies investigating the significance of E-cadherin immunohistochemical (IHC) expression in patients affected by laryngeal SCC.

Materials and methods

Search methods for identification of studies

In September 2017, a computerised MEDLINE search was performed from the start of the database until the end of September 2017 using the PubMed service of the US National Library of Medicine by running the following search string:

("Cadherins"[Mesh] OR "Cadherin Related Proteins"[Mesh]) AND ("Larynx"[Mesh] OR "Laryngeal Neoplasms"[Mesh])

Reference lists from relevant articles were hand searched for further studies.

The initial search returned a total of 89 results. Abstracts and titles obtained were screened independently by two of the authors (FMG and MR), who subsequently met to discuss disagreements on citation inclusion.

Inclusion criteria for citations were:

- cohorts of patients with histological confirmed diagnosis of laryngeal SCC.

Exclusion criteria for citations were:

- analysis including samples of patients with histologically confirmed diagnosis of laryngeal basaloid SCC;
- articles concerning different markers than E-cadherin;
- data obtained from in vitro experiments;
- languages other than English.

Of the 89 articles, 15 met the initial inclusion criteria according to both authors (FMG and MR). These were obtained and reviewed in detail by the same two authors, who met and discussed disagreements on article inclusion. Inclusion criteria for full text articles and single patients identified were:

- sufficient and accurate description of IHC staining;
- sufficient and accurate description of statistical analysis.

Exclusion criteria were:

- analysis performed on specimens of patients with history of previous head and neck radiotherapy;

- analysis including samples of patients affected by SCC of other organs than larynx;
- analysis including duplicate data.

A total of three studies were excluded. The first was ruled out because of insufficient data while other two studies were excluded respectively for the presence of duplicate data (one study) and the inclusion of subjects affected by hypopharynx SCC (one study). A further manual check was performed on the references included in the articles and one additional study was identified that met the inclusion criteria. The final number of articles included in the present review was identified, and the main information was extracted and summarised.

Results

After an initial check, full-text retrieval and manual cross-checking of references included in the articles, 13 studies, comprising a total of 1,121 subjects, clearly met the inclusion criteria and were chosen for analysis (Fig. 1).

The main characteristics of the selected studies are summarised in Tables I, II.

All studies had a retrospective cohort design. The average length of follow-up was reported in six studies, with a mean of 40.3 months and ranging from 24 to 60 months.

Overall, the number of patients included in each study varied from 37 to 289.

The vast majority of patients (n = 467) had a glottic cancer, while supraglottic localisation was described in 445 subjects. A transglottic tumour was described in 66 cases and only 31 patients presented with subglottic localisation. Two studies did not report the specific subsite.

Among the analysed articles, 10 reported at least one significant correlation between E-cadherin IHC expression and the clinical or histopathological parameters evaluated. A significant correlation was found for N stage (5/13), grading (4/13), disease-free survival/disease-specific survival (6/13) and overall survival (3/13). Three studies failed to find any significant correlations.

Discussion

At present, it still appears difficult to forecast the exact prognosis for the clinical course of laryngeal SCC with established clinical parameters such as TNM classification and histopathological grading [2]. TNM classification represents the most powerful parameter, but is criticised as an unreliable prognostic indicator for the head and neck region due to unfavourable clinical outcomes, especially for small tumours [13]. Moreover, analysing the clinical behaviour of laryngeal SCC, it must always take account of the

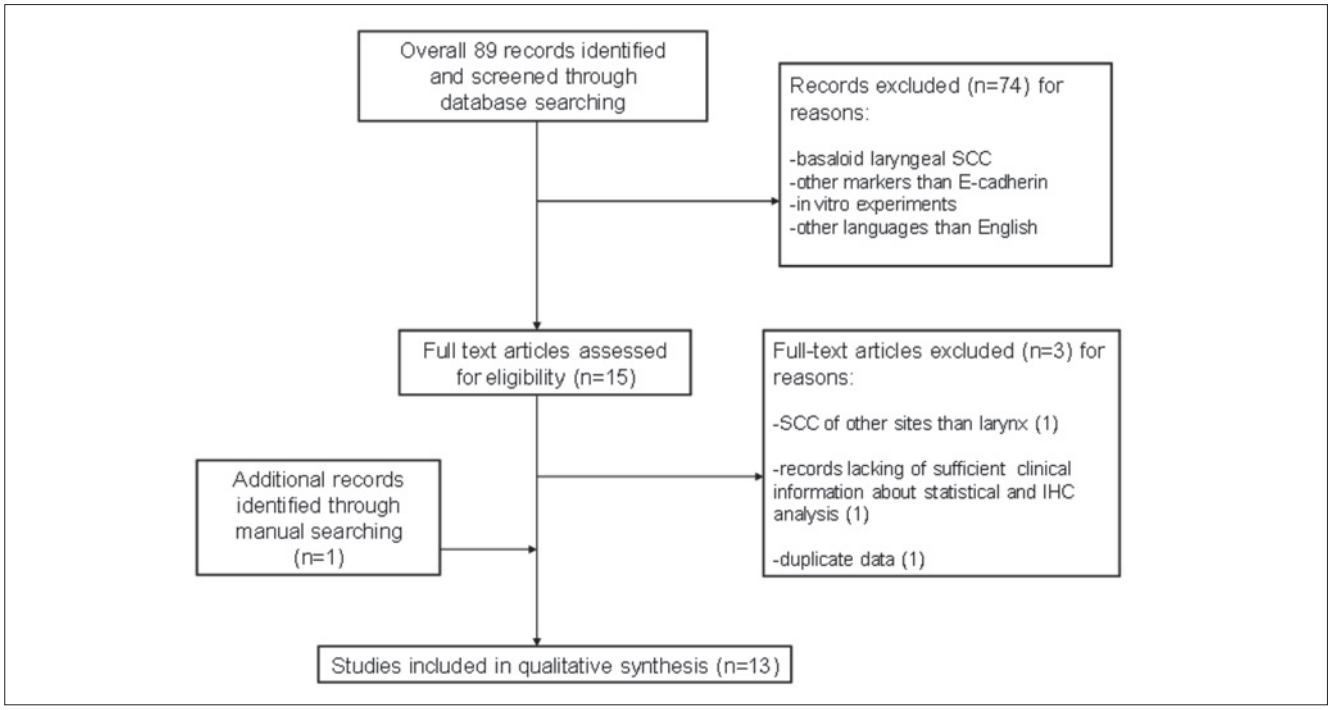

Fig. 1. Flowchart demonstrating study selection.

Table I. Main characteristics of the studies analysed with correlations between clinical-histopathological parameters and expression.

Authors	Year	No. of patients	pT stage				pN stage		Tumour subsites				Mean follow-up period (Mo.)
			T1	T2	T3	T4	N–	N+	Glottic	Supraglottic	Transglottic	Subglottic	
Rodrigo et al. [23]	2007	95	12	35	36	12	42	53	0	95	0	0	n/a
Zou et al. [33]	2010	150	n/a	n/a	n/a	n/a	83	67	122	16	0	12	49
Paksoy et al. [25]	2011	56	0	22	24	10	33	23	24	16	14	2	n/a
Li et al. [6]	2012	64	8	14	32	10	28	36	36	21	0	7	60
Carico et al. [29]	2012	55*	55	0	0	0	55	0	48	7	0	0	36
Akdeniz et al. [26]	2013	38	2	16	9	11	23	15	1	22	15	0	n/a
Ahmed et al. [27]	2014	75	n/a	n/a	n/a	n/a	51	24	n/a	n/a	n/a	n/a	40
Psyrri et al. [34]	2014	289**	n/a	n/a	n/a	n/a	243°	45°	125	135	23	6	n/a
Greco et al. [30]	2015	82	n/a	n/a	n/a	n/a	48	34	47	26	9	0	33
Ali Bayram et al. [35]	2015	60	0	8	36	16	30	30	0	60	0	0	n/a
Cappellesso et al. [28]	2015	37	1	8	23	5	16	21	n/a	n/a	n/a	n/a	n/a
Barutçu et al. [36]	2016	41	14	22	5	0	34	7	25	16	0	0	24
Qian et al. [31]	2016	79	n/a	n/a	n/a	n/a	53	26	39	31	5	4	n/a

**: 4 carcinoma in situ + 4 verrucoid carcinoma; °: one patient missing data; **: IHC analysis performed for 286 patients.*

supraglottis subsite as it has a richer lymphatic supply. That consideration supports the published data showing a higher incidence of lymph node metastases and occult metastases for supraglottic SCC in comparison to glottic SCC [6].

Currently, imaging techniques such as CT, MRI and ultrasound guided fine needle aspiration cytology are employed to assess the status of cervical lymph nodes. However, the limited sensitivity and specificity of CT and MRI in detection of lymph node metastases must be considered. For ultrasound-guided fine-needle aspiration cytology, although it can detect more than 80% lymph node metastases, there is still a risk of occult metastases [14].

During the last years, many studies were planned with the aim to investigate the role played by different cellular biomarkers, which could help to potentiate our diagnostic and therapeutic capability. Indeed, the number of potentially useful biomarkers is large and many studies have been published on this topic. Therefore, in recent years several reviews were published that summarise the literature on specific cellular biomarkers and tumour progression in head and neck [15-20] and laryngeal SCC [2 5 21-24].

E-cadherin is expressed in the lower spinous and basal cell layer and is involved in the transduction of signals controlling various cellular events, including polarity, differentiation, growth and cell migration. E-cadherin provides intercellular adhesion of cancer cells and its suppression in the primary lesion plays a role as a trigger for liberalisation of cancer cells [25].

Regarding the role of E-cadherin in laryngeal SCC, there are some interesting results that could be extrapolated from the selection of the studies included herein. Akdeniz et al. [26], analysing the IHC expression of E-cadherin in tissue specimens of 38 patients with laryngeal SCC, noted that a lower level of E-cadherin protein expression correlated with poor differentiation of the tumour ($p < 0.05$) and a major risk of nodal metastases ($p = 0.045$). Ahmed et al. [27], in their cohort of 75 subjects, found a significant correlation between reduced E-cadherin expression and poor tumour differentiation ($p = 0.004$), lymph node

Table II. E-cadherin thresholds of positivity and correlations with clinical-histopathological parameters.

Authors	E-cadherin assay	E-cadherin location	Cutoff level	Clinical and histopathological investigated parameters					
				T	N	Stage	Grade	DFS/DSS	OS
Rodrigo et al. [23]	IHC	C-M	Score	No	Yes	N/E	No	No	N/E
Zou et al. [33]	IHC	C	Score	Yes	Yes	N/E	Yes	Yes	N/E
Paksoy et al. [25]	IHC	n/a	> 75%	N/E	No	N/E	N/E	N/E	N/E
Li et al. [6]	IHC	C-M	Score	N/E	Yes	N/E	N/E	Yes	Yes
Carico et al. [29]	IHC	M	Score	N/E	N/E	N/E	Yes	No	N/E
Akdeniz et al. [26]	IHC	C-M	Score	N/E	Yes	No	Yes	N/E	N/E
Ahmed et al. [27]	IHC	C-M	> 50%	N/E	Yes	Yes	Yes	Yes	N/E
Psyrri et al. [34]	IHC	C-M	Score	No	No	No	No	Yes	No
Greco et al. [30]	IHC	C-M	> 50%	N/E	N/E	N/E	N/E	Yes	Yes
Ali Bayram et al. [35]	IHC	n/a	> 25%	No	No	No	No	N/E	N/E
Cappellesso et al. [28]	IHC	M	Score	N/E	No	N/E	N/E	Yes	N/E
Barutçu et al. [36]	IHC	n/a	> 50%	No	No	No	No	No	No
Qian et al. [31]	IHC	C-M	> 20%	No	No	No	No	N/E	Yes

IHC: immunohistochemistry; M: membrane; C: cytoplasmic; DFS: disease free survival; DSS: disease specific survival; OS: overall survival; YES: significant correlation; NO: no significant correlation; n/e: not evaluated.

metastasis (p = 0.006), advanced T-stage (p = 0.001) and TNM stage (p = 0.001). Cappellesso et al. [28], in a cohort of 37 patients, observed a significant correlation (p = 0.04) between lower levels of E-cadherin and shorter disease-free survival (DFS), while there was no relation with nodal stage. Carico et al. [29] analysed a group of 55 patients affected by T1N0 laryngeal SCC. The authors did not find a significant relation between low E-cadherin levels and poorer DFS. However, a significant association was noted between scarce presence of E-cadherin and less differentiated tumour grade (p = 0.006). An interesting study was recently performed by Greco et al. [30] who analysed the relation between E-cadherin expression by IHC and survival rates in a cohort of 82 patients. The authors observed that patients whose tumours overexpressed both cytoplasmic and membranous E-cadherin experienced worse 3-year overall survival (OS). Similarly, patients whose tumours overexpressed cytoplasmic E-cadherin experienced significantly worse 3-year disease specific survival (DSS). These results are surprising because overexpression of E-cadherin should result in the stabilisation of cadherin/catenin complexes. Li et al. [6], analysing the specimens of 64 patients, found that reduced E-cadherin expression was significantly correlated with lymph node metastases (p < 0.001). Moreover, the Kaplan-Meier survival curves showed a significant correlation between E-cadherin expression and patient survival (p < 0.05). Indeed, the high expression group of patients presented higher OS and DFS rates.

Recently, Qian et al. [31], in a cohort of 79 patients, found that a significant correlation (p = 0.028) was present between elevated E-cadherin expression by IHC and higher OS. Analysing the specimens of 95 subjects, Rodrigo et al. [32] noted that decreased E-cadherin expression was correlated with the presence of nodal metastases (p = 0.006). In their cohort of 150 patients (mainly affected by supraglottic SCCs), Zou et al. [33] reported a significant association between E-cadherin immunostaining and T-stage

(p = 0.000), cervical lymph node metastasis (p = 0.000) and histological grade (p = 0.048). A tendency for low E-cadherin expression to correlate with tumour recurrence was also found (p = 0.000), but at multivariate logistic regression analysis E-cadherin was not an independent predictor factor of DFS (p = 0.063). Psyrri et al. [34] conducted a study on a larger cohort of 286 patients. On the basis of their analysis, the authors concluded that patients whose tumours overexpressed both cytoplasmic and membranous E-cadherin experienced longer DFS compared to those whose tumours overexpressed only cytoplasmic E-cadherin (p = 0.0106). However, it must be noted that some authors failed to observe a significant relation between E-cadherin IHC expression with oncological features and survival [25 35 36].

Conclusions

On the basis of data collected in our review, the role of E-cadherin in laryngeal SCC progression remains still difficult to elucidate. An important relation seems to exist between reduction of cellular E-cadherin levels and development of nodal metastases with consequent worsening of prognosis. Nevertheless, many inconsistencies were present between the studies analysed, especially regarding the patient populations and IHC scoring system. Thus, in our opinion, new prospective studies with homogeneous cohorts of patients are required to draw definitive conclusions about this topic.

Conflict of interest statement

None declared.

References

1 Re M, Çeka A, Rubini C, et al. *MicroRNA-34c-5p is related to recurrence in laryngeal squamous cell carcinoma.* Laryngoscope 2015;125:E306-12.

2 Gioacchini FM, Alicandri-Ciufelli M, Magliulo G, et al. *The clinical relevance of Ki-67 expression in laryngeal squamous cell carcinoma.* Eur Arch Otorhinolaryngol 2015;272:1569-76.

3 Johnson JT, Myers EN. *Cervical lymph node disease in laryngeal cancer.* In: Silver CE, editor. *Laryngeal cancer.* New York: Thieme Medical Publishers; 1991. pp. 22-6.

4 Liao LJ, Hsu WL, Wang CT, et al. *Analysis of sentinel node biopsy combined with other diagnostic tools in staging cN0 head and neck cancer: a diagnostic meta-analysis.* Head Neck 2016;38:628-34.

5 Gioacchini FM, Alicandri-Ciufelli M, Rubini C, et al. *Prognostic value of Bcl-2 expression in squamous cell carcinoma of the larynx: a systematic review.* Int J Biol Markers 2015;30:e155-60.

6 Li JJ, Zhang GH, Yang XM, et al. *Reduced E-cadherin expression is associated with lymph node metastases in laryngeal squamous cell carcinoma.* Auris Nasus Larynx 2012;39:186-92.

7 Wijnhoven BPL, Dinjens WNM, Pignatelli M. *E-cadherin-catenin cell-cell adhesion complex and human cancer.* Br J Surg 2000;87:992-1005.

8 Kashibuchi K, Tomita K, Schalken JA, et al. *The prognostic value of E-cadherin, alpha-, beta-, and gamma-catenin in urothelial cancer of the upper urinary tract.* Eur Urol 2006;49:839-45.

9 Mikami T, Saegusa M, Mitomi H, et al. *Significant correlations of E-cadherin, catenin, and CD44 variant form expression with carcinoma cell differentiation and prognosis of extrahepatic bile duct carcinomas.* Am J Clin Pathol 2001;116:369-76.

10 Kawano T, Nakamura Y, Yanoma S, et al. *Expression of E-cadherin, and CD44s and CD44v6 and its association with prognosis in head and neck cancer.* Auris Nasus Larynx 2004;31:35-41.

11 Diniz-Freitas M, Garcia-Caballero T, Antunez-Lopez J, et al. *Reduced E-cadherin expression is an indicator of unfavourable prognosis in oral squamous cell carcinoma.* Oral Oncol 2006;42:190-200.

12 Gould Rothberg BE, Bracken MB. *E-cadherin immunohistochemical expression as a prognostic factor in infiltrating ductal carcinoma of the breast: a systematic review and meta-analysis.* Breast Cancer Res Treat 2006;100:139-48.

13 Janot F, Klijanienko J, Russo A, et al. *Prognostic value of clinicopathological parameters in head and neck squamous cell carcinoma: a prospective analysis.* Br J Cancer 1996;73:531-8.

14 Van Den Brekel MWM, Castelijns JA, Snow GB. *Diagnostic evaluation of the neck.* Otolaryngol Clin North Am 1998;31:601-20.

15 Gioacchini FM, Alicandri-Ciufelli M, Kaleci S, et al. *The prognostic value of cyclin D1 expression in head and neck squamous cell carcinoma.* Eur Arch Otorhinolaryngol 2016;273:801-9.

16 Chen J, Zhou J, Lu J, et al. *Significance of CD44 expression in head and neck cancer: a systemic review and meta-analysis.* BMC Cancer 2014;14:15.

17 Rainsbury JW, Ahmed W, Williams HK, et al. *Prognostic biomarkers of survival in oropharyngeal squamous cell carcinoma: systematic review and meta-analysis.* Head Neck 2013;35:1048-55.

18 Tandon S, Tudur-Smith C, Riley RD, et al. *A systematic review of p53 as a prognostic factor of survival in squamous cell carcinoma of the four main anatomical subsites of the head and neck.* Cancer Epidemiol Biomarkers Prev 2010;19:574-87.

19 Almangush A, Heikkinen I, Mäkitie AA, et al. *Prognostic biomarkers for oral tongue squamous cell carcinoma: a systematic review and meta-analysis.* Br J Cancer 2017;117:856-66.

20 Guerra EN, Acevedo AC, Leite AF, et al. *Diagnostic capabil-*

ity of salivary biomarkers in the assessment of head and neck cancer: a systematic review and meta-analysis. Oral Oncol 2015;51:805-18.

[21] Yu X, Li Z. *The role of microRNAs expression in laryngeal cancer.* Oncotarget 2015;6:23297-305.

[22] Lionello M, Staffieri A, Marioni G. *Potential prognostic and therapeutic role for angiogenesis markers in laryngeal carcinoma.* Acta Otolaryngol 2012;132:574-82.

[23] Rodrigo JP, García-Pedrero JM, Suárez C, et al. *Biomarkers predicting malignant progression of laryngeal epithelial precursor lesions: a systematic review.* Eur Arch Otorhinolaryngol 2012;269:1073-83.

[24] Mesolella M, Iorio B, Landi M, et al. *Overexpression of chromatin assembly factor-1/p60 predicts biological behaviour of laryngeal carcinomas.* Acta Otorhinolaryngol Ital 2017;37:17-24.

[25] Paksoy M, Hardal U, Caglar C. *Expression of cathepsin D and E-cadherin in primary laryngeal cancers correlation with neck lymph node involvement.* J Cancer Res Clin Oncol 2011;137:1371-7.

[26] Akdeniz O, Akduman D, Haksever M, et al. *Relationships between clinical behavior of laryngeal squamous cell carcinomas and expression of VEGF, MMP-9 and E-cadherin.* Asian Pac J Cancer Prev 2013;14:5301-10.

[27] Ahmed RA, Shawky Ael-A, Hamed RH. *Prognostic significance of cyclin D1 and E-cadherin expression in laryngeal squamous cell carcinoma.* Pathol Oncol Res 2014;20:625-33.

[28] Cappellesso R, Marioni G, Crescenzi M, et al. *The prognostic role of the epithelial-mesenchymal transition markers E-cadherin and slug in laryngeal squamous cell carcinoma.* Histopathology 2015;67:491-500.

[29] Carico E, Radici M, Losito NS et al. *Expression of E-cadherin and α-catenin in T1 N0 laryngeal cancer.* Anticancer Res 2012;32:5245-9.

[30] Greco A, De Virgilio A, Rizzo MI, et al. *The prognostic role of E-cadherin and β-catenin overexpression in laryngeal squamous cell carcinoma.* Laryngoscope 2016;126:E148-55.

[31] Qian X, Ma X, Zhou H, et al. *Expression and prognostic value of E-cadherin in laryngeal cancer.* Acta Otolaryngol 2016;136:722-8.

[32] Rodrigo JP, Dominguez F, Suárez V, et al. *Focal adhesion kinase and E-cadherin as markers for nodal metastasis in laryngeal cancer.* Arch Otolaryngol Head Neck Surg 2007;133:145-50.

[33] Zou J, Yang H, Chen F, et al. *Prognostic significance of fascin-1 and E-cadherin expression in laryngeal squamous cell carcinoma*. Eur J Cancer Prev 2010;19:11-7.

[34] Psyrri A, Kotoula V, Fountzilas E, et al. *Prognostic significance of the Wnt pathway in squamous cell laryngeal cancer.* Oral Oncol 2014;50:298-305.

[35] Ali Bayram, Yüce İ, Çağlı S, et al. *Predictive value of E-cadherin and Ep-CAM in cervical lymph node metastasis of supraglottic larynx carcinoma.* Am J Otolaryngol 2015;36:736-40.

[36] Barutçu O, Kara M, Muratlı A, et al. *Clinical significance of Ki-67, c-erbB-2 and E-cadherin expressions in open partial laryngectomy patients.* Kulak Burun Bogaz Ihtis Derg 2016;26:283-92.

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LARYNGOLOGY

Aspiration: diagnostic contributions from bedside swallowing evaluation and endoscopy

Aspirazione: contributo diagnostico dalla valutazione clinica non strumentale ed endoscopica

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SUMMARY

The aim of this study was to identify which characteristics, collected by bedside swallowing evaluation (BSE) and fiberoptic endoscopic evaluation of swallowing (FEES), are a risk or a protective factor for aspiration. This retrospective study included data on 1577 consecutive patients, collected by BSE and FEES. Bivariate analysis was performed to verify the association of each variable with aspiration (Chi-Square test). The variables associated with aspiration were entered into a multivariate logistic model to quantify this association. Several variables were significantly associated ($p < 0.05$) with aspiration; cooperation, sensation, laryngeal elevation and direct therapy were found to be protective factors against aspiration. The regression model identified the most variables related with aspiration, among which tracheotomy, material pooling and spillage. Patients able to perform dry swallows were 77% less likely to aspirate (protective factor). Several variables are involved in protection of airways during swallowing. Their interaction, in patients with swallowing disorders, offers the clinician the best means of interpreting BSE and FEES.

KEY WORDS: Deglutition disorders • Aspiration • Residue • FEES • Bedside swallowing evaluation

RIASSUNTO

Lo scopo di questo studio è stato quello di identificare quali caratteristiche, raccolte dalla valutazione clinica non strumentale della deglutizione (BSE) e dalla valutazione fibroendoscopica della deglutizione (FEES), costituiscono un rischio o un fattore protettivo per l'aspirazione. Questo studio retrospettivo comprende dati da 1577 pazienti consecutivi, raccolti con la BSE e FEES. È stata eseguita un'analisi bivariata per verificare l'associazione di ciascuna variabile con l'aspirazione (Chi-Square test). Le variabili associate all'aspirazione sono state inserite in un modello logistico multivariato per verificare e quantificare questa associazione. Diverse variabili sono state trovate significativamente associate (valore di p inferiore a 0,05) con l'aspirazione, alcune rappresentando un fattore protettivo contro l'aspirazione: collaborazione, sensibilità, elevazione laringea, terapia diretta. La regressione logistica ha individuato le variabili più correlate all'aspirazione, tra cui la tracheotomia, il materiale che ristagna e che penetra. I pazienti in grado di eseguire deglutizioni a vuoto sono per il 77% meno esposti ad aspirazione (fattore protettivo). Diverse variabili sono coinvolte nella protezione delle vie aeree durante la deglutizione. La loro interazione, nei pazienti con disturbi di deglutizione, offre al clinico il modo migliore per interpretare i dati della BSE e FEES.

PAROLE CHIAVE: *Disordini della deglutizione • Aspirazione • Ristagno • FEES • Valutazione clinica non strumentale*

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Introduction

Dysphagia defines any difficulty in the progression of the bolus or secretions through the cavities of the upper digestive tract while being kept out from the airway [1]. If airway protection is not guaranteed, material can reach the vocal cords by keeping it above (penetration) or below (aspiration), with or without reaction from the patient. Airway invasion is strictly related with pneumonia and chronic bronchial inflammation [2].

Dysphagia is related to several pathological conditions and to aging [3]. In clinical practice, the possibility of identifying patients at risk of penetration or aspiration in a heterogeneous population is a priority, particularly in settings where the number of patients with impaired swallowing is high (nursing homes, healthcare facilities). In these contexts, patients suspected of having swallowing impairments are submitted to screening or bedside procedures (bedside swallowing evaluation, BSE) [4 5], performed with the aim of identifying those who are at risk

of dysphagia or aspiration, and should determine a further need for instrumental assessments. BSE does not only lack sensitivity and specificity in determining aspiration, but also in determining the underlying swallowing physiology. Thus, to fill this gap an instrumental assessment of swallowing is necessary. The instrumental assessment, be it fiberoptic [6] or modified barium swallow exam (MBS) [7], defines the altered physiology and severity, and aids the team in planning treatment strategies. A documented airway invasion does not define, per sè, the clinical severity of swallowing impairment, which may depend on other factors such as oral intake level and type of diet, quality of life related to dysphagia and self-perceived dysphagia symptoms [8 9]. Therefore, any instrumental result (able to express a criterion of severity) has to be contextualised into a wider clinical scenario, bearing in mind that the non-instrumental assessment tends to underestimate the risk of aspiration, whereas the instrumental assessment tends to overestimate it [10 11].

Previous studies [11 12] have documented the possibility of identifying subjects who are at risk of aspiration by combining certain BSE and instrumental parameters, resulting in a clinical scale of dysphagia severity. Other scales, according to the estimated severity, give information about therapeutic options [13].

With this premise, the aim of this study is to evaluate correlations among clinical information taken from BSE and FEES, and aspiration, in a large sample of patients with different clinical characteristics. The weight of this interaction was considered. Data from such a large sample can reinforce their generalisation and offer parameters to consider in conceiving new clinical scales.

Table I. Characteristics of study participants.

Characteristics		No.	%
Age over 65 years	H	878	55.68%
Male	H	622	39.44%
Traumatic brain injury (TBI)	H	168	10.65%
Stroke	H	865	54.85%
Degenerative neurological pathologies	H	272	17.25%
Spinal cord injuries	H	287	18.20%
Nil per os (NPO) prescription	H	126	7.99%
Nasogastric tube (NGT) already in place	H	354	22.45%
Percutaneous endoscopic gastrostomy (PEG) already in place	H	76	4.82%
Indirect therapy	H	1024	64.93%
Direct therapy	H	1301	82.50%
Videofluoroscopic swallowing study (VFSS) already performed	H	46	2.92%
Tracheotomy	B	286	18.14%
Dysarthria	B	341	21.62%
Aphasia	B	147	9.32%
Cooperation	B	1164	73.81%
Gurgling voice	B	150	9.51%
Laryngeal elevation	B	988	62.65%
Sensation	B	1444	91.57%
Aspiration	E	382	24.22%
Spillage	E	687	43.56%
Pre swallowing penetration	E	581	36.84%
Pooling	E	1110	70.39%
Pooling max amount	E	156	9.89%
Post swallowing penetration	E	110	6.98%
Delayed triggering	E	524	33.23%
Dry swallowing	E	1045	66.27%

H: History; B: BSE; E: Endoscopy, parameters.

Materials and methods

A retrospective analysis was performed on 1577 consecutive adult patients evaluated at our Swallowing Centre from mid-1998 to the end of 2006. Each patient provided his/her clinical history and underwent bedside and complete endoscopic evaluation with bolus tests. Data collection and bedside evaluation were performed alternately by three Speech Pathologists and a Phoniatrician.

Considering the retrospective nature of the study, the heterogeneity of the sample, the evaluators and long-term observation, the data available were considered globally. Table I reports the parameters and characteristics of participants included in the study. With respect to the clinical history, the following data were taken into account: age, sex, pathological conditions causing dysphagia, presence of tracheotomy, alternatives to oral feeding (via tubes or parenterally), previous dysphagia therapies (indirect therapy, i.e. exercises performed to strengthen the oral phase of swallowing, and direct therapy, i.e. use of food and liquids to practice swallowing techniques, manoeuvres, indirect exercises) [14] and MBS tests, even if performed elsewhere.

With respect to BSE [4 5 14], clinical signs closely related to dysphagia and aspiration were considered. For example, gurgling was evaluated as a perceptive parameter of the voice, laryngeal elevation considering the movements of the larynx during a volitional swallow (a movement equal or superior to 2 cm was considered normal), sensation slightly touching with a probe the mouth and pharynx (the answer and/or reaction of the patients were considered), and finally cooperation. Cooperation refers, in the broadest sense, to consciousness, alertness, fatigability and cognitive abilities: it is a parameter affecting clinical evaluation, treatment and the possibility of oral feed-

ing [15 16]. All patients were evaluated by a phoniatrician and submitted to endoscopic evaluation according to the protocol in use in our centre [6 17]. Endoscopic evaluation was performed with a Storz endoscope (model 11101RP2, 30 cm long, 3.5 mm in diameter) and recorded on a workstation (Xion medical products GmbH, Berlin Buchholz). The patients were given three trials of different consistencies: 5 cc puree, 5 cc liquid dye with 5% methylene blue and 1/4 cracker (regular consistency) [18]. Patients were instructed to prepare the bolus and then to swallow without any command. Some patients were not able to test all the three consistencies, owing to the severity of their complaint. After each trial, dry swallows, performed to clear the bolus residue, were counted to apply the pooling score (p-score) (Table II). After FEES, several parameters were considered: spillage, delayed trigger (more than 0.5 sec after bolus' pharyngeal entrance), penetration (before and after swallowing), aspiration and residue. Aspiration during FEES (however it occurred) was considered as the cut-off in dividing the population into two groups, non-aspirating and aspirating, if at least one bolus had passed below the vocal cords. As in previous studies [12 19], material pooling was endoscopically related to site, amount and management, and clinically related to sensation, collaboration and age. Management of pooling was related to the number of dry swallows or any other spontaneous or requested activity attempted by the patient to clear pooling: gurgling, clearing and coughing. Two scores were derived, viz. the pooling score (p-score) and the pooling-sensation, collaboration, age score (p-SCA score) capable of expressing the severity of dysphagia (Table II).

With respect to data available for all the patients, 27 variables were considered (Table I). All the variables were dichotomous, taking on a value of 0 or 1, signifying the absence or presence, respectively, of the characteristic (aspiration). Age dichotomy had a value of 1 if the patient was over 65 years old. The variable "maximum amount" was 1 if the amount of pooling was maximum and 0 if minimum or coating, in accordance with the p-score and p-SCA score.

As just stated, this study was based on a retrospective analysis and much data were either unavailable or irretrievable during collection: the dichotomous collection of data allowed us to fill this gap. Such an approach, although apparently simplistic, was nevertheless appropriate to the nature of certain parameters (i.e. sex, presence of certain pathological conditions, presence of tracheotomy or alternative feeding devices, or some FEES parameters) and, in general, suitable for the purposes of the study.

The pooled data were subsequently submitted to logistic regression to better understand the impact of individual factors (risk factors) with aspiration. The model was assessed using the maximum likelihood method.

Patients with missing data were omitted in bivariate and multivariate analysis, so that the actual number of patients evaluated was 1386.

The study was approved by the institutional Research Review Board.

Statistical analysis was performed with Intercooled STATA 8.0 for Windows software.

Results

The parameters selected (independent variables) are reported in Table I. The bivariate relationship between each of the 27 risk factors and aspiration was studied. Associa-

Table II. Pooling score (p-score) and Pooling sensation-collaboration-age score (p-SCA score).

Pooling	Endoscopic landmarks		Bedside parameters		
			Sensation	Cooperation	Age (yrs)
Site	Vallecule/marginal zone	1			
	Pyriform sinus	2			
	Vestibule/vocal cords	3			
	Lower vocal cords	4			
Amount	Coating	1	Presence = – 1	Presence = – 1	+ 1 (< 65)
	Minimum	2	Absence = + 1	Absence = + 1	+ 2 (65-75)
	Maximum	3			+ 3 (> 75)
Management	< 2	2			
	2 > < 5	3			
	> 5	4			
Score	p 4-11			p-SCA 3-16	

p-score: 4-5: minimum score, corresponding to no endoscopic signs of dysphagia; 6-7: low score, corresponding to a mild dysphagia; 8-9: middle score, corresponding to a moderate dysphagia; 10-11: high score, corresponding to a severe dysphagia.

p-SCA score: 3-4: minimum score, corresponding to no dysphagia; 5-8: low score, corresponding to a mild dysphagia; 9-12: middle score, corresponding to a moderate dysphagia; 13-16: high score, corresponding to severe dysphagia.

tion of categorical variables with aspiration was assessed with the $\chi 2$-test.

The categorical variables found to be significantly associated (p value of less than 0.05) with aspiration were: age over 65, cooperation, gurgling voice, sensation, laryngeal elevation, nil per os (NPO) prescription, nasogastric tube (NGT) already in situ, indirect therapy, direct therapy, tracheotomy, delayed triggering, spillage, penetration, material pooling, post-swallowing penetration, dry swallowing and pooling maximum amount.

The average age of patients in the sample was 66.22: the cut-off age of 65 could indeed represent a risk factor for the appearance of deglutition disorders even as a co-morbidity factor.

Other parameters were not significantly associated with aspiration. Table III summarises the parameters correlated with aspiration and the respective odds ratios.

Although all these variables were eligible for entry into a multiple logistic regression model, some were excluded because they were strongly associated with other variables, thereby avoiding collinearity (delayed triggering, penetration and maximum amount). The association among variables was assessed with a $\chi 2$-test ($p < 0.05$). Other variables were eliminated when statistically insignificant on the basis of likelihood ratio tests ($p > 0.05$). Multiple logistic regression modelling generated a main-effect model containing 8 variables, as reported in Table IV.

Table IV presents (using the maximum likelihood method) the adjusted odds ratios, estimated standard errors (SEs) and 95% confidence intervals (CIs) for the adjusted ratios for the model. It can be seen that the variables closely related with aspiration were age over 65, cooperation, NPO prescription, tracheotomy, spillage, material pooling, post-swallowing penetration and dry swallowing. For example, an odds ratio of 19.24 for pooling means that a patient having this condition (without dry swallowing) would be 19.24 times more likely to aspirate than another patient not having that condition, controlling simultaneously for all other variables in the model. Patients able to perform dry swallows were 77% less likely to aspirate (protective factor).

It is worth pointing out that the retrospective nature of the study and the a priori consideration of aspiration means that the statistical models developed to correlate the data of our sample have no real predictive value. Thus, the odds ratios produced by multivariate analysis indicate the relationship between each variable and endoscopic results, taking into account the other variables in the model.

Discussion

We evaluated data from BSE and FEES in 1386 of 1577 patients with swallowing disorders due to different aetiologies and comorbidities. Of these, 382 (24.24%) were aspirating, without any further information regarding the

Table III. Bivariate analyses: variables associated with aspiration and respective odds ratios.

Risk Factor	No. aspirating with risk factor (%)	No. aspirating without risk factor (%)	Odds ratio	95% CI
Age over 65 years	130 (14.3)	115 (12.7)	1.4	1.1-2.1
Cooperation	160 (17.6)	87 (9.6)	0.3	0.3-0.5
Gurgling voice	34 (3.7)	211 (23.2)	2.6	1.5-43
Sensation	225 (24.8)	21 (2.3)	0.4	0.2-0.8
Laryngeal elevation	89 (9.8)	157 (17.3)	0.11	0.1-0.19
NPO prescription	38 (4.2)	207 (22.8)	3.9	2.8-7.9
NGT already placed	106 (11.7)	141 (15.5)	6.7	4.4-9.2
Indirect therapy	224 (24.6)	23 (2.5)	8.5	5.7-15
Direct therapy	191 (21)	56 (6.2)	0.3	0.2-0.5
Tracheotomy	95 (10.5)	152 (16.7)	9	5.9-13.8
Delayed triggering	130 (14.3)	115 (12.7)	3.3	2.1-4
Spillage	181 (19.9)	65 (7.2)	4.6	3.2-6.2
Pre swallowing penetration	204 (22.5)	41 (4.5)	16.5	10.7-23.8
Pooling	232 (25.6)	13 (1.4)	8.6	4-14.1
Pooling max amount	61 (8.9)	163 (23.8)	4.5	2.5-6.5
Post swallowing penetration	50 (5.5)	195 (21.5)	6.7	4.3-133
Dry swallowing	201 (22.1)	44 (4.9)	2.3	1.4-3

Table IV. Multivariate analyses: variables associated with aspiration and respective odds ratios.

Risk factor	Odds ratio	Std. Err	z	p > z	95% CI
Age over 65 years	1.57	0.2466294	2.90	0.004	1.1-2.1
Cooperation	0.48	0.0870088	– 4.02	0.000	0.3-0.6
NPO prescription	2.34	0.6875621	2.90	0.004	1.31-4.16
Tracheotomy	11.95	2.317162	12.80	0.000	8.17-17,48
Spillage	4.7	0.8057423	9.04	0.000	3.4-6.6
Pooling	19.24	7.121247	7.99	0.000	9.3-39.7
Post swallowing penetration	4.39	1.083994	6.00	0.000	2.7-7.12
Dry swallowing	0.23	0.0672686	– 5.05	0.000	0.13-0.41

timing of aspiration, 581 (36.84%) had penetration before swallowing and 110 (6.98%) after swallowing. This means that overall 1073 (77.41%) patients in our sample had airway invasion. This is probably due to the characteristics of the patients afferent to our centre, selected for their severity. Nevertheless, no aetiological correlation initially considered was, per se, statistically related to aspiration (Table I), but rather factors associated with other conditions (tracheostomy, parenteral nutrition, NGT or PEG) that best express the frailty of patients (Table III). Age was found to be statistically significant [1 12]. The average age of our sample was 66.22 years: the cut-off age of 65 could indeed represent a risk factor for the appearance of deglutition disorders even as a comorbidity factor. Moreover, cooperation was found to be correlated with aspiration, but with a negative odds ratio (0.3), that is cooperating patients are less prone to aspirate than non-cooperative patients.

In bivariate analysis, patients who underwent oro-motor therapy (indirect therapy) maintained a greater risk of aspiration, while the use of manoeuvres and postures (direct therapy) apparently served as protective factors. Although in the literature the clinical utility of oro-motor exercises is an open issue [14 20], this fact, per se, should be evaluated with circumspection. In our sample, many patients were hospitalised in other facilities, and no information about exercise programs for any single patient was available.

Another notable initial finding was the association of all the selected endoscopic parameters with aspiration, including management of material pooling, with dry swallowing or other reflex activities (endoscopically verified): all these parameters had a positive OR (Table III). The amount of material pooling (secretions or residue) and its management is a parameter able to express severity of dysphagia, as expressed by the p-score (Table II). The correlation between spontaneous swallowing activity and respiratory complications in elderly dysphagic patients was underlined decades ago [21], though more recently in stroke patients [22]. In our sample, multivariate analysis (Table IV) showed that dry swallowing becomes a protective factor in patients with residue, who are able to reduce aspiration. With this assumption, the number of dry swallows or other activities attempted by patients to clear secretions or residue can be assumed to be a parameter expressing the efficiency of the swallowing act, related with the effectiveness of the same swallowing act, and protecting the airway from invasion. However, this data does not seem to be in accordance with recent research in the literature [23] documenting an increase of aspiration risk on the subsequent swallow for thin-liquid single bolus in neurological patients.

Nevertheless, most of the instrumental findings can have an equivalent in bedside signs, i.e., wet voice, cough before, during or after bolus passage through the pharynx. FEES, in spite of its limitations, can better define the anatomical-functional events already highlighted through BSE (i.e. determining the amount and site of material pooling in a patient with gurgling voice, the pre/post swallowing nature of cough during the bolus tests, if only and when penetration occurred), optimally evaluate material pooling or residue and its management (clinical severity) and provide the therapist with precise information in order to plan treatment.

With both bedside and instrumental assessment, the clinician collects the best information to balance overestimating and underestimating clinical trends, clarify physiopathology and plan treatment. With the contribution of instrumental evaluation, the risk of lost episodes of silent aspiration/penetration at the bedside is less, but the risk of generalised pathological random or extraordinary airway invasion events is higher [10 11].

Conclusions

In daily clinical practice, the possibility of correlating signs and symptoms with aspiration in patients with deglutition disorders is an important goal to prevent com-

plications. Considering the large sample of patients from which dysphagia parameters were derived, taken from bedside evaluation and FEES, able to support a possible aspiration event, aspiration alone does not define dysphagia and its severity (underestimation/overestimation risk). The data from our sample offer us a range of parameters to better classify patients with a swallowing disorder.
Apart from the aim of our study, bivariate and multivariate analyses underline the parameters that are potentially useful in planning a scale of severity accompanied by therapeutic options.
The main limit of our dataset is that it is not comprehensive of all BSE and FEES parameters, due to the collection of data over a long period and the lack of information that was not retrievable at the moment of assessment of patients.

Conflict of interest statement

None declared.

References

1 Serra-Prat M, Hinojosa G, López D, et al. *Prevalence of oropharyngeal dysphagia and impaired safety and efficacy of swallow in independently living older persons.* J Am Geriatr Soc 2011;59:186-7.

2 Vergis EN, Brennen C, Wagener M, et al. *Pneumonia in long-term care: A prospective case-control study of risk factors and impact on survival.* Arch Intern Med 2001;161:2378-81.

3 Roden DF, Altman KW. *Causes of dysphagia among different age groups: A systematic review of the literature.* Otolaryngol Clin North Am 2013;46:965-87.

4 McCullough GH, Rosenbek JC, Wertz RT, et al. *Utility of clinical/swallowing examination measures for detecting aspiration post-stroke.* J Speech Lang Hear Res 2005;48:1280-93.

5 Speyer R. *Oropharyngeal dysphagia screening and assessment.* Otolaryngol Clin North Am 2013;46:989-1008.

6 Langmore SE, Schatz K, Olsen N. *Fiberoptic endoscopic examination of swallowing safety: a new procedure.* Dysphagia 1988;2:216-9.

7 Logemann JA. *Evaluation and treatment of swallowing disorders.* Austin Texas: Pro Ed 1998.

8 McHorney CA, Robbins J, Lomax K, et al. *The SWAL-QOL and SWAL-CARE outcomes tool for oropharyngeal dysphagia in adults: III. Documentation of reliability and validity*. Dysphagia 2002;17:97-114.

9 Ekberg O, Hamdy S, Woisard V, et al. *Social and psychological burden of dysphagia: its impact on diagnosis and treatment.* Dysphagia 2002;17:139-46.

10 Leder BS, Espinosa JF. *Aspiration risk after acute stroke: comparison of clinical examination and fiberoptic endoscopic evaluation of swallowing.* Dysphagia 2002;17:214-8.

11 Farneti D, Genovese E. *Endoscopic criteria in assessing severity of swallowing disorders.* In: Speyer R, editor. *Seminars in dysphagia.* London: InTech; 2015. pp. 71-90.

12 Farneti D. *Pooling score: an endoscopic model for evaluating severity of dysphagia.* Acta Otorhinolaryngol Ital 2008;28:135-40.

13 O'Neil KH, Purdy M, Falk J, et al. *The dysphagia outcome and severity scale*. Dysphagia 1999;14:139-45.

14 Murry T, Carrau RL. *Clinical manual of swallowing disorders.* San Diego: Singular Thomson Learning; 2001.

15 Logeman JA, Veis S, Colangelo L. *A screening procedure for oropharyngeal dysphagia.* Dysphagia 1999;14:44-51.

16 Parker C, Power M, Hamdy S, et al. *Awareness of dysphagia by patients following stroke predicts swallowing performance.* Dysphagia 2004;19:28-35.

17 Farneti D. *Valutazione video endoscopica.* In: Schindler O, Ruoppolo G, Schindler A, editors. *Deglutologia*. Torino: Omega Editore; 2001. p. 167.

18 Cichero JA, Steele C, Duivestein J, et al. *The need for international terminology and definitions for texture-modified foods and thickened liquids used in dysphagia management: foundations of a global initiative.* Curr Phys Med Rehabil Rep 2013;1:280-91.

19 Farneti D, Fattori B, Nacci A, et al. *The Pooling-score (P-score): inter- and intra-rater reliability in endoscopic assessment of the severity of dysphagia*. Acta Otorhinolaryngol Ital 2014;34:105-10.

20 Langmore SE, Pisegna JM. *Efficacy of exercises to rehabilitate dysphagia: a critique of the literature.* Int J Speech Lang Pathol 2015;17:222-9.

21 Murray J, Langmore SE, Ginsberg S, et al. *The significance of accumulated oropharyngeal secretions and swallowing frequency in predicting aspiration.* Dysphagia 1996;11:99-103.

22 Crary MA, Carnaby GD, Sia I, et al. *Spontaneous swallowing frequency has potential to identify dysphagia in acute stroke.* Stroke 2013;44:3452-7.

23 Molfenter SM, Steele CM. *The relationship between residue and aspiration on the subsequent swallow: an application of the normalized residue ratio scale.* Dysphagia 2013;28:494-500.

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Rhinology

Clinical characteristics of patients with granulomatosis with polyangiitis and microscopic polyangiitis in ENT practice: a comparative analysis

Caratteristiche cliniche dei pazienti con granulomatosi con poliangioite e poliangioite microscopica nella pratica clinica ORL: analisi comparativa

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SUMMARY

ENT manifestations are commonly observed in patients with small vessel vasculitis (SVV). The main aim of this study was to analyse and present the clinicopathological characteristics of individuals with SVV emphasising otorhinolaryngological symptoms. This study evaluated 64 patients, 41 with granulomatosis with polyangiitis (GPA) and 23 with microscopic polyangiitis (MPA). Herein, we compare the clinicopathologic features of GPA and MPA. The average age at diagnosis was 50.2 and 56.2 years, for GPA and MPA, respectively. 57 patients (89%) were antineutrophil cytoplasmic antibody (ANCA) positive, 34 (59.6%) for anti-proteinase 3 (PR3)-ANCA and 21 (36.8%) for myeloperoxidase (MPO)-ANCA. 7 patients (10.9%) were ANCA negative. The most commonly affected organs were lungs (76.56%), ear, nose, throat (ENT) (75%) and kidneys (73.44%). ENT disorders mainly appeared as chronic rhinosinusitis and epistaxis and preceded SVV diagnosis by an average 14.4 months. In the majority of patients, ENT disorders were the first symptoms of SVV and preceded its systemic transformation. Pulmonary, ENT and nervous manifestations were more common in GPA, whereas the prevalence of renal, gastrointestinal, cutaneous, cardiovascular and ocular disorders was higher in MPA. The results of our study emphasise the high prevalence of ENT symptoms in patients with SVV, especially in those with GPA. We highlight the significant role of the otorhinolaryngologist in early SVV diagnosis and management. Any patient with persistent ENT symptoms or ENT dysfunctions not responding to standard otorhinolaryngological treatment should be precisely and rapidly evaluated for the presence of systemic dysfunctions (especially renal and pulmonary). Realising the differences and similarities between GPA and MPA is crucial in undelayed SVV diagnosis and proper treatment.

KEY WORDS: Granulomatosis with polyangiitis • Microscopic polyangiitis • Vasculitis • MPO-ANCA • PR3-ANCA

RIASSUNTO

Nei pazienti con vasculiti dei piccoli vasi (SVV), si osservano frequentemente manifestazioni del distretto otorinolaringoiatrico (ORL). Lo scopo principale di questo studio è stato quello di analizzare e presentare le caratteristiche clinicopatologiche degli individui con SVV, enfatizzando i sintomi della sfera ORL. Sono stati valutati 64 pazienti, 41 con granulomatosi con poliangioite (GPA) e 23 con poliangioite microscopica (MPA). Abbiamo presentato e paragonato le manifestazioni clinicopatologiche di GPA e MPA. L'età media alla diagnosi è stata rispettivamente di 50,2 e 56,2 anni per GPA e MPA. 57 pazienti (89%) erano positivi per gli anticorpi anti citoplasma dei neutrofili (ANCA), 34 (59,6%) per gli anti proteinasi 3-ANCA e 21 (36,8%) per mieloperossidasi (MPO)-ANCA. 7 pazienti erano ANCA negativi. Gli organi più frequentemente colpiti sono stati polmone (76,5%), ORL (75%) e reni (73,4%). Le problematiche ORL si sono manifestate più frequentemente sotto forma di rinosinusite cronica ed epistassi ed hanno preceduto in media la diagnosi di SVV di circa 14,4 mesi. Nella maggior parte dei pazienti i disturbi ORL hanno rappresentato il primo sintomo di SVV, precedendone la trasformazione sistemica. Nella GPA, sono risultate più frequenti le manifestazioni polmonari, ORL e del sistema nervoso, mentre nella MPA quelle renali, gastrointestinali, cutanee, cardiovascolari ed oculari. I risultati del nostro studio hanno enfatizzato l'alta prevalenza di sintomi ORL nei pazienti con SVV, specialmente in quelli con GPA. Vogliamo quindi sottolineare il ruolo importante dello specialista ORL nella diagnosi precoce e nel conseguente precoce trattamento delle SVV. Ogni paziente con sintomi o disfunzioni ORL persistenti e non responsivi alle terapie standard, deve essere valutato per la presenza di manifestazioni sistemiche (specialmente renali e polmonari). Evidenziare le differenze e le somiglianze tra GPA e MPA è cruciale per una precoce diagnosi di SVV e per iniziare una terapia adeguata.

PAROLE CHIAVE: *Granulomatosi con polyangioite • Poliangioite microscopica • Vasculiti • MPO-ANCA • PR3-ANCA*

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Introduction

Small vessel vasculitis (SVV) is a heterogeneous group of idiopathic disorders characterised by necrosis and inflammation of small-sized blood vessels [1]. SVV with the serum presence of antineutrophil cytoplasmic antibody (ANCA) is classified as ANCA-associated vasculitis (AAV). The main variants of AAV are granulomatosis with polyangiitis (GPA; previously Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA), including renal-limited vasculitis (RLV) [2]. The presence of ANCA in sera constitutes a crucial serologic marker of AAV, even if there are cases with negative ANCA. ANCA patterns are classified as anti-proteinase 3 (PR3) – ANCA (cytoplasmic anti-neutrophil cytoplasmic antibody, c-ANCA), and anti-myeloperoxidase (MPO) – ANCA (perinuclear- anti-neutrophil cytoplasmic antibody, p-ANCA) [3]. The majority of cases with ANCA negativity is observed in patients in early stages of the disease or in those with localised disease that is limited to organs of the upper respiratory tract and lungs [4 5]. Besides the upper respiratory tract, AAV typically affects the lower respiratory tract and kidneys. Nevertheless, any organ may be involved. In the great majority of patients with AAV, especially in those with GPA, the initial symptoms of the disease are otorhinolaryngological abnormalities [6 7]. In MPA, involvement of head and neck organs is less common. Besides the fact that exact diagnosis is based on the combination of particular serologic, laboratory, imaging and histopathologic features, clinical manifestations are of great value in early disease recognition and therapy [8]. It has been suggested that *Staphylococcus aureus (S. aureus)* may act as a molecular mimicry for proteinase 3 (PR3) and may be a trigger point of PR3 autoimmunity and PR3-ANCA autoantibody production. It was observed that the nasal carriage of *S. aureus* in patients during GPA remission predisposes to disease relapses. This explains the validity of anti-staphylococcal prophylaxis with trimethoprim/sulfamethoxazole in patients with remission [2 9]. The question of whether or not there is a possible role for *S. aureus* in MPA pathogenesis still remains unanswered.

In this study, we present the clinicopathological features of a group of our patients with AAV. We report in detail the particular manifestations in subjects with GPA and MPA, comparing these two groups. According to the high frequency of ENT disorders in patients with AAV, we highlight the importance of the otorhinolaryngologist in establishing AAV diagnosis and its management.

Materials and methods

Clinical data

An institutional ethics committee approved the study, and the study protocol complied with the Helsinki Declaration. We examined 64 patients with SVV who were admitted to our tertiary referral university hospital between January 2016 and April 2017. Patients' medical SVV-related records gathered before January 2016 were included in the study. The American College of Rheumatology (ACR) classification criteria for vasculitis, and the Chapel Hill Consensus Conference (CHCC) classification were used to assign patients to particular subgroups as GPA or MPA, respectively [10 11]. According to these classifications, 41 patients met the criteria for GPA and 23 patients were classified as suffering from MPA.

Demographic features included gender, age and age at diagnosis. Clinical manifestations and laboratory investigation were examined in all patients at the time of hospitalisation. Clinical assessment was performed by an otolaryngologist (JW) and nephrologist (MK) to minimise bias. Laboratory investigation comprised presence of ANCA, complete blood count (CBC), serum creatinine levels, serum urea levels, urinalysis, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and procalcitonin (PCT) levels. All laboratory tests were performed at the same hospital laboratory.

Measurement of serum ANCA levels was done using indirect immunofluorescence (IFA). In ANCA-positive patients detected by IFA, enzyme-linked immunosorbent assay (ELISA) was used to determine the serum levels of PR3-ANCA and MPO-ANCA. ANCA assessment was done at least twice, in time intervals, to eliminate possible false negative or false positive results.

When available, nasal swabs for bacterial pathogens dwelling in the nasal cavity were examined retrospectively.

Clinical evaluation of systemic involvement was enriched with imaging studies (CT scan) of the thoracic cavity.

Otorhinolaryngological examination

Otorhinolaryngological investigation was performed by an otorhinolaryngologist (JW) and was based on standard clinical examination consequently supported by endoscopic evaluation (flexible and rigid Karl Storz endoscopes) in patients with positive or uncertain findings. Indirect laryngoscopy (Karl Storz laryngoscope) was used in all patients to assess the oropharynx, larynx and hypopharynx. Audiology tests including pure tone audiometry (PTA) and impedance audiometry (IA) were used

in patients with hearing deficits detected in traditional voice tests (TVT) and in tuning fork test (TFT). Computed tomography (CT) of the sinuses was performed in individuals with sinonasal abnormalities found in ENT examination and in those with positive history of sinonasal manifestations.

Histology

Histologic data were obtained from 48 biopsies taken from 42 patients. Five patients with clinical presentation strongly suggesting AAV were biopsied more than once because of nondiagnostic histologic results. Twenty-two patients did not have any biopsy. Four subjects underwent histologic examination of more than one organ.

It was established that biopsy presenting necrotising vasculitis confirmed the presence of AAV. Histologic findings in our patients were classified as positive or negative for particular subgroups of AVV according to standards, i.e. small-vessel granulomatous necrotising vasculitis was classified as GPA, and small-vessel nongranulomatous necrotising vasculitis was classified as MPA [2].

Disease severity

Disease severity stages of enrolled patients were assessed using European Vasculitis Study Group (EUVAS) recommendations [12]. Patients were classified as suffering from localised, early systemic, generalised or severe AAV. A localised form of AAV was characterised by ear, nose, throat (ENT) or lung involvement with serum creatinine levels < 120 μmol/l (1.3 mg/dl); an early systemic form was defined as ENT and pulmonary involvement in combination with involvement of an organ outside the upper respiratory tract and serum creatinine levels < 120 μmol/l (1.3 mg/dl). Generalised forms included cases with vasculitis in organs outside the ENT and lungs, threatened function of vital organ and serum creatinine levels < 500 μmol/l (5.5 mg/dl). A severe form was defined as vasculitis in organs outside the ENT and lungs, failure of vital organ function and serum creatinine levels > 500 μmol/l (5.5 mg/dl).

Results

In total, 64 patients were enrolled in our study. We identified 41 individuals (19 males/22 females) with GPA and 23 individuals (10 males/ 13 females) with MPA. The mean age of patients during hospitalisation in our hospital was 54 years (55.3 years in males/53.1 years in females) for GPA, and 60.3 years (55.9 years in males/63.6 years in females) for MPA, respectively. The average age at the time of AAV diagnosis was 50.2 years and 56.2 years, for GPA and MPA, respectively. In females, the mean age at diagnosis reached 53 years, whereas in men it was 55.3 years (Table I). In the majority of cases the initial symptoms were ENT disorders. The average duration between first ENT disorders and AAV diagnosis was 14.5 months, ranging between 1 month to 36 months. The most common initial ENT manifestations were recurrent epistaxis and persistent chronic rhinosinusitis not responding to standard treatment. Less frequent complaints at disease onset were chronic purulent otitis media and sudden sensorineural hearing loss.

Serology

The majority of patients, 57 patients (89.1%), were ANCA positive, among which 34 (59.6%) were positive for PR3-ANCA and 21 (36.8%) for MPO-ANCA. Two patients (3.5%) were positive for both PR3-ANCA and MPO-ANCA. Thirty-six patients (100%) positive for PR3-ANCA were classified as suffering from GPA. 21 patients (91.3%) positive for MPO-ANCA were classified as suffering from MPA. Seven patients (10.9%) were identified as ANCA negative (negative serum PR3-ANCA and MPO-ANCA levels) and 5 individuals with GPA and 2 with MPA, respectively.

Other biochemical findings

The most common biochemical findings in our patients with GPA were neutrophilia in CBC, microscopic and gross haematuria by urinalysis, and elevated ESR (Table II). In the MPA cohort, the most common abnormalities were neutrophilia, microscopic haematuria, elevated ESR and elevated serum creatinine and urea.

Normal levels of CRP did not exceed 5 mg/l. We classified CRP as elevated when it reached more than 10 mg/l. In our cohort, CRP was increased in 35 subjects (GPA/MPA, 23/13). ESR in normal conditions should not surpass 20 mm/h, depending on age and gender. We categorised ESR as elevated when it exceeded 30 mm/h. 48 patients (GPA/MPA, 31/17) in our cohort presented abnormally high ESR levels. PCT was elevated (> 0.5 ng/ml) in 25 individuals (GPA/MPA, 17/8).

Serum creatinine levels above normal level (> 1.3 mg/dL) was reported in 41 cases (GPA/MPA, 24/17), whereas serum urea levels were increased (> 40 mg/dL) in 41 patients (GPA/MPA, 23/18).

According to ANCA antibody status, patients with the presence of MPO-ANCA antibodies were more prone to have elevated serum creatinine and urea levels than patients with PR3-ANCA antibodies. A similar observation has also been reported by other authors [13 14].

Abnormal urinalysis was reported in 49 patients (GPA/

Table I. Characteristics of patients with GPA and MPA.

	GPA, n = 41	MPA, n = 23
Gender (male/female) %	19/22 (46.3/53.7)	10/13 (43.5/56.5)
Mean age (male/female) in years	54 (55.3/53.1) (range 20-80)	60.3 (55.9/63.6) (range 35-85)
Mean age at diagnosis (male/female) in years	50.2	56.2
PR3-ANCA positivity (+), n (%)	34 (82.9)	0 (0%)
MPO-ANCA positivity (+), n (%)	0 (0%)	21 (91.3%)
PR3-ANCA(+) and MPO-ANCA(+), n (%)	2 (4.88%)	0 (0%)
ANCA negativity (-), n (%)	5 (12.2%)	2 (8.7%)
Colonisation of *Staphylococcus aureus*, n (%)	12 (29.3%)	2 (8.7%)
Histopathologic confirmation, n (%)	32 (78%)	11 (47.8%)
Disease severity stage:		
localised, n (%)	13 (31.7%)	2 (8.7%)
early systemic, n (%)	2 (4.88%)	2 (8.7%)
generalised, n (%)	18 (43.9%	10 (43.48%)
severe, n (%)	8 (19.5%)	9 (39.1%)

MPA, 29/20). In our cohort, patients with MPA were more prone to present disorders in urinalysis. The most frequent urinalysis finding was the concomitant presence of proteinuria, microscopic haematuria, gross haematuria and leukocyturia.

The prevalence of CBC disorders was higher in subjects with MPA than in those with GPA. Abnormalities in CBC were detected in 59 patients (GPA/MPA, 37/22). The most common findings in CBC were leukocytosis, neutrophilia, lymphopenia and anaemia. Thrombocytosis was less frequent and was reported in only 9 cases. ANCA negative patients typically presented concomitant leukocytosis, neutrophilia and lymphopenia. Laboratory findings are presented in Table II.

Table II. Laboratory findings in patients with AAV.

Laboratory findings, n (%)	GPA, n = 41	MPA, n = 23
CRP (> 10 mg/l)	23 (56)	13 (56.5)
ESR (> 30mm/h)	31 (75.6)	17 (73.9)
PCT (> 0,5 ng/ml)	17 (41.46)	8 (34.78)
Serum creatinine (> 1.3 mg/dl)	24 (58.5)	17 (73.9)
Serum urea (> 40 mg/dL)	23 (56.1)	18 (78.3)
Urinalysis – abnormalities:	29 (70.7)	20 (87)
Proteinuria	21 (51.2)	16 (69.6)
Microscopic haematuria	24 (58.5)	19 (82.6)
Gross haematuria	24 (58.5)	15 (65.2)
Leukocyturia	17 (41.5)	13 (56.5)
CBC – abnormalities:	37 (90.2)	22 (95.7)
Leukocytosis	24 (58.5)	13 (56.5)
Neutrophilia	31 (75.6)	19 (82.6)
Lymphopenia	24 (58.5)	16 (69.6)
Anaemia	24 (58.5)	16 (69.6)
Thrombocytosis	8 (19.5)	1 (4.3)

CRP = C-reactive protein; ESR = Erythrocyte sedimentation rate; CBC = Complete blood count; PCT = Procalcitonin.

Microbiology

The majority of patients with GPA, and only two patients with MPA, were colonised by *S. aureus.* The most common staphylococcal nidus was the nasal cavity.

In our study, 37 patients (57.8%) underwent microbiological examination among which we identified 14 individuals (37.8%) colonised by *S. aureus*, 12 patients (85.7%) with GPA and 2 (14.3%) with MPA. The majority of infected patients was PR3-ANCA positive and presented a localised form of the disease. Nasal carriage of *S. aureus* was the most frequently colonised area, and was established in 12 patients (85.7%) in which 2 were ANCA negative. Nasal carriage of *S. aureus* was identified only in one patient with MPA. Other pathogens identified in our patients were *Fussarium* (1 patient; 2.7%), *Acinetobacter baumanii* (2 patients; 5.4%), *Enterobacter cloacae* (1 patient; 2.7%), *Escherichia coli* (2 patients; 5.4%), *Klebsiella pneumoniae* (2 patients; 5.4%), *Pseudomonas aeruginosa* (2 patients; 5.4%) and *Enterecoccus faecium* (1 patient; 2.7%).

Histology

Among 48 biopsies taken from 42 patients, 43 (89.6%) met the criteria for AAV. Thirty-two biopsies (74.4%) were classified as typical for GPA, and 11 (25.6%) suggested MPA. The AAV-positive biopsies were taken from kidney (n = 21), nose (n = 11), ear (n = 4), trachea (n = 1), lung (n = 1), muscle (n = 1), skin (n = 1), auto-amputated

finger (n = 1), sphenoid sinus (n = 1) and spleen (n = 1). 3 biopsies taken from nasal cavity and 2 taken from kidney were not diagnostic for any type of AAV.

Radiologic imaging of the thoracic cavity

CT scan of the thoracic cavity was performed in the majority of patients. We identified various vasculitis-related chest abnormalities in 46 patients (71.88%), 30 patients (73.17%) with GPA and 16 (69.6%) with MPA. The most common radiologic findings were pulmonary nodules (34.38%), diffuse ground-glass opacity (GGO) – a result of diffuse alveolar haemorrhage [DAH] (23.44%), and inflammatory infiltrations (45.3%), respectively. Interstitial fibrosis or thickening were rarer (17.19% of patients), whereas pneumothorax presented only in one patient (1.56%). Pleural effusion was observed in 6 patients (9.38%). In summary, pulmonary nodules, GGO, inflammatory infiltrations, pneumothorax and pleural effusion were more common in those suffering from GPA. In contrast, interstitial fibrosis or thickening was observed more often in patients with MPA.

Disease severity

The most common disease stages in our cohort were generalised AAV, followed by severe form, and they were more often observed in patients with MPA than in those with GPA. The majority of localised forms of AAV was reported in subjects with GPA.

In our study, 15 patients (23.44%), 13 vs. 2, for GPA and MPA, respectively, met the criteria for localised disease. In the group of 13 patients with a localised form, 7 subjects were PR3-ANCA positive, 4 subjects were ANCA negative and 2 individuals were positive for both PR3-ANCA and MPO-ANCA. All patients with localised MPA were positive for MPO-ANCA. 4 patients (6.25%), 2 individuals with GPA and 2 with MPA, were classified as suffering from early systemic disease. 28 people (43.75%) presented a generalised form, 18 with GPA and 10 with MPA. 17 patients (26.56%), 8 vs. 9, for GPA and MPA, respectively, developed severe AAV (Table I).

Clinical manifestations (Table III)

ENT involvement

In general, 48 patients (75%), 35 patients (85.37%) with GPA and 13 patients (56.52%) with MPA, presented ENT involvement (Table IV).

Nose and paranasal sinuses. The most commonly affected ENT organs in patients with AAV were paranasal sinuses. In our study, subjects with GPA were more prone to suffer from sinonasal disorders than those with MPA. In total, 45 patients (70.3%) presented vasculitis-related abnormalities in nose or paranasal sinuses, 33 patients (80.49%) with GPA and 12 (52.17%) with MPA, respectively._32 patients (50%) presented chronic rhinosinusitis (CRS). CRS was diagnosed in 26 patients (63.41%) with GPA and in 6 patients (26.09%) with MPA. 27 patients (42.18%), 21 (51.22%) with GPA and 6 (26.09%) with MPA, suffered from recurrent, persistent epistaxis. These symptoms were the most frequently observed at the initial stage of the disease. We identified 10 cases of nasal septum perforation (NSP). NSP was found in 8 patients (19.51%) with GPA and in 2 patients (8.7%) with MPA. 22 patients (34.38%) presented chronic purulent nasal discharge, 16 individuals (39.02%) with GPA and 2 individuals (8.7%) with MPA, respectively. Nasal ulcerations were identified in 15 patients (23.43%), 12 (29.27%) with GPA and 3 (13.04%) with MPA.

Ears. The most frequent otologic disorders in our patients were sensorineural hearing loss and chronic otitis media followed by conductive hearing loss. Individuals with GPA were more prone to suffer from otologic dysfunction than those with MPA.

In our study, 36 patients (56.25%) presented vasculitis-related abnormalities in ears or in the sense of hearing, 25 patients (60.98%) with GPA and 11 (47.83%) with MPA, respectively. Hearing loss was identified in 32 patients (50%), 24 (58.54%) with GPA and 8 (34.78%) with MPA. There were 18 (28.13%) cases of sensorineural hearing loss, 12 (18.75%) cases of conductive hearing loss, 8 (12.5%) cases of mixed hearing loss, and 2 patients (3.13%) with deafness identified in pure tone audiometry. Tinnitus was observed in 10 patients (15.62%). Chronic otitis media was identified in 13 patients (20.31%), whereas otitis media with effusion was found in 8 patients (12.5%). 4 individuals (6.25%) suffered from recurrent episodes of purulent acute otitis media but without developing chronic otitis media.

Larynx. Laryngeal manifestations of AAV were not frequent in our study. Disorders in this localisation were found more often in patients with GPA than in those with MPA, except for laryngeal ulcerations that were more common in the latter group.

In a group of 64 enrolled patients, 12 (18.75%) presented vasculitis-induced lesions in larynx. There were 8 patients (12.5%) with GPA and 4 (17.4%) with MPA with such involvement. Laryngeal abnormalities were not related to smoking status. Patients with positive smoking status were excluded from the study and statistics to minimalize the bias. 3 patients (4.69%) presented subglottic stenosis, 2 (4.88%) with GPA and 1 (4.35%) with MPA. 2 patients with MPA and 1 patient with GPA were diagnosed with

Table III. Clinical manifestations presenting organ involvement in specific types of AAV.

AAV type organ involvement	GPA n = 41	MPA n = 23	PR3-ANCA (+) n = 34	MPO-ANCA (+) n = 21	ANCA (-) n = 7	MPO-ANCA (+) and PR3-ANCA (+) n = 2	Total n = 64
ENT	35 (85.37%)	13 (56.52%)	29 (85.29%)	12 (57.14%)	5 (71.43%)	2 (100%)	48 (75%)
Eyes	5 (12.2%)	3 (13.04%)	5 (21.74%)	3 (14.29%)	0 (0%)	0 (0%)	8 (12.5%)
Lungs	32 (78.05%)	16 (69.57%)	29 (85.29%)	15 (71.43%)	3 (42.86%)	1 (50%)	49 (76.56%)
Trachea	4 (9.76%)	1 (4.35%)	4 (11.76%)	1 (4.76%)	0 (0%)	0 (0%)	5 (7.81%)
Kidneys	26 (63.41%)	21 (91.3%)	25 (73.53%)	19 (90.48%)	3 (42.86%)	0 (0%)	47 (73.44%)
Cardiovascular system	8 (19.51%)	10 (43.48%)	8 (23.53%)	10 (47.62%)	0 (0%)	0 (0%)	18 (28.13%)
Skin	12 (29.27%)	8 (34.78%)	11 (32.35%)	8 (38.1%)	1 (14.26%)	0 (0%)	20 (31.25%)
Gastrointestinal system	2 (4.88%)	3 (13.04%)	2 (5.88%)	2 (9.52%)	1 (14.26%)	0 (0%)	5 (7.81%)
Musculoskeletal system	10 (24.39%)	6 (26.09%)	10 (29.41%)	6 (28.57%)	0 (0%)	0 (0%)	16 (25%)
Nervous system	8 (19.51%)	0 (0%)	8 (23.53%)	0 (0%)	0 (0%)	0 (0%)	8 (12.5%)

laryngeal ulcerations. Inspiratory dyspnoea was observed in 8 patients (12.5%), 5 (12.2%) with GPA and 3 (13.0%) with MPA. 8 individuals (12.5%), 7 (17.1%) with GPA and 1 (4.35%) with MPA, presented hoarseness. We identified 2 patients (3.13%) with laryngeal oedema (2 individuals with GPA and no case related to MPA), 1 patient (1.56%) with chronic laryngitis suffering from GPA and 1 patient (1.56%) with aphonia and GPA. 2 patients (3.13%) with GPA experienced peripheral unilateral vocal fold paralysis. There were no cases of supraglottic stenosis or laryngeal necrotising granuloma in our study.

Eyes. Ocular disorders were found in 8 patients (12,5%). In general, the majority of ocular manifestations of AAV was identified in patients with GPA (3 patients; 13%). Individuals with GPA (5 patients; 12.2%) were less prone to suffer from ocular involvement in our research. The most common eye-related disorder was episcleritis. Episcleritis was observed in 5 patients (7.8%), 3 (13%) with MPA and 2 (4.9%) with GPA, respectively. 3 individuals (4.69%) from the study group, 2 (4.8%) patients with GPA and 1 (4.3%) with MPA, suffered from scleritis. Subconjuntival haemorrhages were identified in 3 patients (4.69%) with a higher prevalence in patients with MPA. Sudden unilateral visual loss was found in 1 patient (1.57%) diagnosed with GPA.

Unfortunately, there is a limitation of the data on ocular involvement because of the fact that only 36 patients (56.25%) were examined by an ophthalmologist. Accordingly, there could have been undiagnosed cases of ocular AAV-related abnormalities in our patients.

Vertigo. 6 patients (9.38%), 3 patients (7.3%) with GPA and 3 patients (13.0%) with MPA, experienced recurrent episodes of vertigo during vasculitis.

Oral cavity, oropharynx. We identified 4 cases (6.25%) with ulcerations located in the oral cavity or oropharynx. The majority of cases was observed in patients with GPA.

Salivary glands: Involvement of salivary glands was found only in patients with GPA. 2 patients (3.12%) developed inflammation of the parotid gland, whereas 1 (1.57%) experienced non-inflammatory enlargement of parotids.

Lower respiratory tract involvement

Lungs. Pulmonary involvement was a common presentation in the group of our patients. It was reported in 49 individuals (76.56%), 32 (78.04%) with GPA and 16 (69.57%) with MPA, respectively. The most frequent disorder in the lower respiratory tract was pneumonia (29 cases; 45.31%). Haemoptysis was reported in 18 individuals (28.13%). 6 patients (9.38%) suffered from recurrent bronchitis. Persistent cough was observed in 13 patients (20.31%).

Trachea. Tracheal manifestations of AAV were found in a small part of our cohort. Only 5 patients (7.81%) experienced abnormalities in this area, 4 patients (9.8%) with

GPA and 1 patient (4.3%) with MPA. The majority of patients with tracheal involvement presented tracheitis (4 patients; 6.25%). Tracheal necrotising granulomas were found in 1 patient (1.59%) with GPA, similarly to tracheal stenosis (1 patient with GPA).

Renal involvement

AAV-related improper function of kidneys was detected in the vast majority of individuals. Patients with MPA were more prone to suffer from renal involvement than those with GPA.

Kidneys were affected in 47 patients (73.44%), 26 (63.41%) with GPA and 21 (91.3%) with MPA. According to histopathologic findings, the majority of patients (10 patients) presented rapidly progressive glomerulonephritis (RPGN), which was the most common type of glomerulonephritis in our cohort. Additionally, we identified 3 patients with mesangial proliferative glomerulonephritis (MPGN) and 2 cases of focal segmental glomerulonephritis (FSGN).

In the group of patients with renal involvement, 31 (66%) presented affection of ENT area, 20 patients (42.6%) with GPA and 11 (23.4%) with MPA. ENT manifestations preceded kidney dysfunction in all cases.

Cardiovascular manifestations

Cardiovascular disorders were identified in 18 patients (28.13%) with predominance in patients with MPA. The most common presentation was hypertension (11 patients; 17.18%). 6 individuals (9.38%) suffered from valvular heart disease, 2 (3.13%) were diagnosed with cardiomyopathy and 5 (7.81%) presented a history of non-atherosclerotic ischaemic cardiac pain. Heart arrhythmias were reported in 4 cases (6.25%).

Cutaneous manifestations

Vasculitis-induced cutaneous abnormalities occurred more often in patients with GPA than in those with MPA. We identified 20 individuals (31.3%) with AAV-related cutaneous symptoms with purpura as the most common one (13 patients; 20.31%). 4 individuals (6.25%) developed skin ulcerations. Gangrene affected the fingers and toes, and was observed in 2 patients (3.13%), one patient with GPA and one with MPA. Gangrene of fingers and toes was followed by their demarcation in both cases.

Gastrointestinal tract manifestations

Gastrointestinal tract was affected in 5 patients (7.81%), 3 individuals (13%) with MPA and 2 patients (4.88%) with GPA. 3 patients (4.69%), 2 patients (4.88%) with GPA and 1 (4.35%) with MPA, experienced gastrointestinal bleeding. In addition, 2 patients (3.13%), 1 with GPA and 1 with MPA, developed intestinal ischaemia followed by partial necrosis of the small intestine. The necrosis identified in the small intestine required extensive excision. 1 patient (1.56%) diagnosed with MPA and presenting ANCA negative status experienced infarct and rupture of the spleen. The same patient developed acute hepatic and spleen arteries dissections. The group with gastrointestinal involvement consisted of 2 subjects with PR3-ANCA positive antibodies, 2 subjects with positive MPO-ANCA and one patient with ANCA negative profile.

Nervous system involvement

We identified 8 individuals (12.5%) suffering from AAV-related nervous system disorders. All these patients presented GPA form of AAV with positive PR3-ANCA antibodies. Except for one patient, each of these 8 subjects presented ENT involvement. Otorhinolaryngological symptoms preceded nervous dysfunction in every case. We did not observe any nervous manifestations in patients with MPA.

We identified 4 cases of peripheral nervous system dysfunction, 3 cases of various cranial nerves palsies and 1 case of stroke. Peripheral nervous system dysfunction appeared as mononeuritis multiplex.

Cranial nerve palsy. Trigeminal nerve palsy was seen in 1 patient (1.57%), facial nerve palsy in 2 patients (3.13%), glossopharyngeal nerve palsy in 2 patients (3.13%), vagal palsy in 2 patients (3.13%), accessory nerve palsy in 1 patient (1.57%) and hypoglossal nerve palsy in 1 patient (1.57%). Vagal nerve palsy appeared as vocal fold paralysis (paralysis of vagus nerve branch called recurrent laryngeal nerve) in both cases.

1 patient presented bulbar palsy (dysfunction of IX, X, XI and XII cranial nerves).

Musculoskeletal involvement

Musculoskeletal system was affected in 16 patients (25%), 10 patients (24.4%) with GPA and 6 (26.1%) with MPA, respectively. The main presentation in these individuals were recurrent arthritis and joints pain.

Discussion

The estimated annual incidences of GPA and MPA range from 2 to 12 cases per million population, with a prevalence of 23 to 160 cases per million population. While GPA is more frequent in Europe (especially in northern Europe) and United States than in Japan, MPA is more common in Japan and China than in Europe and United States [15]. In the majority of cases, GPA is characterised by

the serum presence of PR3-ANCA antibodies and clinical involvement of organs forming "classic GPA triad". The "classic GPA triad" includes upper and lower respiratory tract affection with coexisting renal dysfunction [16]. Otorhinolaryngological manifestations are the initial symptoms of GPA in 80-95% of cases and usually precede its conversion to systemic disease [17].

Patients with MPA typically present pulmonary abnormalities and renal dysfunction [18]. ENT involvement is not common in this type of vasculitis and is definitely rarer than in patients with GPA [19]. Sera taken from individuals with MPA frequently express MPO-ANCA antibodies [20].

The main aim of this study was to document clinicopathological features of patients with small-vessel vasculitis (GPA and MPA) referred to our university hospital between January 2016 and April 2017. We compared clinicopathological features observed in GPA patients with those seen in MPA individuals focusing on otorhinolaryngological disorders. We tried to understand if ENT involvement correlates with MPA because data on this matter is sparse and inconsistent. We focused on otorhinolaryngological manifestations, which are typically the initial symptoms of AAV (specially GPA) to emphasise the role of the otorhinolaryngologist in early diagnosis and disease management. It is well known that rapid diagnosis may significantly improve prognosis of patients with AAV, whereas delayed diagnosis significantly worsens prognosis.

In our study, the most commonly affected area was the lower respiratory tract (49 patients; 76.56%), followed by ENT involvement (48 patients; 75%). Pulmonary involvement typically appeared as pneumonia and haemoptysis. Similar to other studies, in our cohort the most common radiographic findings in lungs in GPA and MPA were nodules and inflammatory infiltrations [21 22]. Kidney affection was also frequently observed in our cohort (47 subjects; 73.44%). The most common renal disorder was RPGN, consistently with Chachar et al. [23]. Cutaneous involvement with purpura as the most frequent presentation was reported in 19 subjects (31.25%). Cardiovascular manifestations were found in 18 patients (28.13%). The majority of disorders in this group constituted hypertension and valvular heart disease. Musculoskeletal dysfunction appearing as recurrent arthritis and joints pain was detected in 16 individuals (25%). Nervous system was affected in 8 cases (12.5%) with mononeuritis multiplex reported in most. Similarly, ocular involvement was observed in 8 subjects (12.5%) with episcleritis as the most common manifestation. The rarest area involved in our cohort (5 patients; 7.81%) was gastrointestinal involvement with gastrointestinal bleeding as the most frequent manifestation. Pulmonary, ENT and nervous involvements were more common in patients with GPA, whereas renal and gastrointestinal were mostly found in MPA, consistent with another study [14]. Inconsistent with one investigation [13], but consistent with another [13], our results revealed the greater prevalence of cutaneous, cardiovascular and ocular disorders in patients with MPA.

ENT manifestations detected in the study were present at the initial phase of AAV (in all cases with GPA and in several with MPA) and preceded AAV diagnosis. The mean duration since first ENT symptoms to AAV diagnosis in our patients reached 14.5 months, and was longer than reported by another author [24]. The overall prevalence of otorhinolaryngological abnormalities detected in the initial stage of AAV was 75 %. The presence of ENT symptoms in the early clinical picture reached 85.37% in GPA and 56.52% in MPA. In the group of 35 patients with GPA and coexisting ENT involvement, 29 (82.86%) were positive for PR3-ANCA antibodies, 4 subjects (11.43%) were ANCA negative and 2 (5.71%) were positive for both PR3-ANCA and MPO-ANCA. In the cohort of 13 patients with MPA and ENT involvement, 12 (92.3%) were positive for MPO-ANCA, and 1 (7.69%) was seronegative. According to our results, patients with localised SVV are more prone to be ANCA negative. The high prevalence of ENT manifestations in subjects with AAV was confirmed in various studies [14 25]. Similar to another study, herein the localised form of AAV was more frequently observed in individuals with GPA than in those with MPA, whereas MPA rather than GPA predisposed to severe form of AAV [14].

The most common disease manifestation in the head and neck area in both groups, GPA and MPA, was chronic rhinosinusitis followed by epistaxis and purulent nasal discharge. This observation confirmed that reported by Metaxaris et al. [24]. Similar to Ono et al., our study found that ears were also frequently affected with chronic otitis media and sensorineural hearing loss as the most frequent disorders [26]. Otitis media with effusion, conductive hearing loss and deafness were only found in patients with GPA. The majority of laryngeal disorders appeared as hoarseness (not related to smoking) and inspiratory dyspnoea. There were 3 cases of subglottic stenosis and no subject presenting supraglottic stenosis in our study. We observed 2 individuals with peripheral facial nerve palsy and 2 patients with vocal fold palsy.

In our cohort, GPA was more frequently observed in females than in males and in women the disease developed earlier, as in other studies [13 27]. The mean age at diagnosis reached 50.2 years and was similar to observed by other authors [14 25]. The most commonly affected areas in patients with GPA were ENT, kidneys and lower respiratory tract,

reaching 85.37%, 63.41% and 78.05%, respectively. In 21 cases (51.22%), localised GPA with otorhinolaryngological symptoms transformed to systemic disease, with renal and pulmonary involvement in the majority of patients. In contrast, in 14 subjects (34.15%) otorhinolaryngological symptoms have not converted to systemic disease to date. Consistent with previous reports, in our study ENT involvement mainly appeared as chronic rhinosinusitis, purulent nasal discharge, epistaxis, chronic otitis media and sensorineural hearing loss, whereas pulmonary manifestations were mainly haemoptysis and pneumonia [23 25]. CBC typically revealed leukocytosis with neutrophilia, lymphopenia and anaemia, while urinalysis presented proteinuria with microscopic haematuria and gross haematuria in most cases. Increased CRP, ESR, serum creatinine and urea levels were also frequently observed. Moreover, we found that patients with GPA were more frequently colonised by *S. aureus* than individuals with MPA. Interestingly, the majority of patients with *staphylococcal* carriage presented a localised form of the disease.

Similar to other studies, our results show that MPA develops later than GPA [14 26]. MPA was also more frequent in women than in men. Women developed MPA at younger age than men. For MPA, the most frequent manifestations were renal, pulmonary and ENT disorders reaching 91.3%, 69.57% and 56.52%, respectively. Renal involvement in our patients with MPA was more common than in those with GPA. This observation was consistent with the results of other studies [13 28]. Otorhinolaryngological abnormalities typically reported in this group were chronic rhinosinusitis, purulent nasal discharge, epistaxis and sensorineural hearing loss. Similar to GPA, CBC in patients with MPA also mainly revealed leukocytosis with neutrophilia, lymphopenia and anaemia, while urinalysis presented proteinuria with microscopic haematuria and gross haematuria in most cases. Nevertheless, CBC and urine abnormalities were more common in individuals with MPA. This same observation can also be made for serum creatinine and urea levels. In this study, increased serum creatinine levels were more frequently observed in patients with MPA than in those with GPA, consistent with other reports [13 14]. In contrast to GPA, *S. aureus* colonisation in subjects with MPA was rare.

ANCA negative (seronegative) patients typically presented mainly otorhinolaryngological disorders, followed by pulmonary and renal dysfunctions. Significant ENT involvement in seronegative patients was also confirmed by other authors [19]. Five patients (71.4%) in this group were diagnosed with GPA, among which 4 presented localised disease and one subject had a generalised form of disease with no ENT involvement. Two ANCA-negative subjects (28.6%) had MPA; in both cases it was a systemic form of AAV with ENT manifestations in only one subject. Consistent with another study, our seronegative patients were younger at diagnosis (46.1 years) in comparison to their ANCA positive counterparts and were more prone to present a limited form of disease [19 29]. ENT manifestations comprised epistaxis, chronic rhinosinusistis and otitis media, nasal septum perforation, saddle nose, nasal and oral ulcerations, hearing loss (conductive and sensorineural), inspiratory dyspnoea and hoarseness. Sinonasal symptoms were the most frequently observed. Pulmonary involvement appeared as haemoptysis, pneumonia and persistent cough. The most common laboratory finding was neutrophilia and lymphopenia in CBC. Microscopic haematuria and gross haematuria were reported in 3 patients. *S. aureus* colonisation was identified in 2 seronegative individuals with localised GPA. According to our results, we suggest that ANCA-negative patients might present a less systemic form of AAV. Interestingly, it was recently suggested that the presence of oral cavity ulceration, namely palate perforation could be a frequently observed not only in seronegative patients with GPA, but also in cocaine users [30].

In contrast, subjects with positive status for both ANCA antibodies (PR3-ANCA and MPO-ANCA) expressed only a localised form of SVV limited to the upper respiratory tract and lungs. ENT disorders in this group comprised chronic rhinosinusitis, hearing loss (sensorineural and mixed) and laryngeal oedema. Pulmonary manifestations observed in one patient appeared as persistent cough and nodules detected in CT scan of the thoracic cavity. Laboratory abnormalities were detected in CBC (neutrophilia with lymphopenia) and ESR (increased level).

The proportion of organ involvement in particular forms of AAV is described below (Fig. 1, Table III). The results of our study emphasise that ENT involvement is a common presentation, especially in patients with GPA, but it is also observed in patients with MPA. Moreover,

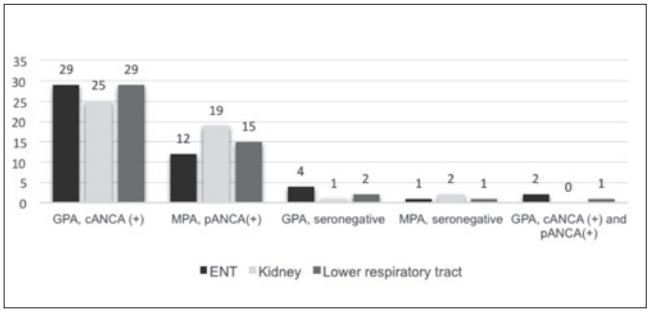

Fig. 1. Main organ involvement in various forms of AAV.

ENT disorders typically precede SVV diagnosis and its transformation to systemic, frequently life-threatening, disease. Accordingly, we highlight the crucial role of the otorhinolaryngologist in early diagnosis of SVV.

Consistent with previously reported findings, according to our research, patients with GPA are more prone to present otorhinolaryngological disorders than those with MPA [23]. In contrast, the prevalence of renal and systemic dysfunctions (especially renal and pulmonary) is higher in subjects with MPA. Of great importance is the fact that ENT manifestations were the initial symptoms of AAV and preceded systemic organ disorders in the majority of cases. The average duration between first ENT symptoms and AAV diagnosis in our cohort was 14.5 months, ranging between 1 to 36 months. The most common initial ENT manifestations were recurrent epistaxis and persistent chronic rhinosinusitis not responding to standard treatment.

Conclusions

Our results highlight the significant role of the otorhinolaryngologist in early AAV diagnosis and management. We emphasise that any patient with persistent ENT symptoms or ENT dysfunctions (especially sinonasal) not responding to standard otorhinolaryngological treatment should be precisely and rapidly evaluated for the presence of systemic dysfunctions (especially renal and pulmonary). According to our observations, biochemical examination including CBC, ESR, CRP and PCT may hasten diagnosis. Evaluation of serum creatinine, serum urea and urinalysis are also strongly encouraged. Microbiological examination (towards *Staphylococcal* colonisation) should be carried out in patients with suspected AAV as well. ANCA presence tests are of great value in establishing AAV diagnosis, but negative results do not exclude the presence of disease. Interestingly, ANCA negative patients are prone to present a localised form of disease with only ENT manifestations. Thus, in such cases, the role of the otorhinolaryngologist is crucial. Early suspicion of SVV, proposed by an inquisitive otorhinolaryngologist, may lead to rapid disease diagnosis and prompt, adequate treatment. This could significantly improve the prognosis of this life-threatening disease.

Conflict of interest statement

None declared.

References

1. Castello E, Caligo G, Ravetti JL, et al. *[Wegener's and Stewart's granulomatosis: a case report of Stewart's granulomatosis]*. Acta Otorhinolaryngol Ital 1998;18:322-31.
2. Gomez-Puerta JA, Bosch X. *Anti-neutrophil cytoplasmic antibody pathogenesis in small-vessel vasculitis: an update*. Am J Pathol 2009;175:1790-8.
3. Miller A, Chan M, Wiik A, et al. *An approach to the diagnosis and management of systemic vasculitis*. Clin Exp Immunol 2010;160:143-60.
4. Vacchi Suzzi M, Frasca G. *[Clinical significance of "ANCA" in the diagnosis of Wegener's granulomatosis: 8 years of experience]*. Acta Otorhinolaryngol Ital 1998;18:239-48.
5. Galli J, Corina L, Larocca LM. *[Unusual case of pharyngeal-laryngeal Wegener's granulomatosis]*. Acta Otorhinolaryngol Ital 2001;21:187-91.
6. Srouji IA, Andrews P, Edwards C, et al. *Patterns of presentation and diagnosis of patients with Wegener's granulomatosis: ENT aspects*. J Laryngol Otol 2007;121:653-8.
7. Kuhn D, Hospowsky C, Both M, et al. *Manifestation of granulomatosis with polyangiitis in head and neck.* Clin Exp Rheumatol 2018;36(Suppl 111):78-84.
8. Gaffo AL. *Diagnostic approach to ANCA-associated vasculitides*. Rheum Dis Clin North Am 2010;36:491-506.
9. Stegeman CA, Tervaert JW, de Jong PE, et al. *Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group*. N Engl J Med 1996;335:16-20.
10. Leavitt RY, Fauci AS, Bloch DA, et al. *The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis*. Arthritis Rheum 1990;33:1101-7.
11. Khan I, Watts RA. *Classification of ANCA-associated vasculitis*. Curr Rheumatol Rep 2013;15:383.
12. Hellmich B, Flossmann O, Gross WL, et al. *EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis*. Ann Rheum Dis 2007;66:605-17.
13. Sada KE, Yamamura M, Harigai M, et al. *Classification and characteristics of Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis in a nationwide, prospective, inception cohort study*. Arthritis Res Ther 2014;16:R101.
14. Mahr A, Katsahian S, Varet H, et al. *Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis*. Ann Rheum Dis 2013;72:1003-10.
15. Mohammad AJ, Jacobsson LT, Westman KW, et al. *Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa*. Rheumatology (Oxford) 2009;48:1560-5.
16. Trimarchi M, Sinico RA, Teggi R, et al. *Otorhinolaryngological manifestations in granulomatosis with polyangiitis (Wegener's)*. Autoimmun Rev 2013;12:501-5.
17. Wojciechowska J, Krajewski W, Krajewski P, et al. *Granulomatosis with polyangiitis in otolaryngologist practice:*

a review of current knowledge. Clin Exp Otorhinolaryngol 2016;9:8-13.

18 Sinico RA, Di Toma L, Radice A. *Renal involvement in anti-neutrophil cytoplasmic autoantibody associated vasculitis*. Autoimmun Rev 2013;12:477-82.

19 Yoo J, Kim HJ, Ahn SS, et al. *Clinical and prognostic features of Korean patients with MPO-ANCA, PR3-ANCA and ANCA-negative vasculitis*. Clin Exp Rheumatol 2017;35(Suppl 103):111-8.

20 Greco A, De Virgilio A, Rizzo MI, et al. *Microscopic polyangiitis: Advances in diagnostic and therapeutic approaches*. Autoimmun Rev 2015;14:837-44.

21 Gomez-Gomez A, Martinez-Martinez MU, Cuevas-Orta E, et al. *Pulmonary manifestations of granulomatosis with polyangiitis*. Reumatol Clin 2014;10:288-93.

22 Tashiro H, Takahashi K, Tanaka M, et al. *Characteristics and prognosis of microscopic polyangiitis with bronchiectasis*. J Thorac Dis 2017;9:303-9.

23 Chachar AZ, Sabir O, Haider I, et al. *Pulmonary renal syndrome in a patient with vasculitis: Case report and review of literature*. Pak J Med Sci 2015;31:1545-8.

24 Metaxaris G, Prokopakis EP, Karatzanis AD, et al. *Otolaryngologic manifestations of small vessel vasculitis*. Auris Nasus Larynx 2002;29:353-6.

25 Morales-Angulo C, Garcia-Zornoza R, Obeso-Aguera S, et al. *[Ear, nose and throat manifestations of Wegener's granulomatosis (granulomatosis with polyangiitis)]*. Acta Otorrinolaringol Esp 2012;63:206-11.

26 Ono N, Niiro H, Ueda A, et al. *Characteristics of MPO-ANCA-positive granulomatosis with polyangiitis: a retrospective multi-center study in Japan*. Rheumatol Int 2015;35:555-9.

27 Tsuchida Y, Shibuya M, Shoda H, et al. *Characteristics of granulomatosis with polyangiitis patients in Japan*. Mod Rheumatol 2015;25:219-23.

28 Hauer HA, Bajema IM, van Houwelingen HC, et al. *Renal histology in ANCA-associated vasculitis: differences between diagnostic and serologic subgroups*. Kidney Int 2002;61:80-9.

29 Cornec D, Cornec-Le Gall E, Fervenza FC, et al. *ANCA-associated vasculitis - clinical utility of using ANCA specificity to classify patients*. Nat Rev Rheumatol 2016;12:570-9.

30 Trimarchi M, Bondi S, Della Torre E, et al. *Palate perforation differentiates cocaine-induced midline destructive lesions from granulomatosis with polyangiitis*. Acta Otorhinolaryngol Ital 2017;374:281-5.

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Rhinology

Septoplasty: is it possible to identify potential "predictors" of surgical success?

Settoplastica: è possibile identificare potenziali "predittori" di successo chirurgico?

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SUMMARY

Septoplasty is one of the most frequent surgical procedures performed by otolaryngologists. Despite successful surgical correction, many patients are not satisfied with their outcomes. So far, in clinical practice there is no consensus of opinion about the reliability of objective measurements of nasal patency and the correlation between objective measurements and subjective nasal patency symptoms. This study aims to assess the reasons for patient dissatisfaction after septoplasty and optimise pre-operative diagnostic management to predict surgical outcomes. We analysed 494 patients undergoing septoplasties with turbinoplasty by subjective Nasal Obstruction Symptom Evaluation questionnaire (NOSE) and objective active anterior rhinomanometric measurements before surgery and after 6 months. In our series, 17% had postoperative septal re-displacement; all patients had an anterior deviations at baseline. We found that the type of septal deviation, anterior vs posterior, was a significant predictor of postoperative functional improvement, whereas demographic characteristics as age, gender and smoke habit were not. Our data suggest that the anterior segment of the nasal septum was the most critical area for nasal airway resistance and more difficult to manage because it is likely to re-displace vs the posterior one and for this reason it represents a negative predictor of postoperative satisfaction.

KEY WORDS: Septoplasty • Nasal obstruction • Rhinomanometry • Outcomes • Septal deviation

RIASSUNTO

La settoplastica è una delle procedure chirurgiche più frequentemente eseguite in otorinolaringoiatria. In molti casi nonostante la correzione sia tecnicamente corretta, i pazienti non sono soddisfatti dei risultati ottenuti. Finora, nella pratica clinica non vi è consenso sull'affidabilità della diagnostica funzionale oggettiva, né sulla correlazione tra la misura oggettiva della pervietà nasale e i sintomi soggettivi riferiti dal paziente. Questo studio si propone di valutare le ragioni dell'insoddisfazione del paziente dopo settoplastica e di ottimizzare la gestione diagnostica pre-operatoria al fine di prevedere i risultati chirurgici. Abbiamo valutato 494 pazienti sottoposti a settoplastica con turbinoplastica con il questionario sulla valutazione dell' ostruzione nasale, NOSE, e rinomanometria attiva anteriore. Le misurazioni sono state effettuate prima dell'intervento chirurgico e 6 mesi dopo. Nel 17% dei casi abbiamo osservato una re-dislocazione del setto, tutti i casi di redislocazione presentavano una deviazione anteriore preoperatoria. I nostri risultati suggeriscono che il tipo di deviazione del setto, anteriore vs posteriore, rappresenta un predittore statisticamente significativo del miglioramento funzionale postoperatorio, mentre le caratteristiche demografiche come età, sesso e abitudine al fumo, non lo sono. I dati ottenuti hanno, inoltre, dimostrato che relativamente alle resistenze nasali, l'area più critica e difficile da trattare è il segmento anteriore del setto poiché più a rischio di re-dislocazione rispetto al segmento posteriore, e per questo rappresenta un fattore predittivo negativo di soddisfazione post-operatoria.

PAROLE CHIAVE: *Settoplastica • Ostruzione nasale • Rinomanometria • Risultati • Deviazione settale*

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Introduction

Nasal obstruction is one the most common symptoms observed in rhinological practice [1] and septoplasty is one of the most frequent surgical procedures performed by otolaryngologists [2]. Despite successful surgical correction, many patients are not satisfied with their postoperative outcomes, which may lead to medicolegal problems [2].
So far, to avoid postoperative dissatisfaction, surgeons have developed a variety of techniques, but sometimes, regardless of the surgical technique, nasal obstruction can persist [3].

On the other hand, inadequate surgical procedures lead patients to re-consult an otolaryngologist. This happens because there are often many underestimated causes for nasal obstruction, such as allergy, nasal valve collapse or lateral wall insufficiency, which may alter the physiological dynamics of nasal airflow [1].

In addition to persistent septal deviation, septal perforation, synechiae, loss of nasal dorsum and tip support are the main reasons for persistent postoperative nasal obstruction and represent the most frequent complications after septoplasty [2 4].

In clinical practice there is still no consensus of opinion about the reliability of objective measurements of nasal patency and the correlation between objective measurements and subjective symptoms reported by patients [5]. Indeed, there is no diagnostic tool to predict postoperative outcomes, objectively evaluate the geometry of the nose and measure nasal resistances and degree of obstruction. For instance, several studies have shown no correlation between objective measurements and patient satisfaction, whereas other studies did not use validated questionnaires to assess postoperative outcomes after septoplasty [5].

To the best of our knowledge, this is the first prospective study examining, in a large sample size, the medium-term outcomes of septoplasty in terms of both objective and subjective assessment, with the use of active anterior rhinomanometry (AAR) and a validated questionnaire specifically designed for nasal obstruction, the Nasal Obstruction Symptoms Evaluation (NOSE).

Materials and methods

This is a prospective cohort study including 537 consecutive patients who underwent septoplasties with turbinoplasty performed at the ear nose and throat (ENT) Departments of the "Federico II" University and Cardarelli Hospital in Naples. Patients were enrolled between 2010 and 2017. We analysed 494 septoplasties that completed the study with at least 6 months follow-up; there were 284 females and 210 males, 18 to 50 years old (Table I). Enrolled subjects gave informed consent to the study, which was approved by the local Board of Medical Ethics. The study was carried out according to the Declaration of Helsinki.

Inclusion criteria were: patients complaining of nasal obstruction due to septal deviation and inferior turbinate hypertrophy who underwent septoplasty and turbinoplasty; nasal endoscopy confirming septal deviation and negative for chronic rhinosinusitis; previous maxillofacial computed tomography scan (CT) confirming septal nasal deviation and negative for chronic rhinosinusitis.

Table I. Patient characteristics. Study population at baseline.

Population (N = 494)	
Sex	284 F; 210 M
Age	39.6 ±3.2
Allergy	321 (65%)
Smoking habit	142 (28%)
Septal deviation:	
anterior deviations	312 (63%)
posterior deviations	182 (37%)

Exclusion criteria were: age < 18 years, previous nasal surgery, patients requiring rhinoseptoplasty, malformative and neuropsychiatric diseases, previous diagnosis of chronic rhinosinusitis (cystic fibrosis, immotile cilia syndrome etc.), uncontrolled rhinitis and asthma (to prevent interference of medical therapy with surgical and functional outcomes). Furthermore, we excluded patients with serious pathologies such as previous head or neck radiotherapy, immunologic disorders, diabetes, heart disease, neoplasms etc.

Before surgery (T_0) enrolled subjects underwent:

- Nasal endoscopy with a 4 mm 30° rigid endoscope (Storz, Tuttlingen, Germany).
- Skin prick test (SPT) using a standard allergen extract panel [(Stallergenes Company, Anthony, France). Positive (histamine) and negative (distilled water) controls were also performed. Aeroallergens included house dust mite, pollens, alternaria, aspergillus, cladosporium, grasses, weeds, wheat, cockroach] [6].
- The Italian version of the NOSE questionnaire to evaluate the subjective sensation of nasal obstruction, usually used in the literature to evaluate the success of septoplasty and related quality of life (QoL). The NOSE consists of 5 questions (nasal congestion or stuffiness, nasal blockage or obstruction, trouble breathing through nose, trouble sleeping, and unable to get enough air through the nose during exercise or exertion), each with a score ranging from 0 to 4. The range of raw scores is from 0 to 20. The final sum is then scaled to a total score of 0 to 100 by multiplying the raw score by 5. A score of 0 means no problems with nasal obstruction and a score of 100 means the worst possible problems with nasal obstruction [7 8].
- Active anterior rhinomanometry (AAR) [Diagnostic cube, Rhino 31 Atmos Medizintechnik, Lenzkirch, Germany] to calculate nasal resistance (NAR). All measurements were performed without decongestion by the same two experienced consultants (EC, FR) and under the same standard conditions, in accordance with the recommendations of the International Standardization Committee for Rhinomanometry [9].

We distinguished anterior and posterior septal deviation in relation to the nasal valve (Table I). In particular, we considered anterior the deviations corresponding to the dorso-caudal septal cartilage as previously described [10 11].
Enrolled subjects underwent septoplasty and turbinoplasty as described by Cottle and later by Sulsenti [12 13] under general anaesthesia by the same three experienced consultants (MI, EC, FR). The maxilla-premaxilla approach combining mobilisation and/or removal of any deranged portion of the bony and/or cartilaginous septum, followed by reconstruction of the septum support and the submucous inferior turbinoplasty (without bony resection) with lateral out-fracture of inferior turbinates were performed [13]. The septum was fixed through trans-septal sutures and the septal caudal incision was closed. Nasal packing was used and removed 48 hours after surgery.
After removal of nasal packing, all patients subjectively recovered normal nasal flow; they were treated with intranasal saline irrigation alone, twice a day for 20 days.
At 6 months' post-operative evaluation (T_6), patients repeated endoscopy to assess septal displacement and rhinomanometric evaluation, and were asked to fill out the Nose Scale questionnaire. As reported in the literature, we considered surgical success as a significant decrease in the postoperative NOSE score [8].

Statistical analysis

Statistical analyses were performed using the SPSS-PC program (version 16; SPSS Inc., Chicago, IL). Three dependent AAR variables were considered: nasal resistance in the wider nasal cavity (WNR), nasal resistance in the narrower nasal cavity (NNR), and total nasal resistance (TNR), each recorded at sample pressures of 150 Pa [14]. A Student's t test was used to evaluate differences in nasal obstruction metrics at T_0 and T_6. To evaluate the relationship between nasal obstruction metrics and patient characteristics using linear regression we created a multivariable model. Pearson's correlation was used to determine the correlation between two numerical variables (Wessa P. Free Statistics Software, Office for Research Development and Education, version 1.1.23-r7, 2017L; www.wessa.net).
For data analysis, we used the Δ, i.e. the difference in values detected at baseline and at T_6 ($\Delta = T_0\text{-}T_6$).
A p-value was considered statistically significant if < 0.05.

Results

At 6 months' post-operative evaluation, we observed septal re-displacement (R) in 84 of (17%) 494 enrolled patients. According to the type of septal deviation, we observed septal re-displacement in 84 out of 312 anterior septal deviation patients; whereas we observed no displacement in patients with posterior septal deviation at baseline. Furthermore, we observed the following complications: 3 (0.6%) infections, 6 (1.2%) haemorrhage, 12 (2.5%) valvular and 82 (16.5%) intra-nasal synechias, 6 (1.2%) perforations and 13 (2.6%) haematomas.
The analysis demonstrated that the type of deviation (D) anterior (a) vs posterior (p) and the occurrence of a re-displacement (R) at T_6 represented significant ($p < 0.01$) predictors of the change (= Δ, i.e. differences between parameters at T_0 and T_6) in subjective, ΔNOSE (T_0NOSE-T_6NOSE) and objective, ΔTNR (T_0TNR-T_6TNR), ΔWNR (T_0WNR-T_6WNR), ΔNNR (T_0NNR-T_6NNR) measures. Only for ΔNNR did the presence of allergy represent an additional significant predictor (Table II).
By applying Pearson's test, we found no correlation between ΔNOSE, ΔTNR, ΔWNR, ΔNNR and age, (respectively $r = 0.021$; $r = -0.026$; $r = -0.013$; $r = 0.041$. $p > 0.05$).
To evaluate whether the patients' starting point impacted postoperative functional outcomes, we used a t-test for paired samples comparing T_0 and T_6 values of NOSE, TNR, WNR, NNR. We found that parameters (mean ± SD) improved ($p < 0.01$) in all subjects (T6NOSE 24.06 ± 19 vs T_0NOSE 49.60 ± 20; T_6TNR 0.25 ± 0.15 vs T_0TNR 0.50 ± 0.23; T_6WNR 0.39 ± 0.14 vs T_0WNR 0.57 ± 0.14; T_6NNR 0.44 ± 0.16 vs T_0NNR 0.76 ± 0.22).
To evaluate whether the type of deviation (D), anterior (a) vs posterior (p), the occurrence of displacement (R), allergy status (A) and smoking (s) habit (independent variables) influenced the improvement (Δ) of each outcome measure (dependent variable), we used a t test.

Table II. Multivariate linear regression between nasal obstruction metrics and patient characteristics.

Obstruction metrics	R^2	F (ANOVA)	Independent variables	P
ΔNOSE	0.298	103.9	D and R*	0.001
ΔTNR	0.441	139.4	D and R*	0.001
ΔWNR	0.601	369.7	D and R*	0.001
ΔNNR	0.355	89.7	D, R* and A	0.001

The table shows the model that explains most of the statistically significant variance. Subjective, ΔNOSE (T_6NOSE-T_0NOSE) and objective, ΔTNR (T_6TNR-T_0TNR), ΔWNR (T_6WNR-T_0WNR), ΔNNR (T_6NNR-T_0NNR) measures. D: type of dislocation, anterior-posterior; R: re-displacement at T_6; A: allergy.*

All obstruction metrics improved ($p < 0.01$) after surgery in both anterior and posterior deviations, although the change (Δ) was more relevant ($p < 0.01$) in the anterior-a- (aΔNOSE: 28.16 ± 24.7; aΔTNR: 0.35 ± 0.28; aΔWNR: 0.27 ± 0.19; aΔNNR: 0.39 ± 0.28) than in the posterior-p- ones (pΔNOSE: 21.07 ± 12.5; pΔTNR: 0.08 ± 0.16; pΔWNR: 0.02 ± 0.1; pΔNNR: 0.17 ± 0.20).

Our data demonstrated that allergic (A) subjects presented a more statistically relevant change (Δ) ($p < 0.05$) only for AΔWNR (0.16 ± 0.19) and AΔNNR (0.28 ± 0.26) than non-allergic (NA) ones (NAΔNNR: 0.36 ± 0.28; NAΔWNR: 0.20 ± 0.22).

In addition, we found no differences ($p > 0.05$) between smokers – s – (sΔNOSE: 27.48 ± 19.8; sΔTNR: 0.27 ± 0.28; sΔWNR: 0.19 ± 0.20; sΔNNR: 0.30 ± 0.27) and non-smokers – ns – (nsΔNOSE: 24.77 ± 21.91; nsΔTNR: 0.24 ± 0.27; nsΔWNR: 0.17 ± 0.20; nsΔNNR: 0.31 ± 0.27).

We found a positive significant ($p < 0.05$) correlation between NOSE and AAR measures. For instance, in all sample populations we found a positive significant ($p < 0.05$) correlation between T_0NOSE and T_0TNR (r: 0,58), T_0WNR (r: 0,51), and T_0NNR (r: 0,57), and between T_6NOSE and T_6TNR (r: 0,43), T_6WNR (r: 0,27), and T_6NNR (r: 0,40) (Figs. 1, 2). In the posterior deviations we also found a positive significant ($p < 0.05$) correlation between T_0NOSE and T_0TNR (r: 0,59) (Fig. 3), T_0WNR (r: 0,27), and T_0NNR (r: 0,53), and between T_6NOSE and T_6TNR (r: 0,18). Conversely, we found no correlation between T_6NOSE and T_6WNR (r: 0,06), and T_6NNR (r: – 0,03).

In anterior deviations, we found a significant positive correlation ($p < 0.05$) between T_0NOSE and T_0TNR (r: ,38), T_0WNR (r: 0,44) and T_0NNR (r: 0,45), and between T_6NOSE and T_6TNR (r: 0,55), T_6WNR (r: 0,61), T_6NNR (r: 0,53) (Fig. 4). In the re-displaced septoplasties, we found no correlation between T_6NOSE and T_6TNR (r: 0,012), T_6WNR (r: 0,09), and T_6NNR (r: 0,12) (Fig. 5).

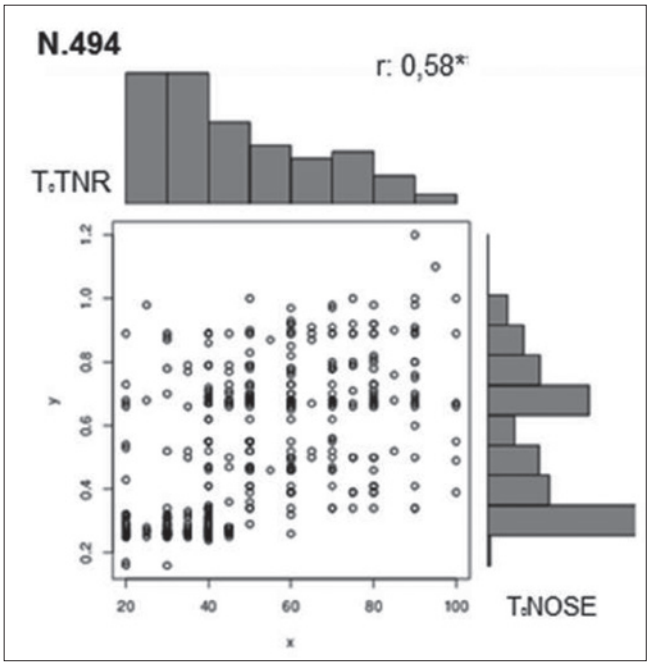

Fig. 1. Correlation between T_0NOSE and T_0TNR, T_0WNR and T_0NNR in all subjects, *correlation 0.01.

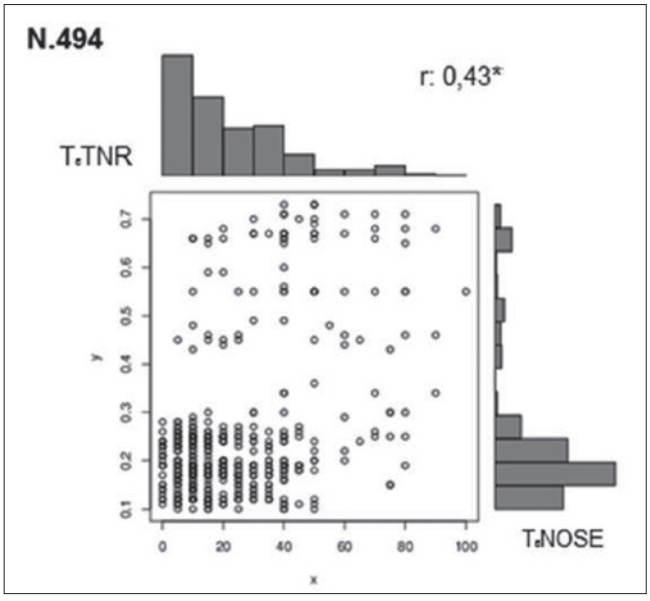

Fig. 2. Correlation between T_6NOSE and T_6TNR, T_6WNR and T_6NNR in all subjects, *correlation 0.01.

Discussion

Comfortable nasal breathing is a condition that is directly related to QoL. Currently, there is evidence that the patient's perspective on treatment outcomes is a crucial element for improving high-quality care and patient-rated therapeutic outcomes in terms of symptoms, and that it can provide a much more realistic picture of the effectiveness of a treatment than those of objective outcomes [15].

For instance, symptoms score questionnaires provide valuable information about how patients perceive the severity of their nasal obstruction and, consequently, about the degree of postoperative satisfaction [15].

Sometimes, after surgery nasal obstruction can persist with consequent dissatisfaction and poor QoL [2]; other times persistent septal deviations are associated with good patient satisfaction, whereas completely corrected deviations are not.

According to the literature, the risk of relapse or re-displacement after septoplasty is a common condition. Very

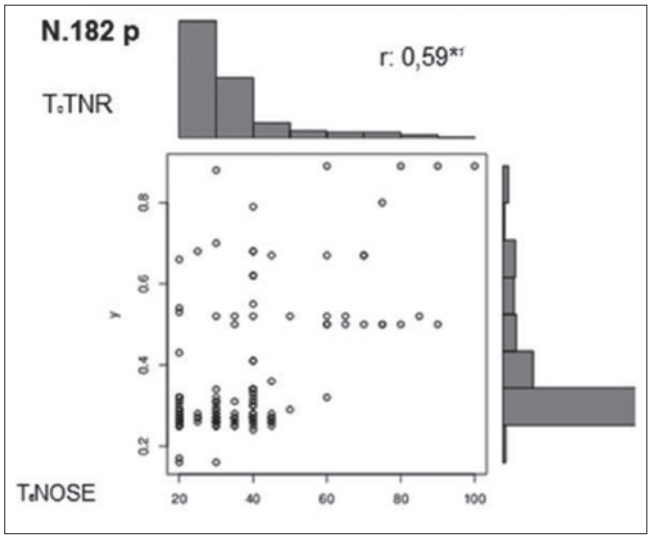

Fig. 3. Correlation between T_0NOSE and T_0TNR, T_0WNR and T_0NNR in the posterior deviations (p), *correlation 0.01.

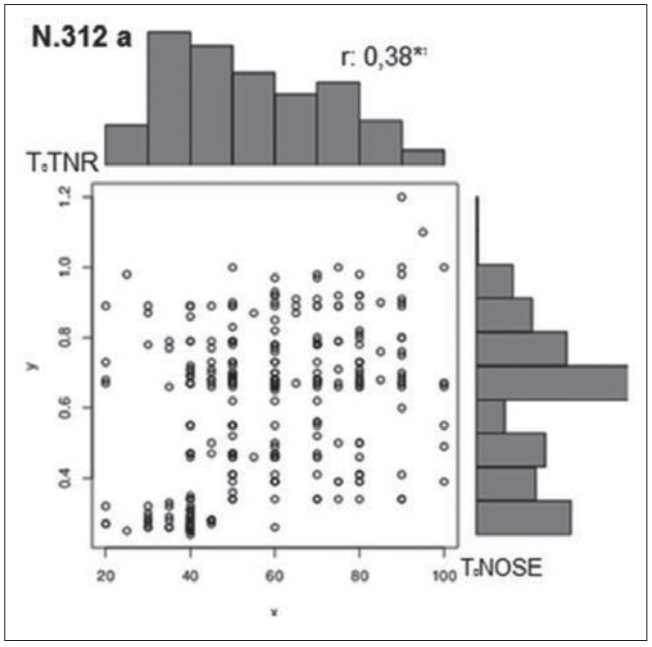

Fig. 4. Correlation between T_0NOSE and T_0TNR, T_0WNR and T_0NNR in the anterior deviations (a), *correlation 0.01.

often, an excellent postoperative result immediately after surgery evolves in a partial or total failure a few months later on the reappearance of deviation to some degree. This mostly depends on septal cartilaginous structures, which tend to retain the "memory" of the deviation due to their elasticity and so, over time, tend to curve again [16]. This phenomenon is the result of two, extrinsic and intrinsic, forces acting on the cartilaginous nasal septum and causing, if they are not released during surgery, relapse. The extrinsic forces are exerted on by deviated nasal bony structures, whereas the intrinsic forces are due to the impaired growth of septal cartilage or to trauma deforming tissue ultrastructure [16]. Another common cause of septal displacement is the difficult repositioning of the caudal margin of the quadrangular cartilage along its bony rail [13]. Thus, despite structural differences, all relapsed patients will predictably share certain features: surgically distorted native anatomy, disrupted tissue planes, altered microcirculation and potentially postsurgical mucosal dysfunction [17].

At baseline anterior deformities not only prevailed (Table I) in our surgical population, but also showed higher NOSE and ARR scores suggesting the prevalence of anterior deviations in candidates for septoplasty and a higher impact on symptom severity and nasal resistances than posterior ones.

Furthermore, our data demonstrated that the type of deviation, anterior vs posterior, represented significant predictors of the change (Δ) both in subjective and objective measures. According to the literature, these findings suggest a role of the type of deviation as a potential predictor for surgical success in terms of symptoms score improvement [18]. The study of Shiryaeva et al. using only subjective scores demonstrated that the type of septal deviation, unilateral vs bilateral, and preoperative obstruction scores, may aid in predicting outcomes of nasal surgery. However, they did not evaluate the anterior vs posterior septal deviation and did not use objective measurements [18].

In our population, the presence of allergy represented an additional significant predictor; our findings demonstrated that allergic subjects presented a more relevant change (Δ) in ARR (ΔWNR and ΔNNR) scores than non-allergic (NA) ones, probably for worse starting scores.

In allergic subjects, the hypertrophy of turbinates plays a primary role in the genesis of nasal obstruction, but while septoplasty corrects the septal deviation, literature data has shown that it is unclear whether turbinoplasty is beneficial in the long term for treatment of nasal obstruction. Recent studies reported improvement in symptoms and subjective evaluation at early post treatment evaluation and decreased benefits at the long term observation [19]. As allergy is a chronic inflammatory disease, in the long-term it tends to cause turbinate hypertrophy even after surgery [20]. Our data showed worse baseline AAR subscores in allergic individuals, although they did not clarify the impact of the allergy on septoplasty outcomes.

In any case, these data pointed out the utility of studying preoperative allergic status as an additional putative predictive factor for surgical outcomes [19].

Based on our results, smoking status, as well as age and gender, were not crucial as predictors of postoperative results. In particular, our findings confirmed recent research demonstrating that both smokers and non-smokers benefit from septoplasty [21].

At T_6 we found that all parameters improved ($p = 0.01$) in the overall population, in agreement with the literature (satisfactory outcomes in 65% to 80% of patients) [17].

So far, the correlation between subjective nasal patency symptoms and objective nasal measurements is still debated in the literature. For instance, some authors reported the presence of correlation, whereas others did not [22 23].

Hong et al. pointed out that only the preoperative NOSE scale, reflects post-septoplasty outcomes. Although the study by Hong provided useful information, it included a non-homogeneous (43 males and 6 females), small sample of patients undergoing septoplasty with or without turbinoplasty treated with different surgical techniques and different follow-up times (1, 3 or 6 months). Furthermore, the authors used acoustic rhinometry as an objective measurement that produces detailed evaluation of the geometry of nasal cavities, but it does not evaluate the flow field or provide any information on the physiology of nasal pressure [1].

In our study population, we found a significant correlation between subjective and objective measures (Figs. 1-5), whereas among re-displaced anterior deviations, we did not find any correlation at T_6 (Fig. 5).

This lack of correlation, again in accordance with the literature, pointed out that the AAR provides only a global assessment and does not consider the local details of the nasal air flow (i.e. the anterior regions of inferior meatus or nasal valve) that are often extremely significant from clinical and QoL standpoints [22 25].

From a merely speculative point of view, we can hypothesise that re-displacement occurs almost exclusively in the nasal valve region, where the ARR presents some limitations in the evaluation of nasal air flow [22 23]; in such cases a dilation test could be useful [26].

On the basis of these observations, in our opinion surgeons should always perform both objective and subjective nasal measurements before and after septoplasty, even if the predictive value of these methods is still controversial [22 23].

In our clinical setting we always administer the subjective NOSE questionnaire and the objective ARR. This assessment helps us to evaluate the nasal airways and to select patients who would benefit most from septoplasty.

Literature data have also demonstrated that patients with significant nasal obstruction may have a small septal deviation, whereas other patients with severe anatomical deformity may have mild symptoms [27].

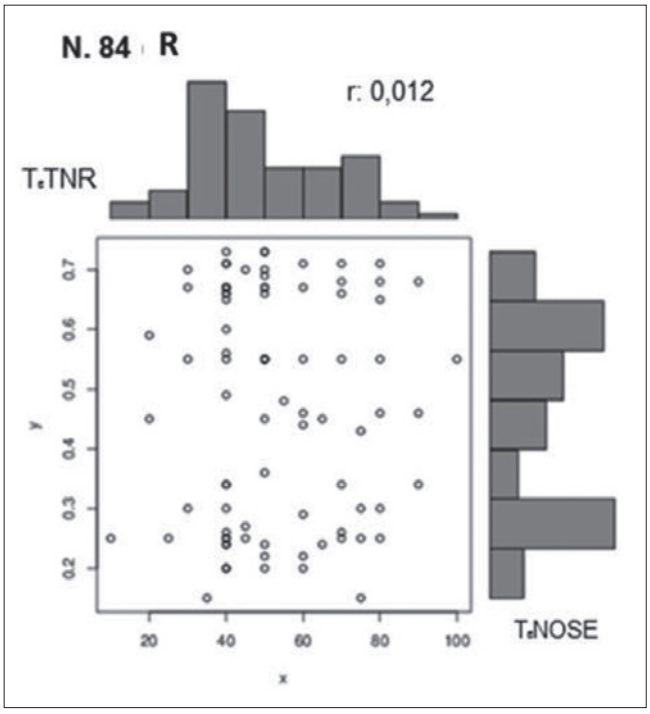

Fig. 5. Lack of correlation between T_6NOSE and T_6TNR, T_6WNR and T_6NNR in the re-displaced septoplasty (R).

Therefore, the goal of septoplasty should not be to obtain a perfectly midline aligned septum, but to improve breathing, making the nasal cavities pervious [13].

Consequently, in clinical practice the presence at nasal endoscopy and/or imaging as CT of non-perfectly aligned portions of the septum or the presence of septal spurs in different nasal subsites that do not impact nasal airflow (posterior regions of nasal cavities, high regions of the septal cartilage) should not be considered a surgical failure, especially in association with improvement in objective and subjective measures. Although preoperative CT scan can be used for further examination of nasal anatomy and can be helpful in identifying ancillary sinonasal pathologies, there is little correlation between septal deviation findings on CT scan and symptoms of nasal obstruction as demonstrated by previous studies that did not support a role for CT as a clinically meaningful or necessary test to investigate residual postoperative nasal obstruction [28 29].

Since patients generally tend to rate the results of their septal surgery less positively as the postoperative period gets longer, it should be mandatory to evaluate surgical outcomes in the long term; although the most literature data on septoplasty outcomes reports postoperative results after 6 months [27 30 31].

Another limitation of this study is the lack of nasal decongestion, but given the large sample size reported in

the study the decongestion test was not available for all patients. However, in our opinion this limitation does not affect the validity of the study. Indeed, some authors reported a mean nasal airway resistance reduction after decongestion only of 33% [32] and many others do not perform decongestion in nasal assessment [33 34].

Conclusions

In conclusion, our data suggest that anterior septal deviations significantly impact the QoL, they are more difficult to manage and disposed to re-dislocate than posterior ones. In particular, the nasal valve is the hardest site to evaluate with objective measures like AAR [2].
Surgeons should always perform both objective and subjective nasal measurements before and after septoplasty, although their predictive value is still controversial. Furthermore, as previously demonstrated, CT does not correlate with septal deviation findings, and is not recommended as a postoperative diagnostic tool.

Conflict of interest statement

None declared.

References

1 Gamerra M, Cantone E, Sorrentino G, et al. *Mathematical model for the preoperative identification of obstructed nasal subsites.* Acta Otorhinolaryngol Ital 2017;37:410-5.

2 Kuduban O, Bingol F, Budak A, et al. *The reason of dissatisfaction of patient after septoplasty.* Eurasian J Med 2015;47:190-3.

3 Bezerra TP, Steward MG, Fornazierei MA, et al. *Quality of life assessment septoplasty in patient with nasal obstruction.* Braz J Otorhinolaryngol 2012;78:57-62.

4 Bloom JD, Kaplan SE, Bleier BS, et al. *Septoplasty complications: avoidance and management.* Otolaryngol Clin North Am 2009;42:463-81.

5 Mondina M, Marro M, Maurice S, et al. *Assessment of nasal septoplasty using NOSE and RhinoQoL questionnaires.* Eur Arch Otorhinolaryngol 2012;269:2189-95.

6 Dogru M, Bostanci I, Ozmen S, et al. *Is there a need for repetition of skin test in childhood allergic diseases? Repetition of skin test and allergic diseases.* Allergol Int 2014;63:227-33.

7 Stewart M, Witsell D, Timothy L, et al. *Development and validation of the nasal obstruction symptom evaluation (NOSE) scale.* Otolaryngol Head Neck Surg 2004;130:157-63.

8 Habesoglu M, Kilic O, Caypinar B, et al. *Aging as the impact factor on septoplasty success.* J Craniofac Surg 2015;26:e419-22.

9 Clement PAR. *Committee report on standardization of rhinomanometry.* Rhinology 1984;22:151-5.

10 Surowitz J, Lee MK, Most SP. *Anterior septal reconstruction for treatment of severe caudal septal deviation: clinical severity and outcomes.* Otolaryngol Head Neck Surg 2015;153:27-33.

11 Huizing E. *Incorrect terminology in nasal anatomy and surgery, suggestions for improvement.* Rhinology 2003;41:129-33.

12 Cottle MH, Loring RM, Fischer GG, et al. *The maxilla-premaxilla approach to extensive nasal septum surgery*, AMA Arch Otolaryngol 1958;68:301-13.

13 Sulsenti G, Palma P. *Tailored nasal surgery for normalization of nasal resistance.* Facial Plast Surg 1996;12:333-45.

14 Ng TY, Chen YF, Tsai MH, et al. *Objective measurements differ for perception of left and right nasal obstruction.* Auris Nasus Larynx 2013;40:81-4.

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

16 Boccieri A. *The crooked nose.* Acta Otorhinolaryngol Ital 2013;33:163-8.

17 Gillman GS, Egloff AM, Rivera-Serrano CM. *Revision septoplasty: a prospective disease-specific outcome study.* Laryngoscope 2014;124:1290-5.

18 Shiryaeva O, Tarangen M, Gay C, et al. *Preoperative signs and symptoms as prognostic markers in nasal septoplasty.* Int J Otolaryngol 2017;2017:4718108.

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

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

21 Yazici ZM, Sayin I, Erdim I, et al. *The effect of tobacco smoking on septoplasty outcomes: a prospective controlled study.* Hippokratia 2015;19:219-24.

22 Hsu HC, Tan CD, Chang CW, et al. *Evaluation of nasal patency by visual analogue scale/nasal obstruction symptom evaluation questionnaires and anterior active rhinomanometry after septoplasty: a retrospective one-year follow-up cohort study.* Clin Otolaryngol 2017;42:53-9.

23 Quadrio M, Pipolo C, Corti S, et al. *Review of computational fluid dynamics in the assessment of nasal air flow and analysis of its limitations.* Eur Arch Otorhinolaryngol 2014;271:2349-54.

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

25 Hamerschmidt R, Hamerschmidt R, Moreira AT, et al. *Comparison of turbinoplasty surgery efficacy in patients with and without allergic rhinitis.* Braz J Otorhinolaryngol 2016;82:131-9.

[26] Tasca I, Ceroni Compadretti G, Sorace F. *Nasal valve surgery.* Acta Otorhinolaryngol Ital 2013;33:196-201.

[27] Konstantinidis I, Triaridis S, Triaridis A, et al. *Long term results following nasal septal surgery focus on patients' satisfaction.* Auris Nasus Larynx 2005;32:369-74.

[28] Ardeshirpour F, McCarn KE, McKinney AM, et al. *Computed tomography scan does not correlate with patient experience of nasal obstruction.* Laryngoscope 2016;126:820-5.

[29] Wotman M, Kacker A. *What are the indications for the use of computed tomography before septoplasty?* Laryngoscope 2016;126:1268-70.

[30] Sundh C, Sunnergren O. *Long-term symptom relief after septoplasty.* Eur Arch Otorhinolaryngol 2015;272:2871-5.

[31] Tsang CLN, Nguyen T, Sivesind T, et al. *Long-term patient-related outcome measures of septoplasty: a systematic review.* Eur Arch Otorhinolaryngol 2018;275:1039-48.

[32] Thulesius HL, Cervin A, Jessen M. *Can we always trust rhinomanometry?* Rhinology 2011;49:46-52.

[33] Canakcioglu S, Tahamiler R, Saritzali G, et al. *Nasal patency by rhinomanometry in patients with sensation of nasal obstruction.* Am J Rhinol Allergy 2009;23:300-2.

[34] Cantone E, Iengo M. *Effect of sodium hyaluronate added to topical corticosteroids in chronic rhinosinusitis with nasal polyposis.* Am J Rhinol Allergy 2016;30:340-3.

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AUDIOLOGY

Speech perception in noise by young sequential bilingual children

Percezione del parlato nel rumore in bambini bilingue sequenziali

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SUMMARY

The objective of this study was to ascertain the effects of competitive noise on second language perception skills of sequentially bilingual children and to compare the results with those relating to matched monolingual peers. Fifteen bilingual immigrant children (aged 6-10 years) (BL) learning through their second language (L2), which was Italian, were matched with 15 peers who only spoke Italian (IO). All immigrant children had arrived in Italy and were exposed to L2 after their 4th year of life. The speech-to-noise ratio (SNR) needed to obtain 50% intelligibility – the speech reception threshold (SRT) – for Italian words was measured against the Italian version of ICRA noise, using an adaptive method. Moreover, presentation of phrases against a contralateral continuous discourse (informational masking) was carried out to exclude possible biases due to differences in memory, attention, or other central auditory processing disorders between groups. The SNR was -2.7 dB (SD 1.7; range: -5.5 to + 0.9) for the BL group and -5.3 dB (SD 2.3; range: -8.8 to -0.9) for the IO group ($p < 0.01$). With contralateral continuous discourse presentation the SNR were -32.8 dB (SD 2.4; range: -36.1 to -28.2) for the BL group and -27.8 dB (SD 2.1; range: -31.7 to -24.1) for the OI group ($p < 0.01$). Even sequential bilingual individuals exposed to L2 at 4 years old had worse speech perception in noise than their matched IO peers. On the other hand, the BL group demonstrated superior divided attention skills in tests with competitive contralateral discourse ($p < 0.01$).

KEY WORDS: Bilingual • Speech perception in noise • Phonological competence • Critical period • Energetic masking

RIASSUNTO

Obiettivo dello studio è stato quello di valutare gli effetti del rumore sulle capacità di percezione linguistica di bambini bilingue sequenziali e di confrontare i risultati con quelli relativi a coetanei monolingue. Sono stati inclusi nello studio quindici bambini immigrati bilingue, di età compresa tra i 6 e i 10 anni (BL), la cui seconda lingua era l'italiano (L2) e 15 bambini di età corrispondente che parlano solo italiano (IO). Tutti i bambini erano arrivati in Italia e sono stati esposti a L2 dopo il loro quarto anno di vita. Il rapporto tra segnale e rumore (SNR) necessario per ottenere una intelligibilità del 50% – la soglia di ricezione vocale (SRT) – per le parole italiane è stato misurato utilizzando la versione italiana di ICRA noise, grazie a un metodica adattativa. I bambini sono stati inoltre sottoposti a un secondo test che prevedeva la presentazione di frasi in lingua italiana con un mascheramento informativo controlaterale, per escludere eventuali problemi legati a deficit di memoria, attenzione o altri disordini di processazione uditiva centrale. La SNR era pari a -2,7 dB (SD 1,7; range: -5,5/+0,9) per il gruppo BL e -5,3 dB (SD 2,3; range: -8,8/-0,9) per il gruppo IO ($p < 0,01$). Nel test con il mascheramento informativo controlaterale la SNR era -32,8 dB (SD 2,4; range: -36,1/-28,2 per il gruppo BL e -27,8 dB (SD 2,1; range: -31,7/-24,1) per il gruppo OI ($p < 0,01$). I bambini bilingue sequenziali esposti a L2 a 4 anni hanno dimostrato una percezione del parlato nel rumore peggiore rispetto ai loro coetanei monolingue. D'altra parte, il gruppo BL ha dimostrato una migliore attenzione condivisa nelle prove con un il mascheramento controlaterale informativo ($p < 0,01$).

PAROLE CHIAVE: *Bilinguismo • Percezione del parlato nel rumore • Competenze fonologiche • Periodo critico • Mascheramento energetico*

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Introduction

Understanding speech through noise is a skill that develops well into an individual's adolescent years and becomes adult-like at around the age of 15 [1-4]. Younger children's developmental listening disadvantage is of particular concern at school because early educational skills may be taught in noisy settings. Some children also appear to be at a double disadvantage when listening under adverse conditions (noise, reverberation, background

babble) [5-7]: this subgroup may account for 5-10% of the scholastic population in many European countries [8], and corresponds to sequential bilingual children learning in their second language (L2). In fact, within a short space of time, these children generally acquire the same lexical and morpho-syntactic skills as their monolingual peers, but do not reach the same level of phonological skills in their L2 [5 6] especially when they are exposed to the L2 beyond the critical period for complete phonological code acquisition. Several studies have demonstrated that phonological competences are important in achieving good intelligibility in adverse listening conditions [6 7 9].

To date, most of the research on bilingualism has focused on simultaneous bilinguals who are exposed to both languages from birth. Immigrant children are generally sequential bilingual, however, either because they arrive in the host country during their childhood, having already learned their mother language (L1), or because they are exposed primarily to the family language, and it is not until they attend nursery school at around 3 years of age that they gradually become immersed in their L2 [10]. With increasing immigration, it is becoming common for children to grow up sequential bilingual in many developed countries, including Italy. In some northern Italian regions, 10% of schoolchildren are of foreign nationality and, among them, the incidence of those who start their education in Italian schools has increased (from 3.7% in 2013 to 4.9% in 2014) [11].

It is well established that by 6 months infants recognise native-language phonetic categories. Moreover, early and simultaneously bilingual infants are able to discriminate the sounds of both their languages by 12 months of age [12]. On the other hand, by the end of the first year of life, monolinguals' perception of speech has been dramatically altered by exposure to their single native language. In fact, at the phonetic level, exposure to a specific language reduces infants' abilities to discriminate foreign-language speech sounds and this ability declines sharply between 6 and 12 months of age [13 14]. In other words, exposure to a specific language results in "neural commitment" to the acoustic properties of that language. Neural commitment to the native language interferes with foreign-language processing, causing difficulty in foreign-language speech perception in infancy and adulthood. Thus, with respect to early and simultaneously bilingual infants, sequential bilingual children are faced with the task of learning their host country's language when they already have a still-developing phonology that reflects their L1. Most authors agree that the influence of L1 categories is strong enough to interfere with native-like processing of L2 categories, even in infants exposed to L2 very early. In other words, early and intensive exposure to a second language may not necessarily be sufficient to build native-like phonemic categories, or to perform as well as native speakers in discriminating between the two languages [10 15].

Unfortunately, the findings of current studies on perceptual skills in sequential bilingual individuals are still controversial, mostly because they differ in terms of how much children have been exposed to L2, and at what age they started to learn it [16 17].

Moreover, several factors may explain replication difficulties, including the specific language, sociodemographic variables, the location of research in conjunction with language status, and the fact that experimental tasks are not always sensitive and controlled well enough (particularly from an audiological standpoint) to detect subtle differences in speech-in-noise perception [18].

In contrast, bilinguals may have cognitive advantages over monolingual speakers in verbal tasks when it comes to solving conflicting information and inhibiting irrelevant information [2 19 20]. For both these aspects, the underlying mechanisms and their interactions have yet to be fully understood, and the factors influencing bilingual immigrant children's speech comprehension in noisy settings need to be investigated more systematically.

The aims of the present study were to ascertain the effects of noise on speech perception skills (due to a reduced audibility of several acoustic cues) in 15 typically-developing sequential bilingual (BL) children (aged 6-12) learning their L2; compare the results with those of 15 matched monolingual peers speaking only Italian (OI). Our first hypothesis was that BL children might have more difficulties in listening under adverse conditions, compared to their matched peers, due to their lower phonological competences. For this purpose, we presented lists of words in competition with the Italian version of the ICRA (International Collegium of Rehabilitative Audiology) noise (Test 1).

To exclude possible biases due to differences in memory, attention, or other central auditory processing disorders, we carried out a second test using sentences presented in competition with a contralateral continuous discourse.

This different task was more demanding with regards to memory (children had to repeat phrases, not single words), to divided attention skills (they had to solve conflicting information) and to other central auditory functions (they had to use morpho-syntactic competences, i.e. top-down control). On the other hand, in the second test both the target and the masker were clearly audible.

Materials and methods

Participants

Fifteen sequentially bilingual immigrant children (BL

group) and 15 native Italian only speakers (IO group) with no self-reported hearing impairments were enrolled, for a perspective study, from three different primary schools in Padua (Italy). These schools had similar socio-economic conditions and no significant differences in mean scores of the INVALSI (Italian National Institute for the Evaluation of the School System) [21] tests.

Parents gave their informed consent to each child's participation in the study.

The Institutional Review Board of the Azienda Universitaria-Ospedaliera di Padova, Italy, approved the study.

The BL group was represented by 8 females and 7 males, aged 6-10 years (mean = 8.66, SD = 1.71); the IO group included 7 females and 8 males, aged 6-12 years (mean = 8.60; SD = 1.72), matched for gender, age and school proficiency with the BL group. The details of all the children involved in the study are given in Table I.

All participants had normal otoscopic findings and a hearing threshold of 20 dB HL or better bilaterally for the frequencies 250, 500, 1000, 2000, 4000, 8000 Hz. Moreover, they responded correctly in over 90% of trials in quiet speech audiometry with words and phrases presented at 40 dB SL.

Parents reported that participants had no history of neurological, cognitive, or communication disorders. Their school teachers completed a simple form for each participant concerning biographical details, potential socio-economic disadvantages, and grades obtained in the previous 6 months in the following subjects: math, Italian language, history and geography. Grades were expressed on a scale from 1 to 10, where 10 was the highest and 1 the lowest, and 6 is a pass. A school proficiency (SP) with an average grade of ≥ 7 and no socio-economic disadvantages were established as an inclusion criterion.

For the BL group, there were additional inclusion criteria: no exposure to the Italian language (L2) before the age of 4 years; having lived in Italy for at least 2 years, with regular, constant exposure to Italian at school and in the community, and to their first language (L1) at home.

To establish the children's age at the time of their exposure to L2 and their need to use the language, all parents of the immigrant children completed a questionnaire reporting when they arrived in Italy, the language environment at home, and the percentage of output in L1 and L2, the language used for specific activities, and the language(s) used for interactions between family members [22].

Finally, a further inclusion criterion for BL participants was that the percentage of L1 *vs* L2 exposure ranged between 35% to 65%, so all children could be considered competent speakers in both languages [23].

Stimuli

For test # 1, the speech signal consisted of 20 lists of 10 Italian words familiar to children in competition with the ICRA noise generated by multiple superposition of all words (available at http://acustica.ing.unife.it/). These

Table I. Age, gender and language background of the bilingual or monolingual participants.

Bilingual participants = BL group									Monolingual participants = IO Group				
Subject	**Age**	**Gender**	**L1**	**L2 - Age**	**%L1**	**%L2**	**L2 - Years**	**SP**	**Subject**	**Age**	**Gender**	**L1**	**SP**
S01	7	M	Romanian	4	60	40	3	8	**C01**	6	M	Italian	8
S02	7	M	Albanian	4	65	35	3	9	**C02**	8	M	Italian	8
S03	9	M	Romanian	4	55	45	5	9	**C03**	8	M	Italian	9
S04	6	F	Ukrainian	4	60	40	2	7	**C04**	7	M	Italian	7
S05	7	F	Russian	4	50	50	3	8	**C05**	7	F	Italian	8
S06	10	F	Romanian	4	45	55	6	9	**C06**	9	F	Italian	9
S07	10	F	Bulgarian	7	65	35	3	9	**C07**	10	F	Italian	9
S08	12	M	Serbo-Croatian	7	45	55	5	9	**C08**	12	M	Italian	7
S09	10	F	Serbo-Croatian	5	60	40	5	7	**C09**	11	F	Italian	8
S10	8	F	Romanian	5	50	50	3	8	**C10**	9	F	Italian	9
S11	9	F	Albanian	6	55	45	3	9	**C11**	8	F	Italian	8
S12	7	M	Romanian	4	65	35	3	8	**C12**	7	M	Italian	9
S13	11	M	Romanian	6	50	50	5	9	**C13**	11	M	Italian	9
S14	9	F	Romanian	6	60	40	3	7	**C14**	8	F	Italian	8
S15	8	M	Belarusian	5	55	45	3	8	**C15**	8	M	Italian	7

L2-Age: age at time of first exposure to second language; %L1: percentage of daily exposure to L1; %L2: percentage of daily exposure to L2; L2-Years: years since they arrived in Italy, SP: school proficiency.

tests were validated with Italian normal hearing subjects and impaired hearing patients of different ages. ICRA noise is similar to "cocktail party noise", but has long-term spectrums and modulation characteristics like natural speech. Thus, it overlaps in time and frequency in such a way that portions of the primary speech signal are rendered inaudible. A monotic presentation was used, i.e. words and noise to a single ear randomly chosen among subjects.

For test # 2 the target speech signal consisted of 20 lists, each comprising 10 Italian phrases. The masking was represented by the Italian translation of a passage from a novel by Conrad with the silent pauses (between words and periods) omitted, but still perfectly and easily comprehensible.

This masking signal was presented contralaterally to the primary message. The mixture stimuli were constructed by having the interferers precede the target sentence (for about a second), and then following the target sentence for another second. Thus, this masking paradigm produced a listening situation where the target and masker signals were clearly audible but the listener had difficulties in segregating the elements of the target signal from the elements of the similar-sounding distracters. This masking is called "informational" and has different effects with respect to the energetic one used in test # 1.

Procedures

All tests were conducted in a sound treated acoustic chamber. None of the participants had heard or read the test material before the experiments and, to avoid memory effects, each list was used only once with each child. The full assessment took 30 minutes to complete for each child and was divided into three 10-minute sessions, with two breaks.

Recorded stimuli were delivered with a portable compact disc player through a two-channel Madsen Astera 2 audiometer and a set of Sennheiser HDA 200 headphones. Before testing participants, a precision sound level meter (Bruel & Kjaer, type 2231) was used to calibrate each channel separately. Audiometer intensity (linearity) was also checked to ensure that noise levels were accurate and achievable on audiometer potentiometer manipulation. Words were presented at a constant level of 70 dB SPL. After a period of familiarisation with the test words, the speech-to-noise ratio (SNR) needed to obtain a 50% Italian word intelligibility, the speech reception threshold (SRT), was measured for the two tests using a one-down/one-up adaptive procedure in 2-dB steps [24].

Briefly, a word was presented, and the children then responded by orally repeating the word to an experimenter. They were encouraged to guess if they were unsure. The experimenter (who was blinded to the experimental hypothesis) compared their response with the target sentence. If every word in their sentence was correct, the noise level for the next sentence was increased by 2 dB; if they made a mistake, the noise level was decreased by 2 dB. The SNR was calculated as the median of at least 6 track inversions, and after two trial lists. We adopted this traditional adaptive assessment (i.e. measuring the SNR needed to reach the SRT), as generally recommended in studies with normal hearing subjects [25 26] and previously validated for Italian subjects [27].

The following test variables were randomised: right vs. left ear presentation, word list sequences and time-ordered sequences of the two different speech tests.

The demands on executive function were low, with the primary demand being the need to keep arbitrary rules in mind to respond appropriately.

In test 2, the procedure was identical but with different stimuli and masking, as reported in the previous paragraph. They had to correctly repeat each word of the phrase. The executive demand was higher because it included remembering the 6 to 8 words of the simple phrases.

Data analysis

STATISTICA 7.1 software (Stat Soft Italia srl, Milan, Italy) was used for basic statistical analysis, and t-test to assess the differences between the BL and OI groups. The regression tendency curves were calculated on the SNRs as a function of age, or of each L2 background descriptor. All data were expressed as mean ± standard deviation from the mean (SD). Values where $p < 0.05$ were considered statistically significant and a $p \leq 0.001$ was judged highly significant.

Results

In the BL group, the children's age at the time of their first exposure to L2 ranged from 4 to 7 years (mean 5.0 ± 1.1), and the number of years since they had been learning L2 ranged from 2 to 6 (mean 3.7 ± 1.2). Language output was 56% for their mother tongue (SD = 6.2; range = 45-65%) and 44% for L2 (SD = 15.3; range = 35-55%). As reported in last paragraph of the Methods section, a range of L2 exposure between 35% to 65% was an inclusion criterion. Average school proficiency was 8.3 ± 0.8 for the BL group, and 8.2 ± 0.8 for the IO group.

The SNR values needed to obtain a 50% intelligibility (the SRT) are given in Table II for each child. The mean SNR was higher in the BL group (worse performance) than in the IO group, with a significant difference ($p < 0.01$) (Fig. 1).

Table II. SNRs needed to obtain 50% intelligibility (SRT) of words in noise and of phrases against contralateral discourse, for each bilingual or monolingual participant.

Bilingual group (BL)			Monolingual group (IO)		
Subject	**SNR noise**	**SNR phrases**	**Subject**	**SNR noise**	**SNR phrases**
S 1	-2.9	-34.5	**C1**	-3.5	-25.4
S 2	-1.8	-32.8	**C2**	-4.9	-28.6
S 3	0.09	-33.5	**C3**	-5.1	-28.6
S 4	-4.3	-33.5	**C4**	-1.6	-24.1
S 5	-3.6	-32.4	**C5**	-0.9	-27.3
S 6	-0.7	-35.3	**C6**	-5.2	-26.6
S 7	-2.1	-32.9	**C7**	-5.4	-29.9
S 8	-2.5	-34.8	**C8**	-8	-29.2
S 9	-1.2	-35.7	**C9**	-6.3	-27.9
S10	-1.5	-30.1	**C10**	-7	-25.7
S11	-5.5	-31.2	**C11**	-8.8	-26.9
S12	-5.2	-28.8	**C12**	-3.1	-25.7
S13	-3.9	-36.1	**C13**	-6.8	-31.7
S14	-3.1	-28.2	**C14**	-5.8	-30.5
S15	-2.5	-32.9	**C15**	-7.3	-29.6
Average	-2.7	-32.8	**Average**	-5.3	-27.8
Median	-2.5	-32.9	**Median**	-5.4	-27.9
SD	1.07	2.04	**SD**	2.03	2.01

SNR noise: SNRs needed to obtain a 50% intelligibility (the SRT) of words in noise; SNR phrases: SNRs needed to obtain a 50% intelligibility (the SRT) of phrases against contralateral discourse; SD: Standard deviation. SNRs are expressed in dB.

Regarding test # 2, the SNR for each child are shown in Table II. Mean SNR was significantly higher in the IO group (worse performance) ($p < 0.01$) (Fig. 2).

The mean age, SP, SNR with noise and with contralateral competitive continuous discourse for the two groups were compared with a t-test after checking for the adequacy of sample sizes, normal distribution of the data, and homogeneity of variances.

There were no significant differences in age or school proficiency between the BL and IO groups. Moreover, SP did not correlate with age in either of the groups.

SNR correlated significantly with age in the IO group (perception in noise improved with age) ($p < 0.05$), but not in the BL group.

To understand which factor could influence SNR performance, the BL group was analysed in more detail, looking at: range of exposure to L1 *vs* L2, the effect of mother language (Slavic *vs* Romance), age at the time of exposure

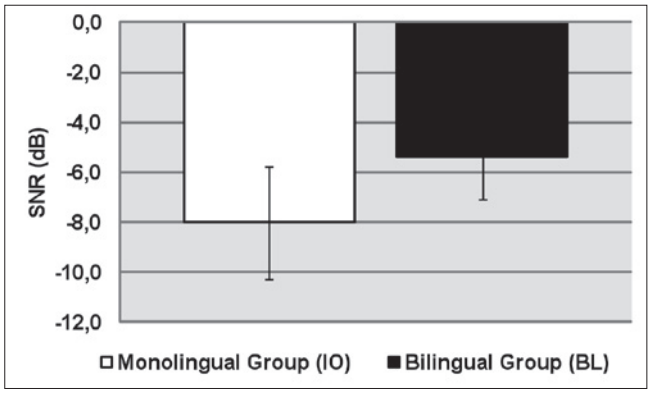

Fig. 1. Mean SNRs needed to obtain 50% intelligibility (the SRT) of words in noise for both groups. Bars indicate standard deviation.

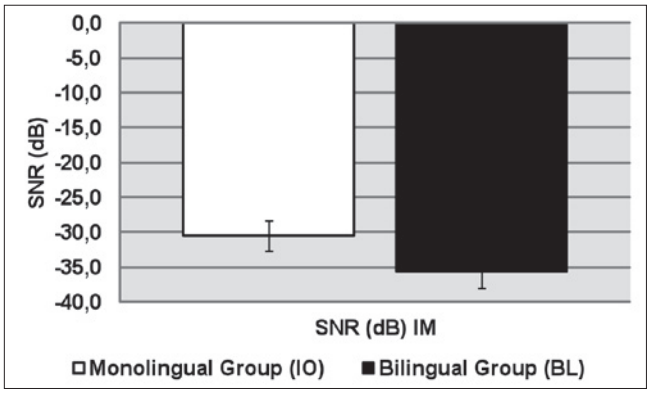

Fig. 2. Mean SNRs needed to obtain 50% intelligibility (the SRT) of phrases against contralateral continuous discourse for both groups. Bars indicate standard deviation.

Table III. Correlation between % of exposure to L2 and SNRs.

	Mean	SD	r(X,Y)	r^2	t	p-value
% exposure to L2	44.0	6.86				
SNR noise	-2.6	1.71	0.192	0.036	0.705	0.492
% exposure to L2	44.0	6.86				
SNR phrases	-32.8	2.39	-0.356	0.127	-1.375	0.192

SNR noise: SNRs needed to obtain 50% intelligibility (the SRT) of words in noise; SNR phrases: SNRs needed to obtain 50% intelligibility (the SRT) of phrases against contralateral discourse; SD: standard deviation. SNRs are expressed in dB. Correlations significant for $p < 0.05$.

to L2 (4 years old *vs* 5 to 7 years old) and the number of years since starting to learn L2 (more or less than 3 years) Within the range of exposure to L1 *vs* L2 above reported, there was no significant correlation with speech intelligibility (Table III). No differences emerged between Slavic and Romance L1 background ($T^2H = 9.697$ $F(7.7) = 0.746$ $p > 0.5$), and the significant differences in the SNRs between these two subgroups and IO speakers was confirmed (Table IV).
Age at time of first exposure to L2 did not correlate with SNR, whereas years of exposure to L2 did significantly correlate (Table V).

Discussion

Our group of sequential bilingual children needed a significantly higher SNR than their mother-tongue peers when the primary message was masked with noise. These children might therefore have speech perception difficulties in adverse listening conditions, where many phonetic cues (particularly low-energy ones) are masked by noise and reverberation. In other words, many consonant contrasts become less audible, so listeners must rely on secondary cues [5] and that is why they should have an intrinsic redundancy of acoustic indexes. While learning in their second language, these children should acquire acoustic indexes as complete as possible in order to process the foreign language, but beyond a critical period their acquisition of these indexes will never reach the level of mother-language individuals.
A limit of this study is the small number of participants. However, our data might demonstrate that even sequential bilingual individuals exposed to L2 at 4 years old had worse speech perception in noise than their matched IO peers. Most probably, the acquisition of L2 phonological skills at the age of 4 might be already too late to catch up to their mother language peers with regards to these competences. These data are in agreement with that observed in a group of 9-year-old Turkish-German bilingual children, who demonstrated difficulties with certain German vowel contrasts, despite having started learning German at 2 to 4 years of age [16]. Although in the past some authors considered that the critical period for acquiring phonological skills might be restricted to 5-6 years of age [28], more recent studies demonstrated that these

Table IV. Correlation between mother tongue (Slavic vs. Romance), age at time of exposure to L2, L2 output, number of years since starting to learn L2, and SNRs.

	BL subgroups $F(7,7) = 0.74591$; $p < 0.646$				
	Slavic	Romance	t value	gl	p-value
Age	8.6	8.7	-0.0968	13	0,924
SP	8.3	8.3	-0.0833	13	0.935
SNR noise	-2.9	-2.3	-0.6578	13	0.522
SNR phrases	-33.3	-32.4	-0.7267	13	0.480
L2 Age	5.3	4.7	0.90707	13	0.381
L2 %	43%	45%	0.51358	13	0.616
L2 Years	3.4	4.0	-1.0299	13	0.322
	Italian *vs* Romance $F(7,14) = 137.29$; $p < 0.000$	Italian *vs* Slavic $F(7,15) = 126.26$; $p < 0.000$			
	t value	gl	p value	t value	gl	p-value
Age	-0.1505	20	0.882	-0.0314	21	0.975
SP	-0.2435	20	0.810	-0.1404	21	0.890
SNR noise	-2.9517	20	0.008	-2.6889	21	0.014
SNR phrases	3.8991	20	0.001	6.4348	21	0.000

SNR noise: SNRs needed to obtain 50% intelligibility (the SRT) of words in noise; SNR phrases; SNRs needed to obtain 50% intelligibility (the SRT) of phrases against contralateral discourse; SD: standard deviation. SNRs are expressed in dB. Correlations significant for $p < 0.05$.

Table V.

Correlation between age at time of first exposure to L2 and SNR for words in noise						
	Mean	SD	r(X,Y)	r^2	t	p- value
Age at time of first exposure to L2	5.00	1.13				
SNR noise	-2.6	0.09097	-0.150	0.022	-0.550	0.41042
Correlation between years of exposure to L2 and SNR for words in noise						
	Mean	SD	r(X,Y)	r^2	t	p- value
Years of exposure to L2	3.06	1.175				
SNR noise	-2.6	1.710	0.37986	0.20764	2.356	0.034

SNR noise: SNRs needed to obtain 50% intelligibility (the SRT) of words in noise; SD: Standard deviation. SNRs are expressed in dB.

abilities decline sharply between 6 and 12 months of age [13]. The above reported study by Darcy & Krüger together with the present demonstrate that early and intensive exposure to a second language may not necessarily be sufficient to build native-like phonemic categories, or to perform as well as native speakers in difficult listening conditions [10 15].

In the IO group, speech perception in noise was correlated with age. As previously observed, this is a process that improves gradually and reaches adult-like performances at the age of 15-16, because of the improvement in auditory processing efficiency and attentional control with age [1 2 29].

However, in the BL group speech perception in noise did not correlate with age per se, but did correlate significantly with years of exposure to L2. In this regard, one should consider that phonemic categories continue to be refined with age, providing children have a significant exposure to a given language. It may be that, between the two mechanisms involved in L2 perception in noise, further refinement of phonemic categories with exposure to the language becomes more relevant than the age-related improvement in auditory central processing and divided attention. This explains why in our BL group perception in noise correlated significantly with years of exposure to L2 and not with age per se.

Regarding test # 2, bilingual children needed a significantly lower SNR than their IO-speaking counterparts. In other words, they demonstrated better performance when distracted by contralateral continuous conversation. In fact, this masking interferes with selective attention to the primary signal, not with the acoustic cues. These results reinforced test # 1 hypothesis, i.e. that bilingual children's worse speech perception in noise was only due to their weaker phonological competences, not to any lexical, grammatical or other cognitive factors, such as attention or memory. Thus, the selection criteria used to recruit BL children were strong enough to avoid inclusion of any subject with reduced skills in these last aspects, due to socio-economic disadvantage, previous pathologies, or unknown factors.

The strength of our study lies in that we carefully selected a homogeneous group of bilingual children who were competent speakers in both languages, and had been exposed to L2 between 4 and 7 years of age. Some studies have reported greater individual differences in non-native than in native speakers, a finding that probably reflects heterogeneity of the population of non-native speakers considered [19]. Our data demonstrated very similar SDs between the IO and BL groups, probably due to our strict participant selection.

On the other hand, a possible bias might stem from the fact that L1 was represented by two different language groups, i.e. Slavic languages in 7 of our bilinguals, and Romance languages in 8. No significant differences emerged in the test scores between these two subgroups, however. It is likely that the different degrees of phonetic similarity between these languages and Italian are not strong enough to modify the children's responses.

Moreover, the remote possibility of differences in the basic auditory function between children of various ethnic groups has already been excluded.

Conclusions

Sequential bilingual children might have speech perception difficulties in adverse listening conditions. We feel it could be important to test the effect of different ages of initial exposure to L2, and compare laboratory results with tests conducted in the classroom (or in virtually-reproduced classroom listening conditions) regarding comprehension of less redundant speech material.

Finally, as the numbers of immigrant children are increasing in many developed countries and effective listening is a linchpin of school learning [30], we hope these findings are kept in mind in the future and applied directly to more engineering-oriented disciplines associated with verbal communication (i.e. design of classrooms acoustic and classrooms communication systems).

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Conflict of interest statement

None declared.

References

1. Elliott LL. *Performance of children aged 9 to 17 years on a test of speech intelligibility in noise using sentence material with controlled word predictability*. J Acoust Soc Am 1979;66:651-3.
2. Johnson CE. *Children's phoneme identification in reverberation and noise*. J Speech Lang Hear Res 2000;43:144-57.
3. Stuart A. *Reception thresholds for sentences in quiet, continuous noise, and interrupted noise in school-age children*. J Am Acad Audiol 2008;19:135-46.
4. Valente DL, Plevinsky HM, Franco JM, et al. *Experimental investigation of the effects of the acoustical conditions in a simulated classroom on speech recognition and learning in children*. J Acoust Soc Am 2000;131:232-46.
5. Cutler A, Weber A, Smits R, et al. *Patterns of English phoneme confusions by native and non-native listeners*. J Acoust Soc Am 2004;116: 3668-78.
6. Goldstein BA, Fabiano L, Washington PS. *Phonological skills in predominantly English-speaking, predominantly Spanish-speaking, and Spanish-English bilingual children*. Lang Speech Hear Serv Sch 2005;36:201-18.
7. Mayo LH, Florentine M, Buus S. *Age of second-language acquisition and perception of speech in noise*. J Speech Lang Hear Res 1997;40:686-93.
8. European Commission/EACEA/Eurydice/Eurostat, 2014. *Key Data on Early Childhood Education and Care in Europe*. 2014 Edition. Eurydice and Eurostat Report. Luxembourg: Publications Office of the European Union.
9. Calandruccio L, Buss E, Hall JW. *Effects of linguistic experience on the ability to benefit from temporal and spectral masker modulation*. J Acoust Soc Am 2014;135:1335-43.
10. McCarthy KM, Mahon M, Rosen S, et al. *Speech perception and production by sequential bilingual children: a longitudinal study of voice onset time acquisition*. Child Dev 2014;85:1965-80.
11. Ministero dell'Istruzione. *Gli alunni stranieri nel sistema scolastico italiano. A.S. 2013/2014*. MIUR - Ufficio di Statistica. Ottobre 2014 .
12. Fabiano-Smith L, Barlow J. *Interaction in bilingual phonological acquisition: evidence from phonetic inventories*. Int J Biling Educ Biling 2010;13:81-97.
13. Maurer D, Werker JF. *Perceptual narrowing during infancy: a comparison of language and faces*. Dev Psychobiol 2014;56:154-78.
14. Werker JF, Hensch TK. *Critical periods in speech perception: new directions*. Annu Rev Psychol 2015; 66:173-96.
15. Sebastián-Gallés N. *Cross-language speech perception*. In: Pisoni DB, Remez RE, editors. *The handbook of speech perception*. Oxford: Blackwell; 2005. p. 546-66.
16. Darcy I, Krüger F. *Vowel perception and production in Turkish children acquiring L2 German*. J Phonetics 2012;40: 568-81.
17. Tsukada K, Birdsong D, Bialystok E, et al. *A developmental study of English vowel production and perception by native Korean adults and children*. J Phonetics 2005;33:263-90.
18. Rivera Mindt M, Arentoft A, Kubo Germano K, et al. *Neuropsychological, cognitive, and theoretical considerations for evaluation of bilingual individuals*. Neuropsychol Rev 2008;18:255-68.
19. Nabelek AK, Donahue AM. *Perception of consonants in reverberation by native and non-native listeners*. J Acoust Soc Am 1984;75:632-4.
20. Gutiérrez-Clellen VF, Kreiter J. *Understanding child bilingual acquisition using parent and teacher reports*. Applied Psycholinguistics 2003;24:267-88.
21. Invalsi Istituto Nazionale per la Valutazione del Sistema educativo di Istruzione e formazione (Available at: http://www.invalsi.it).
22. Pena E, Bedore LM, Rappazzo C. *Comparison of Spanish, English, and bilingual children's performance across semantic tasks*. Lang Speech Hear Serv Schools 2003;34:5-16.
23. Stuart A, Zhang J, Swink S. *Reception thresholds for sentences in quiet and noise for monolingual English and bilingual Mandarin-English listeners*. J Am Acad Audiol 2010;21:239-48.
24. Levitt H. *Transformed up-down methods in psychoacoustics*. J Acoust Soc Am 1971;49(Suppl 2):467+.
25. Hagerman B, Kinnefors C. *Efficient adaptive methods for measuring speech reception threshold in quiet and in noise*. Scand Audiol 1995;24:71-7.
26. Hawley ML, Litovsky RY, Culling JF. *The benefit of binaural hearing in a cocktail party: effect of location and type of interferer*. J Acoust Soc Am 2004;115:833-43.
27. Prosser S, Martini A, Bovo R. *Reception threshold for sentences under stationary noise and speech competition in normal and hearing impaired*. J Audiol Med 1997;6:134-46.
28. Larsen-Freeman D, Long MH. *An Introduction to second language acquisition research*. New York: Routledge; 2004.
29. Moore DR. *Maturation and aging*. In: Eggermont JJ, Ed. *Auditory temporal processing and its disorders*. Oxford: Oxford University Press; 2015.
30. Klatte M, Bergstrom K, Lachmann T. *Does noise affect learning? A short review on noise effects on cognitive performance in children*. Front Psychol 2013;4:578.

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Otology

Otologic manifestations of Susac syndrome

Manifestazioni otologiche della sindrome di Susac

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SUMMARY

Susac syndrome, a rare autoimmune disorder first described as a classic triad (encephalopathy, branch retinal artery occlusion, and sensorineural hearing loss) in 1979 by renowned physician John O. Susac, has been an advancing area of clinical interest and scientific research over the last several decades. This comprehensive review aims to succinctly highlight the breadth and detail of this enigmatic disease, with a primary focus on otologic manifestations. Topics discussed include epidemiology, pathophysiology, clinical manifestations, differential diagnoses, classification schema, laboratory investigations, characteristic audiometric findings, high-yield radiographic imaging, temporal bone histopathology, treatment strategies and overall prognosis.

KEY WORDS: Otology • Sensorineural hearing loss • Temporal bone histopathology • Susac syndrome • Update

RIASSUNTO

La sindrome di Susac, una rara malattia descritta nel 1979 dal celebre medico John O. Susac con la classica triade di encefalopatia, occlusione dell'arteria retinica ed ipoacusia neurosensoriale, ha rappresentato negli ultimi decenni un tema di notevole interesse clinico e di ricerca scientifica. La presente revisione ha lo scopo di evidenziare i dettagli e le dimensioni di questa enigmatica patologia, focalizzandosi principalmente sulle manifestazioni otologiche. Le tematiche discusse includono epidemiologia, fisiopatologia, manifestazioni cliniche, diagnostica differenziale, classificazione, indagini di laboratorio, caratteristiche audiometriche, imaging, anatomopatologia dell'osso temporale, strategie terapeutiche e prognosi.

PAROLE CHIAVE: *Otologia • Perdita dell'udito neurosensoriale • Istopatologia dell'osso temporale • Sindrome di Susac • Aggiornamento*

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Introduction

Susac Syndrome (SS) is a unique clinical condition first described in 1979 by Dr. Susac, who identified two young women with the clinical triad of subacute multifocal encephalopathy, visual changes and hearing loss secondary to systemic microangiopathy of the cerebrum, retina and cochlea [1]. While the underlying aetiology of this disease remains unknown, it is widely believed the observed clinical manifestations are the result of an autoimmune endotheliopathy of the cerebral, retinal and cochlear microvasculature [2 3]. This hypothesis has been further purported by both ex vivo histopathologic specimens of the cerebrum and temporal bone as well as in vivo findings of the retina via fluorescein angiography [4-9]. Despite significant advances in the understanding of this disorder, the presentation of SS remains highly variable with respect to disease onset, course, duration and prognosis. Similarly, data enumeration on patterns and ramifications of SS are also limited given the small number of cases presently available in the published literature worldwide [10]. The heterogeneity of presenting symptomology associated with this condition, along with its similarities to other more ubiquitous disease states indeed makes SS a challenging undertaking to astutely diagnose. This is particularly true of the otologic manifestations of SS, where the observed sensorineural hearing loss is often irreversible and progressive in nature, despite early and aggressive therapies. This comprehensive review aims to concisely highlight the current understanding of this enigmatic condition with a distinct emphasis on otologic features pertinent to the field of otolaryngology. To briefly summarise, this study was designed and performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) Protocol. Independent searches of the PubMed MEDLINE database were performed on February 12, 2018, by the first and second authors to identify studies which specifically described the otologic manifestations of SS using the Boolean method and relevant search term combinations. English and full-length original articles were employed as inclusion criteria to assess for data extraction eligibility. Exclusion criteria include absent full-text articles and non-English articles, resulting in the omission of 33 and 14 articles, respectively. The search strategy is summarised as follows: 250 articles retrieved, 203 full-length titles and abstracts screened, and 13 studies included in final study data synthesis (i.e. 12 case reports and 1 original article). The abstracted clinical information was supplemented with targeted searches to address specific needs identified in writing this comprehensive review.

Discussion

Epidemiology

SS is a rare autoimmune disorder with a slight female-to-male preponderance of 3:1 and predilection in those of Caucasian ancestry [11]. Most reports of SS are derived from the North American and European continents, with the first clinical ramifications of SS noted between 16-40 years, with an extended age range of 7-72 years [12]. As SS remains both underdiagnosed and misdiagnosed, this results in an unknown true incidence and prevalence. Currently, there are a total of 304 documented cases of SS worldwide, with a higher reported incidence during the spring and summer months [10 13].

Pathophysiology and clinical manifestations

Although the exact aetiology of SS remains elusive, histopathological findings support an autoimmune endotheliopathy of cerebral, retinal and cochlear microvasculature (Fig. 1). Visualised changes include an affinity for small (< 100 mm) precapillary arterioles with endothelial cell necrosis, basement membrane thickening, inflammatory cell infiltration and complement deposition (C4d and C3d). Following this injury, diffuse microvascular changes ultimately result in microischaemia and infarction leading to the observed clinical manifestations of encephalopathy, visual changes, and sensorineural hearing loss [14]. Nevertheless, SS is a considerable challenge to diagnose as it is very uncommon for patients to initially present with all features of the classically described triad (Table I) [7]. There are two broad categories of SS; the first is a primarily encephalopathic presentation with either concurrent or eventual manifestation of visual disturbances and sensorineural hearing loss and the second is a recurrent course of branched retinal artery occlusion and hearing loss, which may be accompanied with encephalopathy months to years later [15].

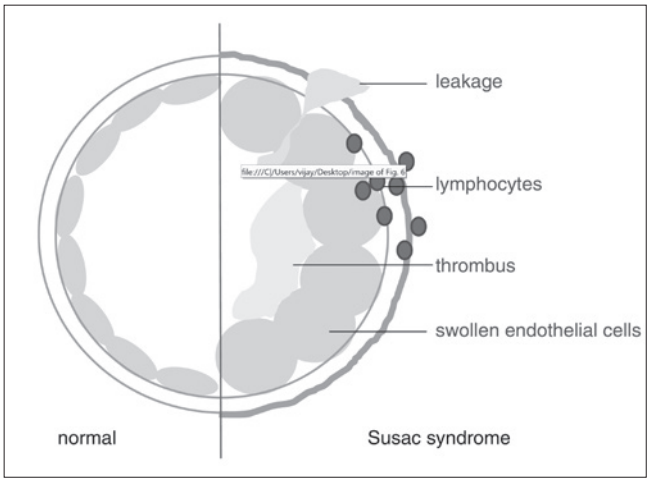

Fig. 1. Proposed model of pathogenesis for Susac syndrome. Used with permission from E. Bernd Ringelstein. The endothelial cells and basement membrane are oedematous, with loss of vessel wall integrity. As a result, there is subsequent lymphocytic infiltration and thrombotic material accumulation within the vessel lumen. This ultimately results in occlusion of the affected microvasculature (from Kleffner et al., 2012 [2], mod.).

Table I. Clinical presentation in Susac syndrome.

System	Prevalence
Brain (corpus callosum)	88% (100%)
Retina	46%
Cochlea	52%
All three structures	20%

Organ involvement at clinical presentation of Susac syndrome (from García-Carrasco et al., 2011 [3], mod.).

a. Nervous system

Encephalopathic features typically follow a subacute or acute course and are often preceded by or concurrent with a migrainous headache, likely secondary to leptomeningeal involvement [10]. Encephalopathic signs may be the initial presentation of SS or secondary to retinal or vestibulocochlear pathology. Encephalopathy often manifests with the abrupt onset of multifocal neurologic deficits and/or neuropsychiatric disturbances. Symptoms may be dominated by confusion, memory and cognitive disturbances or by acute and profound changes in mood and personality. Focal findings such as seizures, pyramidal signs, dysarthria and hyperreflexia may also be present [16]. While generally reversible, some initial deficits may be permanent depending on the location and extent of the involved cerebral vasculopathy. In the original descriptions by Susac and colleagues, multifocal microinfarctions of the cerebral grey and white

matter were noted with associated necrosis and gliosis [1]. Subsequent developments via brain biopsy highlighted characteristic findings of an autoimmune vasculopathy primarily affecting the precapillary arteriolar endothelium in both the cortex and leptomeninges. Visualised changes also include subacute microinfarctions, perivascular oedema, chronic inflammation and gliosis/reactive astrocytosis [4 5]. The absence of fibrinoid necrosis, necrotising vasculitis, or demyelination assists in the pathologic distinction of SS from other systemic vasculidities or autoimmune demyelinating conditions [6 7].

b. Visual system

Visual disturbances related to branched retinal artery occlusion are heterogeneous in nature and depend on the location and extent of diseased vessels within the retina. Those with small, peripheral arteriolar occlusions may be asymptomatic or have subtle visual changes, with a normal funduscopic exam [17]. Conversely, those who suffer from more extensive lesions of the retina and macula may experience profound or complete vison loss. Patients may also present with additional ocular complaints of blurred vision, scintillating scotoma, or photopsia [18]. Fluorescein angiography assists in visualising the extent of the occlusive retinal microangiopathy and illustrates characteristic ocular findings such as arteriolar narrowing, arteriolar wall hyperfluorescence, and segmental non-perfusion [19]. Additionally, yellow-white arterial wall plaques (Gass plaques) located at the midarteriolar segments may be seen, proposed to be the result of arteriolar wall damage and subsequent extravasation of blood and lipids forming atheromatous plaques [20]. Their location at the midarteriolar segments is indicative of endothelial integrity loss, rather than an end-artery embolic pathology. These plaques may be transient throughout the clinical progression of this condition; however, their presence is confirmatory of SS [9].

c. Auditory and vestibular systems

Sensorineural hearing loss is a prominent feature of SS with highly variable characteristics [4 7 21-24]. Hearing loss is often precipitous in onset and typically rapidly progressive, sometimes resulting in complete deafness in either one or both ears. In some instances, hearing loss may abruptly occur in one ear, followed by loss in the contralateral ear days to weeks later, resulting in the so-called "bang-bang" type of hearing loss [15 25]. Due to the commonly detected pattern of low and middle-frequency sensorineural hearing loss, microinfarctions of end arterioles and damage to the apical cochlea are thought to be responsible in the setting of the observed endotheliopathy [6 19 26]. This pattern of damage is further supported by the clinical observation of sensorineural hearing loss with maintained acoustic reflexes, rather than localised damage to the vestibulocochlear nerve, which suggests cochlear disease as the underlying aetiology [24]. Simultaneous vestibular dysfunction is also common in the early phase of SS; patients can present with severe tinnitus accompanying their abrupt sensorineural hearing loss, which often leads to the misdiagnosis of Ménière's disease [27]. The presence of vestibular dysfunction may indicate lesions in the vestibular apparatus itself or may be the result of central microinfarctions within the cerebellum or brainstem [7]. This is in stark contrast to other autoimmune inner ear diseases such as Cogan syndrome, where the pattern of damage demonstrates extensive endolymphatic hydrops, saccular collapse following intense dilation, fibrotic changes in the perilymphatic space of the posterior semicircular canal, and absorption of enchondral bone with no pathological changes within the inner ear vasculature [28]. Additional symptoms which may be present in SS include gait ataxia, aural pressure, and prominent jerky nystagmus, which is hypothesised to be due to infarction within the membranous labyrinth [12]. In SS patients with prominent encephalopathic features, it may be difficult to assess the presence or extent of vestibulocochlear dysfunction, in which case brainstem auditory evoked potential testing may be necessary [18].

d. Integumentary and musculoskeletal systems

Historically, patients have described both myalgias as well as skin changes during the early phase of SS [6 7]. Turc and colleagues noted skin lesions consistent with livedo reticularis in a patient with SS; skin biopsies performed demonstrated similar pathologic findings in other affected systems with evidence of microvascular thrombi in dermal arterioles, minimal perivascular lymphocytic infiltration and endothelial cell swelling [29]. Similarly, Petty and colleagues reported subclinical microangiopathy involving muscular arterioles in 5 biopsy specimens with SS, further supporting the notion of a systemic endotheliopathy, unifying features of this condition [7].

Differential diagnoses and classification schema

SS is an orphan disease which must be considered in the differential diagnosis of a broad variety of medical disorders [30]. Given the potential for diversely presenting symptomatology, SS remains a pertinent diagnosis chiefly in the realm of neurologic, ophthalmologic, rheumatologic and otolaryngologic practitioners. A concise yet non-exhaustive list which outlines conditions that present with similar clinical characteristics is outlined in Table II. A classification system described by Vishnevskia-Dai and colleagues can also be applied to assist clinicians in the early diagnosis of this enigmatic condition. This schema

was designed in part using a combination of clinical information derived from the medical literature (case reports, reviews and meta-analysis) as well as the author's case series of 10 patients, with a focus on clinical presentation and diagnostic imaging findings (Table III) [31]. Although novel in applicability, studies have suggested that early diagnosis may lead to better prognosis in young patients, prompting a high level of suspicion and early intervention in patients with SS [30].

Diagnostic workup

a. Audiometry

Audiological evaluation in the form of pure tone audiometry remains essential to confirm the presence of sensorineural hearing loss in patients presenting with concern for SS. While audiometric data on SS patients is limited, the observed sensorineural hearing loss appears to affect the low and middle frequencies, with an occasional loss appreciated at the high frequencies [4 7 22-24 27]. To date, Roeser and colleagues have provided the most comprehensive description of audiometric findings in SS patients. In their cases series of 23 patients, representing a total of 34 affected ears, most frequencies were found to be affected, with losses noted at 500 and 1,000 Hz and an overall "upsloping" pattern of sensorineural hearing loss (Fig. 2). Tympanometry for all 23 patients was found to be type A, indicating a normal middle ear system. The pure-tone average of the 34 affected ears was 41.5 dB, with a mean percent binaural hearing loss of 26.4%. The American Academy of Otolaryngology-Head and Neck Surgery hearing classification of this cohort demonstrated primarily type A (47%) hearing, with losses also noted in categories type B (23.5%), type C (6.0%), and type D (23.5%). Finally, word recognition scores were poor in this study group, with only 26.5% of affected ears exhibiting 100%-word recognition [24].

Table II. Differential diagnosis of Susac syndrome.

Inflammatory demyelinating CNS* disease	• Acute disseminated encephalomyelitis • Multiple sclerosis • Neuromyelitis optica (Devic's disease)
Cerebrovascular disease	• Cerebral autosomal dominant Arteriopathy with subcortical infarcts and Leukoencephalopathy (CADASIL) • Stroke • Transient ischaemic attack
Vasculitic, connective tissue, and autoimmune disease	• Antiphospholipid antibody syndrome • Behçet disease • Churg-Strauss syndrome • Dermatomyositis • Eales disease • Limbic encephalitis • Polyarteritis nodosa • Primary CNS* vasculitis • Sarcoidosis • Sjögren syndrome • Systemic lupus erythematosus • Takayasu Disease • Vogt-Koyanagi-Harada syndrome • Wegener granulomatosis
Infectious CNS* disease	• Creutzfeldt-Jakob disease • Lyme disease • Progressive multifocal leukoencephalopathy • Syphilis • Toxoplasmosis • Tuberculosis • Viral encephalitis
Malignancy	• CNS* metastases • Primary CNS* lymphoma • Paraneoplastic syndrome
Otologic disease	• Cogan syndrome • Ménière's disease • Sudden sensorineural hearing loss
Other	• Cryoglobulinemia • Lactate acidosis and stroke-like Episodes (MELAS) • Marchiafava-Bignami disease • Migraines • Psychotic disorders

*: Central nervous system (from Dörr et al., 2013 [10], mod.).

b. Vestibular-evoked myogenic potentials

Vestibular-evoked myogenic potentials can be applied in the workup of a patient with suspected SS, particularly if there is evidence of acute vestibular dysfunction upon clinical presentation. In a study by Magliulo and colleagues, they were able to successfully characterise a vestibular-evoked myogenic potential deficit, with both delayed latency and reduced amplitude in a patient with SS (Fig. 3). It is reasonable to extrapolate that the initial otologic damage in SS may involve a restricted portion of the vestibular apparatus [32]. Further investigation is necessary to explore such mechanistic details.

c. Laboratory investigations

Due to variability in presenting features of SS, individuals are often subjected to a myriad of diagnostic laboratory tests, often with few abnormal findings. Focused serologic testing is recommended, with expansion as indicated to evaluate for related differential diagnoses (Table II).

- *Antibody markers.* Mild elevation of antinuclear, antiphospholipid, anti-thyroid microsomal, anti-thyroid peroxidase, perinuclear anti-neutrophil cytoplasmic, and rheumatoid factor autoantibodies have all been reported in SS patients. In a case series by Jarius and colleagues of 25 SS patients, 3 patients (13.0%) were reported to have anti-nuclear antibody positivity, 1 patient (4.0%) was reported to have perinuclear anti-neutrophil cytoplasmic antibody positivity, 1 patient

Table III. Susac syndrome classification.

Category	Definition
Suspected	One triad manifestation†
	One risk factor*
	1. Female
	a. 20-40 Years
	b. Within 1 year of pregnancy
	2. Characteristic MRI findings
	a. Corpus callosum lesions
	b. Periventricular lesions
Incomplete	Two triad manifestations†
Complete	Three triad manifestations†

**: With no known risk factors for arteriosclerosis and/or coagulopathy. †: Clinical triad of encephalopathy, sensorineural hearing loss, and branch retinal artery occlusion. Susac syndrome classification system (from Vishnevskia-dai et al., 2016 [31], mod.).*

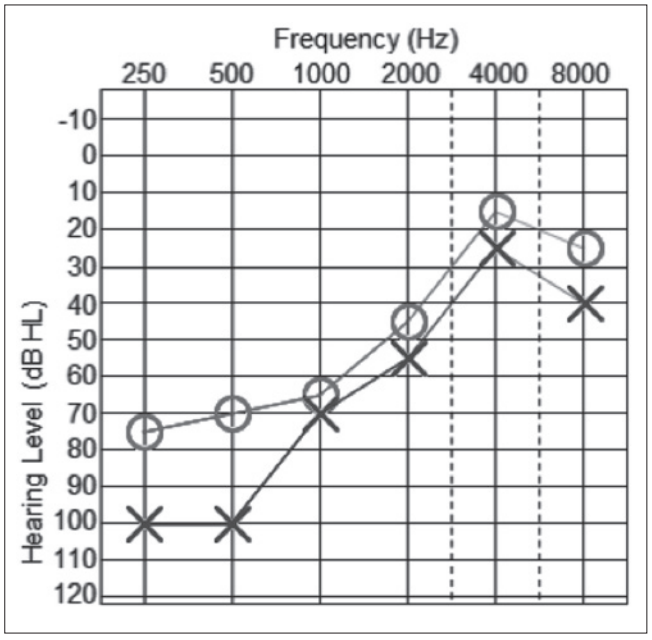

Fig. 2. 36-year-old female with sensorineural hearing loss in the setting of Susac Syndrome. Pure tone audiometry reveals bilateral asymmetric sensorineural hearing loss, predominantly at the low and middle frequencies. The right ear is graphed with a "o" and the left ear is graphed with an "x". These responses represent the air conduction results, masked if necessary in both ears. Speech recognition thresholds were 45 decibels in the right ear and 60 decibels in the left ear; word discrimination scores were 96% in the right ear and 88% in the left ear.

was reported to have anti-thyroid microsomal antibody positivity, and 1 patient (4.0%) was reported to have anti-thyroid peroxidase antibody positivity [33]. Anti-endothelial cell antibodies, a heterogeneous family of antibodies which bind to various endothelial cell antigens, have also been detected in the serum of SS patients; it has been postulated to serve as a biomarker of disease activity [34 35]. In the case series by Jarius and

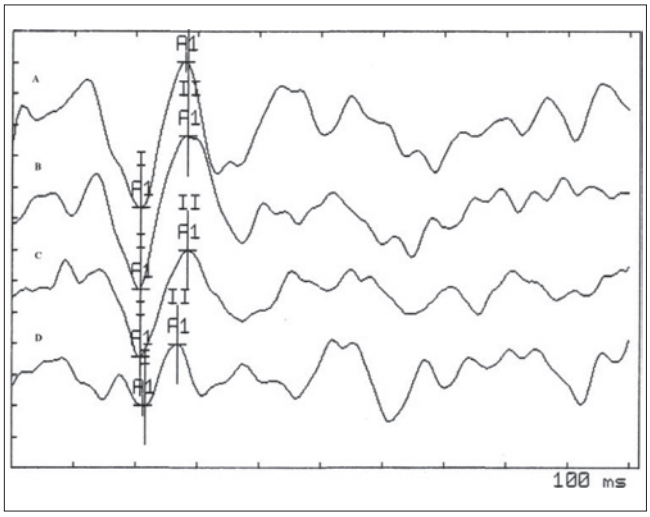

Fig 3. 24-year-old female with acute vertigo in the setting of Susac syndrome. Side, left; stimulus, logon; frequency, 500 Hz; number of stimuli, 200; intensity, A 130, B 130, C 120, D 110 dB sound pressure level; masking, off; rate, 4/s; polarity, negative; sensitivity, 10 μV per division; amplitude, A 23.42, B 24.35, C 34.09, D 9.68; latency A 20.8, B 20.8, C 20.8, D 21.6 (from Magliulo et al., 2008 [32], used with permission from Giuseppe Magliulo).

colleagues, 7 patients (28%) were found to have anti-endothelial cell antibody positivity [33]. However, it remains uncertain whether these antibodies are unique to SS or represent a non-specific epiphenomenon. At this time, it remains a non-specific assay as it has been reported in other vasculitic and autoimmune processes including systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome and sarcoidosis. There are several methods to detect anti-endothelial cell antibodies but sensitivity and specificity of these antibodies as biomarkers for SS have yet to be established.

- *Haematologic panel.* A complete blood count with differential may be performed, which occasionally reveals monocytosis and eosinophilia [36]. Similarly, mild elevation in acute phase reactants including erythrocyte sedimentation rate and C-reactive protein has been reported in SS patients. Elevated levels of factor VIII and von Willebrand factor antigen have also been documented in SS, likely due to endothelial perturbation, as the close association of these factors with endothelium would be consistent with the observed endotheliopathy [1 9].
- *Cerebrospinal fluid analysis.* Cerebrospinal fluid examination reveals lymphocytic pleocytosis (5-30 cells/mm^3), elevated protein levels (range: 100-3000 mg/dl), usually during the encephalopathic phase, and occasionally elevated myelin basic protein [37]. In a case series by Mateen and colleagues of 29 patients with SS, the mean cerebrospinal fluid protein level was found to be 130 mg/dl (median: 129, range: 35-268, normal range:

15-45 mg/dl), with a mean cell count of 14 cells/ml (median: 5, range: 0-86, normal range: 0-5 cells/ml) [38]. Analysis for oligoclonal bands is often performed due to overlapping clinical features of SS with multiple sclerosis as SS patients have no evidence of oligoclonal bands or an elevated Immunoglobulin G index.

d. Radiographic imaging

Subclinical pathology occurs in many patients with suspected SS without overt clinical manifestations, prompting emphasis on an appropriate diagnostic workup with dedicated imaging to confirm the diagnosis of SS. To date, SS patients with documented evidence of sensorineural hearing loss lack visualised radiographic aberrations within the external, middle and inner ear [24].

- *Computed tomography.* Computed tomography of the brain is typically normal in the initial stages of SS, however with disease progression, this could progress to radiographically evident cortical atrophy [23]. In parallel, single-photon emission computed tomography of the brain can also be utilised which reveals multifocal involvement corresponding to areas of cerebral hypoperfusion, confirming the presence of microangiopathy seen in SS [3].
- *Magnetic resonance imaging.* Magnetic resonance imaging is the neuroimaging study of choice to evaluate for SS. Typical findings include central corpus callosum involvement and brain infarctions (Fig. 4). The cerebellum, cerebellar peduncles, brain stem and thalamus are less frequently involved. The deep gray matter is involved in approximately 70% of SS cases and the leptomeninges is affected in about 33% of SS cases [39]. T2-weighted sequences typically reveal multifocal, small, hyperintense foci which mainly involve the central aspect of the corpus callosum with peripheral sparing. Fluid-attenuated inversion recovery sequences may also show lesions in the corpus callosum centrally located in the periventricular and subcortical white matter. T1-weighted sequences reveal hypointense areas during the subacute or late phase of SS [3 40]. During periods of encephalopathy, the corpus callosum is universally affected and reveals a characteristic pattern of small-to-large round white matter lesions ("snowballs") best visualised on sagittal T2-weighted fluid-attenuated inversion recovery sequences and linear defects ("spokes") found in the central fibres of the corpus callosum. As acute changes resolve over time, central callosal lesions develop ("holes") and are best visualised on sagittal T1-weighted sequences [41]. Diffusion tensor imaging can also be used to evaluate for SS as it is specifically sensitive to structural impairment of axonal integrity based on normal values for fractional anisotropy, a measure which reflects spatial directionality of water diffusion [42]. The mean fractional anisotropy reduction in the genu of the corpus callosum and prefrontal white matter, as well as widespread impairment of white matter fibre integrity and fiber disruption involving the genu of the corpus callosum, appears to be typical for SS, revealing microstructural degeneration of cerebral fibres and extensive microstructural dysfunction [43 44].

e. Temporal bone histopathology

The first description of otopathologic findings in SS was described by Francis and colleagues in 2011 who harvested two post-mortem temporal bones from a 51-year-old female with SS and audiometrically confirmed bilateral severe sensorineural hearing loss without concomitant vestibular symptomology [8]. Pertinent histopathologic findings in SS are outlined in detail below with generalised atrophy and degeneration involving the apical half of the cochlear duct with preservation of cochlear neurons (Fig. 5).

- *Cochlea.* The organs of Corti were found to be absent or represented by a mound of supporting cells and devoid of hair cells. The tectorial membranes revealed marked pathologic changes, which were more extensive in the left ear and characterised by cellular encapsulation and detachment from the spiral limbus. The lateral cochlear walls revealed near-total atrophy of the stria vascularis and severe degeneration of spiral ligament fibrocytes with replacement via connective tissue cells. The stria vascularis revealed patchy atrophy in the 3-7 mm region on the right and

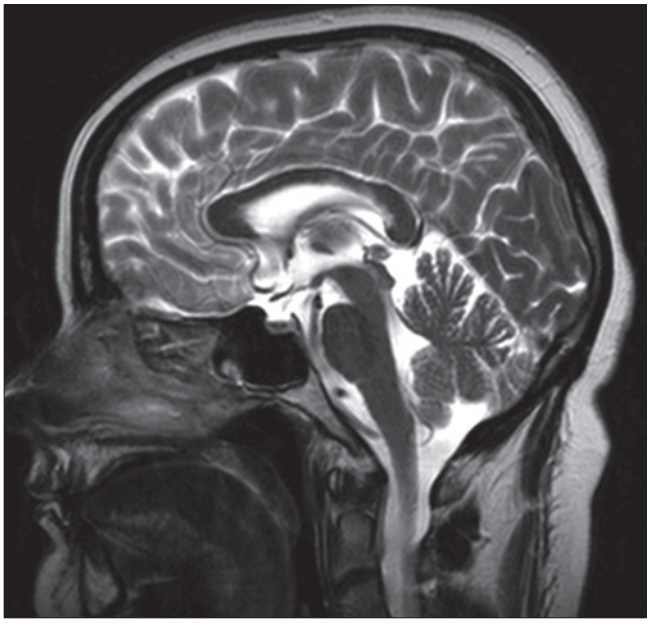

Fig. 4. 43-year-old female with Susac syndrome characterised by the clinical triad of encephalopathy, branch retinal artery occlusion, and sensorineural hearing loss. T2-weighted midline sagittal imaging reveals mild thinning of the corpus callosum near the junction of the body and the splenium.

0-3 mm region in the left. Some capillaries within the stria vascularis revealed likely occlusion of the vessel lumen by an acellular substance or thickening of the vessel wall. The number of capillaries appeared to be reduced in the lateral cochlear wall of the middle and apical turns. The scala media in the middle and apical turns demonstrated scattered cellular debris, likely secondary to sloughing cells degenerating within the stria vascularis and organ of Corti. Finally, dendrites leading up to the organ of Corti similarly revealed atrophy in the middle and apical turns [8].

- *Saccule.* The saccular macula in the left ear reveals diminution of type I hair cells; the saccular lumen in both ears contains free-floating cells, arranged in strands and folded strips. The origin of these cells is unclear, but they could represent detached cells which formerly lined the saccular duct [8].
- *Leptomeninges.* The leptomeninges within the internal auditory canals revealed numerous psammoma bodies. Several small arterioles within the leptomeninges also revealed thickening of the vessel lumen to the point of occlusion. In some instances, there was cellular proliferation within or around the vessel wall causing occlusion, whereas other areas revealed a dense basophilic material occluding the vessel lumen [8].

Management principles

Given the small number of SS cases reported worldwide as well as an incomplete understanding of disease pathogenesis, determination of an optimal treatment strategy remains difficult. As the observed clinical fractures are postulated to be vasculitic in nature, management of SS is primarily focused on anti-inflammatory and disease-modifying therapies. Although recommendations for treatment protocols do exist, it is important to note most therapies are based on limited cohorts of SS patients. As such, response to proposed medical regimens may be highly variable based upon individual disease characteristics. Initial treatment protocols were first designed for patients presenting with primarily encephalopathic forms of SS; however, current literature supports a different approach for patients with the recurrent branch retinal artery occlusion and hearing loss subset of SS [34]. This has prompted in parallel a significant interest in the exploration of otologic surgical interventions for SS patients [5 25]. Regardless of disease subtype, it is increasingly evident as well as imperative that early, aggressive treatment should be initiated whenever possible [15 34 45 46].

a. Corticosteroids

In the acute phase, intravenous steroids are employed in an aggressive fashion as the initial treatment modality. Treatment begins with intravenous methylprednisone 1,000 mg/day over 3 days, followed by high dose oral prednisone 60-80 mg/day for a period of 2-4 weeks. This is followed by a slow taper with a daily dose reduction of 10% every 2 weeks, with a maintenance dose of 5-10 mg every other day [45]. An alternative to a prolonged course of oral prednisone, given long-term ramifications of corticosteroid use, is to utilize frequent pulses of intravenous methylprednisone, which may be beneficial particularly for SS relapses [15]. When inner ear disease accompanies central disease pathology, treatment of encephalopathic features using methylprednisone will simultaneously address any existing inner ear disease. Should otologic symptoms (acute sensorineural hearing loss, tinnitus and vertigo) predominate, it would be appropriate to promptly administer both intravenous methylprednisolone and intravenous immunoglobulin, with at least a moderate course of prednisone [46].

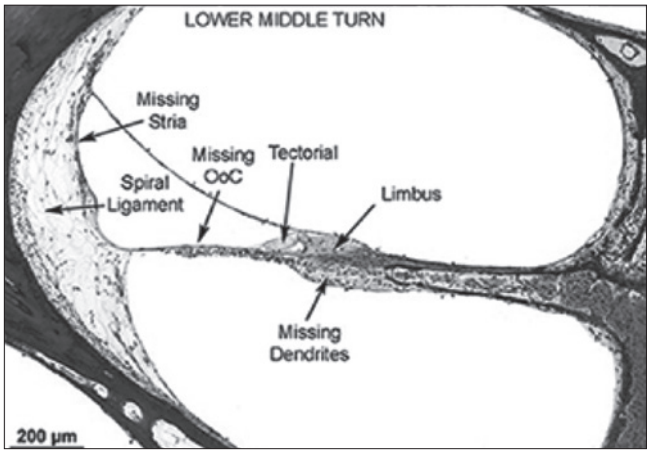

Fig. 5. 51-year old female with Susac syndrome and postmortem histopathological findings of the right temporal bone. Used with permission from Chadi Makary. Lower middle turn reveals widespread atrophy and degeneration. The organ of Corti is absent. The tectorial membrane is retracted and partially covered by cells. The spiral limbus reveals patchy atrophy and absent dendrites within the osseous spiral lamina. The stria vascularis is completely atrophic with significant loss of fibrocytes within the spiral ligament (from Francis et al., 2011 [8], mod.).

b. Intravenous immunoglobulin and plasmapheresis

Along with corticosteroids, concomitant intravenous immunoglobulin should be initiated in the first week of definitive treatment. The most commonly reported regimen consists of 2 g/kg the first week, followed by 2 g/kg every 2-4 weeks over a treatment period of 6 months [45]. Plasmapheresis may also have a role for SS patients with severe or relapsing patterns of disease who have not responded to conventional medical therapies [38].

c. Immunomodulators

Immunomodulatory drugs should be initiated early in the

treatment of SS patients suffering from severe disease. This consists of intravenous cyclophosphamide 10-15 mg/kg spaced 2 weeks apart, followed by additional doses if no change in symptomatology is seen. If notable improvement in symptoms does occur, patients should be switched to mycophenolate mofetil 1000-1500 mg twice daily for maintenance therapy. Alternatives to this regimen include a combination of mycophenolate mofetil and tacrolimus. This should be administered as mycophenolate mofetil 500 mg twice daily + tacrolimus 2 mg BID via intravenous formulation as maintenance therapy. For patients with extremely severe disease who fail to respond to previously described therapies, rituximab may be of benefit. This should be administered with an initial dose of 1,000 mg, followed by the same dose 2 weeks later and subsequent doses at intervals of 4-6 months and 6-12 months. In rare instances, new additive ischaemic ''hits'' to the cochlea may occur, even during active treatment with corticosteroids, intravenous immunoglobulin, mycophenolate mofetil and rituximab. As the window of opportunity to protect the inner ear is short, replacement of mycophenolate mofetil, with cyclophosphamide and mycophenolate mofetil plus tacrolimus, may be indicated. Intravenous cyclophosphamide should be administered at a dose of 10-15 mg/kg every 2 weeks for a total of 2 doses. If improvement is unsatisfactory, one additional dose may be administered in 2 weeks, with future doses every 3 weeks for a total of 3 doses followed with a final round every 4 weeks with a total of 1-3 doses [46].

d. Anticoagulants

Owing to the microischaemic and prothrombotic state associated with SS, some authors advocate to administer aspirin 81 mg on a daily basis as part of a maintenance medical therapy [2]. Observations of improvement in sensorineural hearing loss with a combination of aspirin and nimodipine have also been reported, likely secondary to an improved microvascular blood supply within the cochlea [5 47]. Other anticoagulants, such as clopidogrel, dipyridamole and fondaparinux, have been tested, although their efficacy in the management of SS has yet to be established [33].

e. Transtympanic dexamethasone

Transtympanic dexamethasone injections can be utilised in patients with SS and concomitant findings of sensorineural hearing loss confirmed via audiometry [24]. Advantages of intratympanic perfusion include a higher concentration of medication delivered locally to the inner ear, ease of administration, the diseased ear is preferentially treated without adversely affecting the contralateral ear, and potential avoidance of systemic side effects [48]. Transtympanic injection of dexamethasone in the acute phase of sensorineural hearing loss in the setting of SS may provide transient benefit with respect to halting progressive hearing loss and justify more aggressive systemic immunotherapy on grounds of potential reversibility.

f. Cochlear implantation

Should conservative medical therapies and transtympanic dexamethasone injections fail to result in notable clinical improvement, cochlear implantation is recommended for SS patients with irreversible otologic disease. Currently, cochlear implantation has been successfully employed in 5 patients who met surgical candidacy within the otolaryngology literature. Postoperatively, there was evidence of functional hearing restoration and notable improvement in communication abilities for all implanted SS patients [21 24 49-51].

Prognosis

Early diagnosis and treatment of SS is hallmark to avoid devastating neurological, visual, and auditory sequelae. Overall, the prognosis can be significantly improved following prompt, aggressive, and sustained therapies, although poor outcomes often result from delayed, suboptimal management with premature, rapid tapering of treatment schedules [18]. Three major clinical courses have been described in SS: monocyclic, polycyclic and chronic continuous. In the monocyclic course, the disease remits spontaneously after 1-2 years without evidence of recurrence. The polycyclic course includes variable periods of remission which may persist for years. SS patients with branch retinal artery occlusion and sensorineural hearing loss are at increased risk for following a prolonged polycyclic course. The chronic continuous course demonstrates variations in severity of symptoms. Remission may occur in this group but there is no clear evidence of complete disease diminution. It remains difficult on initial presentation to identify which patients may regress spontaneously or progress with more fulminant symptomology [52]. In addition, relapses after decades of quiescence have also been described, further muddling long-term outcomes [53 54]. Accordingly, this disease entity requires lifetime monitoring in conjunction with an ophthalmologist, otolaryngologist, neurologist and rheumatologist. Risk factors for relapse include pregnancy, as SS patients will often be tapered off treatment regimens to minimise risk of foetal toxicity [52]. Unlike other features of this condition, sensorineural hearing loss associated with SS is often irreversible and sometimes progressive in nature, despite early and aggressive treatment [19 55]. Surgical interventions, chiefly transtympanic dexamethasone as well as cochlear implantation, are viable options to halt progression of otologic disease and augment serviceable hearing for those who meet surgical candidacy, respectively.

Conclusions

Although modern advances have significantly extended our scope of knowledge regarding SS, this enigmatic disorder remains incompletely understood. As insights into the pathophysiology of SS continue to evolve, research endeavours remain broadly focused within several disciplines, which may provide evidence-based standardised diagnostic and treatment protocols for disease sufferers in the future. The current body of available evidence suggests SS is likely due to a selective endotheliopathy of the systemic microvasculature, which appears to vasculitic in origin. This distinction is critical, as the inner ear is not an immunologically privileged site; cochlear injury typically occurs via a robust response to foreign and self-antigens through both humoral and cell-mediated mechanisms. Thus, not only should SS be routinely considered as part of the differential diagnosis in patients presenting with multi-system disease and hearing loss, but also it should be considered as a unique vasculitic otologic entity-akin, yet pathologically dissimilar to traditional autoimmune otologic disease. Important otologic manifestations of SS include fluctuating sensorineural hearing loss, tinnitus and vertigo. Audiometric evaluation typically reveals an upsloping pattern of sensorineural hearing loss in the low to middle frequencies. Given the observed sensorineural hearing loss is often irreversible and progressive, surgical interventions including transtympanic cexamethasone and cochlear implantation are viable options to halt disease progression and augment serviceable hearing for those who meet device candidacy, respectively. Multicentre prospective studies are needed to expand our experience with SS and plan future consensus-based recommendations. This comprehensive review has been designed to serve as a centralised and up-to-date resource for clinicians and should be updated whenever novel and high-level clinical evidence becomes available.

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Conflict of interest statement

None declared.

References

1 Susac JO, Hardman JM, Selhorst JB. *Microangiopathy of the brain and retina.* Neurology 1979;29:313-6.

2 Kleffner I, Duning T, Lohmann H, et al. *A brief review of Susac syndrome.* J Neurol Sci 2012;322:35-40.

3 García-Carrasco M, Jiménez-Hernández C, Jiménez-Hernández M, et al. *Susac's syndrome: an update.* Autoimmun Rev 2011;10:548-52.

4 Do TH, Fisch C, Evoy F. *Susac syndrome: report of four cases and review of the literature.* AJNR Am J Neuroradiol 2004;25:382-8.

5 Fox RJ, Costello F, Judkins AR, et al. *Treatment of Susac syndrome with gamma globulin and corticosteroids.* J Neurol Sci 2006;251:17-22.

6 O'Halloran HS, Pearson PA, Lee WB, et al. *Microangiopathy of the brain, retina, and cochlea (Susac syndrome). A report of five cases and a review of the literature.* Ophthalmology 1998;105:1038-44.

7 Petty GW, Engel AG, Younge BR, et al. *Retinocochleocerebral vasculopathy.* Medicine (Baltimore) 1998;77:12-40.

8 Francis HW, Makary C, Halpin C, et al. *Temporal bone findings in a case of Susac's syndrome.* Otol Neurotol 2011;32:1198-204.

9 Egan RA, Ha Nguyen T, Gass DM, et al. *Retinal arterial wall plaques in Susac syndrome.* Am J Ophthalmol 2003;135:483-6.

10 Dörr J, Krautwald S, Wildemann B, et al. *Characteristics of Susac syndrome: a review of all reported cases.* Nat Rev Neurol 2013;9:307-16.

11 Greco A, De Virgilio A, Gallo A, et al. *Susac's syndrome pathogenesis, clinical variants and treatment approaches.* Autoimmun Rev 2014;13:814-21.

12 Susac JO. *Susac's syndrome: the triad of microangiopathy of the brain and retina with hearing loss in young women.* Neurology 1994;44:591-3.

13 Aubert-Cohen F, Klein I, Alexandra JF, et al. *Longterm outcome in Susac syndrome.* Medicine 2007;86:93-102.

14 Magro CM. *Susac's syndrome: an autoimmune endotheliopathy.* Paper presented at 1st Susac's Syndrome Symposium. Columbus, OH: Ohio State University; 2005.

15 Rennebohm RM, Susac JO. *Treatment of Susac's syndrome.* J Neurol Sci 2007;257:215-20.

16 Pawate S, Agarwal A, Moses H, et al. *The spectrum of Susac's syndrome.* Neurol Sci 2009;30:59-64.

17 Papo T, Biousse V, Lehoang P, et al. *Susac syndrome.* Medicine 1998;77:3-11.

18 Bitra RK, Eggenberger E. *Review of Susac syndrome.* Curr Opin Ophthalmol 2011;22:472-6.

19 Saw VPJ, Canty PA, Green CM, et al. *Susac syndrome: Microangiopathy of the retina, cochlea and brain.* Clin Exp Ophthalmol 2000;28:373-81.

20 Gass JDM. *Stereoscopic atlas of macular disease: diagnosis and treatment*. 4th ed. St. Louis: Mosby; 1997.

21 Bittencourt AG, Santos AF, Goffi-gomez MV, et al. *Microangiopathy of the inner ear, deafness, and cochlear implantation in a patient with Susac syndrome.* Acta Otolaryngol 2011;131:1123-8.

22 Karelle S, Demanez L, Zangerle PF, et al. *Sudden sensorineural hearing loss: when ophthalmology meets otolaryngology.* B-Ent 2012;8:135-9.

23 Gross M, Banin E, Eliashar R, et al. *Susac syndrome.* Otol Neurotol 2004;25:470-3.

[24] Roeser MM, Driscoll CL, Shallop JK, et al. *Susac syndrome - a report of cochlear implantation and review of otologic manifestations in twenty-three patients.* Otol Neurotol 2009;30:34-40.

[25] Yurtsever B, Çabalar M, Kaya H, et al. *A rare cause of hearing loss: Susac syndrome.* J Int Adv Otol 2015;11:167-9.

[26] Monteiro ML, Swanson RA, Coppeto JR, et al. *A microangiopathic syndrome of encephalopathy, hearing loss and retinal arteriolar occlusions.* Neurology 1985;35:1113-21.

[27] Turner BW, Digre KB, Shelton C. *Susac syndrome.* Otolaryngol Head Neck Surg 1998;118:866-7.

[28] Ishii T, Watanabe I, Suzuki J. *Temporal bone findings in Cogan's syndrome.* Acta Otolaryngol Suppl 1995;519:118-23.

[29] Turc G, Monnet D, Dupin N, et al. *Skin involvement in Susac's syndrome.* J Neurol Sci 2011;305:152-5.

[30] Dorr J, Jarius S, Wildemann B, et al. *Susac syndrome: an interdisciplinary challenge.* Nervenarzt 2011;82:1250-63.

[31] Vishnevskia-dai V, Chapman J, Sheinfeld R, et al. *Susac syndrome: clinical characteristics, clinical classification, and long-term prognosis.* Medicine (Baltimore) 2016;95:e5223.

[32] Magliulo G, Al-Ansi W, Parrotto D, et al. *Susac syndrome and vestibular-evoked myogenic potentials.* Otolaryngol Head Neck Surg 2008;138:542-3.

[33] Jarius S, Neumayer B, Wandinger KP, et al. *Anti-endothelial serum antibodies in a patient with Susac's syndrome.* J Neurol Sci 2009;285:259-61.

[34] Rennebohm R, Susac JO, Egan RA, et al. *Susac's syndrome - update.* J Neurol Sci 2010;299:86-91.

[35] Magro CM, Poe JC, Lubow M, et al. *Susac syndrome: an organ-specific autoimmune endotheliopathy syndrome associated with anti-endothelial cell antibodies.* Am J Clin Pathol 2011;136:903-12.

[36] Westreich R, Chandrasekhar S. *Is Susac syndrome (microangiopathy of the inner ear, retina, and central nervous system) an underdiagnosed cause of sensorineural hearing loss?* Ear Nose Throat J 2008;87:E4-7.

[37] Rennebohm RM, Lubow M, Rusin J, et al. *Aggressive immunosuppressive treatment of Susac's syndrome in an adolescent: using treatment of dermatomyositis as a model.* Pediatr Rheumatol Online J 2008;6:3.

[38] Mateen FJ, Zubkov AY, Muralidharan R, et al. *Susac syndrome: clinical characteristics and treatment in 29 new cases.* Eur J Neurol 2012;19:800-11.

[39] Raets I, Gelin G. *Susac's syndrome: a clinical and radiological challenge.* JBR-BTR 2012;95:355-6.

[40] Allmendinger AM, Spektor V, Destian S. *CT and MR imaging of Susac syndrome in a young male presenting with acute disorientation.* Clin Imaging 2010;34:138-42.

[41] Saenz R, Quan AW, Magalhaes A, et al. *MRI of Susac's syndrome.* AJR 2005;184:1688-90.

[42] Deppe M, Duning T, Mohammadi S, et al. *Diffusion-tensor imaging at 3 T: detection of white matter alterations in neurological patients on the basis of normal values.* Invest Radiol 2007;42:338-45.

[43] Kleffner I, Deppe M, Mohammadi S, et al. *Neuroimaging in Susac's syndrome: focus on DTI.* J Neurol Sci 2010;29:92-6.

[44] Kleffner I, Deppe M, Mohammadi S, et al. *Diffusion tensor imaging demonstrates fiber impairment in Susac syndrome.* Neurology 2008;70:1867-9.

[45] Rennebohm RM, Susac JO. *Treatment of Susac's syndrome.* Curr Treat Options Neurol 2008;10:67-74.

[46] Rennebohm RM, Asdaghi N, Srivastava S, et al. *Guidelines for treatment of Susac syndrome - an update.* Int J Stroke 2018; 1747493017751737.

[47] Manor RS, Ouaknine L, Ouaknine G. *Susac-RED-M syndrome [abstract].* Neuroophthalmology 1994;14 (Suppl. 1):113.

[48] Jackson LE, Silverstein H. *Chemical perfusion of the inner ear.* Otolaryngol Clin North Am 2002;35:639-53.

[49] Lavinsky L, Scarton F, Lavinsky-Wolff M, et al. *Successful cochlear implantation in a Susac syndrome patient.* Braz J Otorhinolaryngol 2012;78:123.

[50] Connell SS, Brodie HA. *Role of cochlear implantation in Susac's syndrome.* Otolaryngol Head Neck Surg 2004;131:P280.

[51] Grover N, Whiteside OJ, Ramsden JD. *Susac syndrome: outcome of unilateral cochlear implantation.* J Laryngol Otol 2011;125:856-8.

[52] Deane KD, Tyler KN, Johnson DW, et al. *Susac syndrome and pregnancy: disease management.* J Clin Rheumatol 2011;17:83-8.

[53] Petty GW, Matteson EL, Younge BR, et al. *Recurrence of Susac syndrome (retinocochleocerebral vasculopathy) after remission of 18 years.* Mayo Clin Proc 2001;76:958-60.

[54] Feresiadou A, Eriksson U, Larsen HC, et al. *Recurrence of Susac syndrome following 23 years of remission.* Case Rep Neurol 2014;6:171-5.

[55] Bateman ND, Johnson IJ, Gibbin KP. *Susac's syndrome: a rare cause of fluctuating sensorineural hearing loss.* J Laryngol Otol 1997;111:1072-4.

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Otology

Surgical outcomes of tympanoplasty using a sterile acellular dermal allograft: a prospective randomised controlled study

Outcome chirurgici nella timpanoplastica con graft dermico acellulare: studio prospettico randomizzato controllato

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SUMMARY

Acellular human dermal allografts have been shown to be effective for soft-tissue implantation. We compared treatment outcomes of tympanoplasty using tragal perichondrium and acellular human dermal allograft (MegaDerm®). In a prospective randomised controlled study, 60 patients scheduled to undergo tympanoplasty were randomly assigned to the autologous tragal perichondrium group (n = 33) or acellular human dermal allograft group (n = 27). Postoperative hearing gain, graft success rate at 1 and 6 months and operation times were compared between groups. Graft success rate, defined as the complete closure of tympanic membrane perforation, did not show any significant intergroup difference (75.8% vs 85.2%, p = 0.519). Air conduction thresholds and air-bone gaps showed significant improvements in both groups; from 38.7 ± 15.9 dB to 30.2 ± 15.6 dB (p < 0.001) and from 17.8 ± 7.3 dB to 11.5 ± 7.0 (p = 0.001) in the autologous tragal perichondrium group, and from 30.4 ± 12.2 dB to 24.5 ± 13.0 dB (p = 0.006) and from 14.3 ± 5.1 dB to 7.6 ± 4.6 dB (p < 0.001) in the acellular human dermal allograft group. The amount of hearing gain (p = 0.31) and closure of air-bone gap (p = 0.863) were not meaningfully different between groups. The mean operation time was significantly lower in the acellular human dermal allograft group (35.2 min vs 27.4 min, p = 0.039). In this prospective randomised controlled study, acellular human dermal allograft was shown to be an effective alternative to tragal perichondrium, with similar graft success rates and postoperative hearing results, but with reduced operation times.

KEY WORDS: Tympanoplasty •Allograft •Acellular dermal matrix • Tympanic membrane perforation

RIASSUNTO

Gli innesti eterologhi di materiale dermico acellulare hanno dimostrato la loro efficacia nei trapianti di tessuti molli. Nel presente studio sono stati paragonati i risultati derivati dall'utilizzo di pericondrio tragale e da innesto eterologo di materiale dermico acellulare (MegaDerm®) negli interventi di timpanoplastica. In modo prospettico randomizzato, 60 pazienti in nota per intervento di timpanoplastica sono stati assegnati casualmente ad un gruppo sottoposto ad intervento che prevedeva ricostruzione con cartilagine tragale (n = 33) o con innesto eterologo di materiale dermico acellulare (n = 27). Tra i due gruppi sono stati paragonati il guadagno uditivo postoperatorio, il tasso di successo della chirurgia ad 1 e 6 mesi e il tempo operatorio. Il tasso di successo della chirurgia, definito dalla completa chiusura della perforazione della membrana timpanica non ha mostrato alcuna differenza significativa tra i gruppi (75,8% vs 85,2%, p = 0,519). La soglia di conduzione per via aerea e il gap tra via aerea e via ossea hanno mostrato invece un significativo miglioramento in entrambi i gruppi considerati, da 38,7 ± 15,9 dB a 30,2 ± 15,6 dB (p < 0,001) e da 17,8 ± 7,3 dB a 11,5 ± 7,0 (p = 0,001) nel gruppo di pericondrio tragale autologo; da 30,4 ± 12,2 dB a 24,5 ± 13,0 dB (p = 0,006) e da 14,3 ± 5,1 dB a 7,6 ± 4,6 dB (p < 0,001) nel gruppo di innesto eterologo di materiale dermico acellulare. La differenza di guadagno uditivo (p = 0,31) e la chiusura del gap tra via aerea e via ossea (p = 0,863) non sono però risultati significativi tra i gruppi. Il tempo operatorio medio è risultato significativamente minore nel gruppo sottoposto ad innesto eterologo (35,2 min vs 27,4 min, p = 0,039). In questo studio prospettico randomizzato controllato, l'innesto eterologo di derma acellulare si è dimostrato come efficace alternativa all'utilizzo di pericondrio tragale, con tasso di successo chirurgico e risultati uditivi simili e minor tempo operatorio.

PAROLE CHIAVE: *Timpanoplastica • Innesto eterologo • Matrice acellulare • Perforazione timpanica*

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Introduction

Perforation of the tympanic membrane (TM) is a common disorder encountered by otologists. It is caused by trauma, chronic otitis media, or as a complication of otologic surgeries, and presents with conductive hearing loss. The goals of tympanoplasty are to obtain an intact TM, eradicate pathological tissues in the middle ear and mastoid and reconstruct the sound transmission mechanism.

Since first described by Berthold in 1878, various materials have been used for TM grafting [1]. Mostly, tissue located near the operative field is harvested for grafting, and temporalis fascia and tragal perichondrium are the most commonly used grafting materials [2]. These materials may be used solely or compositely such as perichondrium-cartilage island graft [3]. In addition, various allografts, xenografts and alloplasts have been used in tympanoplasty [4]. Among the various materials, human acellular dermal matrix has been used for TM grafting since late 20th century with promising results. However, there has been few prospective randomised trials to provide objective evidence justifying the use of this material. MegaDerm® (L&C BIO, Seongnam-si, Korea) is one such human acellular dermal allograft derived from donated human skin that is supplied by US tissue banks under the guidelines of the American Association of Tissue Banks and US Food and Drug Administration. It consists of an intact basement membrane matrix processed directly from cadaveric skin, and allows for revascularisation by the recipient's native fibroblasts and endothelial cells [5]. Previous human acellular dermal allografts (e.g., AlloDerm, LifeCell Corp., Branchbug, MJ, USA) are offered as an aseptic material; they are processed using methods to prevent, restrict, or minimise contamination with microorganisms. MegaDerm® is a sterile and non-immunogenic acellular dermal allograft. While processing the material, the cellular components of the epidermis and dermis are removed to allow the graft to be tolerated in the host without inciting an immune response [6]. While sterility cannot be assured in an aseptic condition, MegaDerm® is produced using electron-beam sterilisation to eliminate viruses, bacteria and spores, achieving a 10^{-6} sterility level. Thus, theoretically, the use of a sterile allograft may also reduce the risk of infection.

MegaDerm® has been shown to be effective in breast reconstruction [7], and numerous clinical applications including rhinoplasty, penile augmentation, rotator cuff repair and preventing skin retraction after thyroidectomy and parotidectomy are under investigation. The use of MegaDerm® as a TM graft provides several benefits over native tissue. It can eliminate donor site morbidity, provide enough amount for grafting at any time and preserve native tissue for later use. In revision cases, in which the native tissue has already been consumed, it can be a good alternative available in infinite quantity. Moreover, since the procedures for harvesting and preparing graft tissue are unnecessary, operation times can also be reduced.

Herein, we compared a group of similar, consecutive patients undergoing type I tympanoplasty using MegaDerm® and native tissue (tragal perichondrium) in a prospective randomised controlled study. We compared outcomes of successful closure of TM perforation, audiologic outcomes and operation times for the different graft materials.

Materials and methods

Patients

Sixty patients who underwent type I tympanoplasty for TM perforation between March 2015 and March 2016 were included in the study. They were between 14 and 79 years of age (mean age = 53.3 years); 17 (28.3%) were men and 43 (71.7%) were women. Patients who underwent other procedures (e.g., ossiculoplasty or mastoidectomy) simultaneously were excluded. None had a history of previous ear surgery, and their ear canal and middle ear were completely dried up without otorrhoea. Preoperative records showed that all of the perforations failed to close spontaneously over a 6-month period. They were randomly assigned to the native-tissue group (tympanoplasty using tragal perichondrium) or the MegaDerm® group (tympanoplasty using MegaDerm®). A third person assigned patients to each group by using a random number table, and informed the surgeon which materials were to be used on the same day of surgery. TM perforation was assessed using a 0°, 3 mm diameter straight telescope (Karl Storz GmbH & Co. KG, Tuttlingen, Germany) and a high-definition liquid crystal display monitor (Olympus, Tokyo, Japan). The perforations were grouped according to Saliba's subdivision [8] as follows: small, less than 25% and less than 1 quadrant size of the total TM; medium, more than 25% and less than 50%, and more than 1 quadrant and less than 2 quadrant size; large, more than 50% but not total, and more than 2 quadrant size but not total; and total, 100% and 4 quadrant size. Patient information is listed in Table I. All procedures were in accordance with the Declaration of Helsinki of 1964. The study was approved by the Institutional Review Board of the Severance Hospital in Seoul, Korea (approval number: 4-2014-1072) and informed consent was obtained from all enrolled patients before surgery.

Table I. Demographic and clinical characteristics of the study groups.

Variables	Native Tissue Group (n = 33)	MegaDerm Group (n = 27)	P value
Age (yr)	53.7 ±15.2	52.8 ±13.5	0.808
Sex, n (%)			0.031
Male	13 (39.4%)	4 (14.8%)	
Female	20 (60.6%)	23 (85.2%)	
Site of graft, n (%)			0.244
Right	16 (48.5%)	9 (33.3%)	
Left	17 (51.5%)	18 (66.7%)	
Perforation Size, n (%)			0.295
Small	16 (48.5%)	13 (48.1%)	
Medium	16 (48.5%)	9 (33.3%)	
Large	1 (3.0%)	4 (14.8%)	
Total	0 (0)	1 (3.8%)	
Hearing level (dB HL)			
Air conduction	41.6 ±18.2	36.4 ±17.1	0.266
Bone conduction	23.4 ±17.0	20.9 ±14.9	0.548
Air-bone gap	18.1 ± 6.8	15.5 ± 5.3	0.106

Surgical procedure

All patients underwent type I tympanoplasty via the transcanal approach under local anaesthesia. An ear speculum was inserted into the external auditory canal to visualise the perforation. The margins of the perforation were trimmed by using a sharp pick. Then, the tympanomeatal flap was elevated, and the graft material was placed via an underlay technique. After grafting, the external auditory canal was packed with antibiotic-coated gelfoam and sealed using an aseptic cotton ball and plaster. Patients were prescribed broad-spectrum oral antibiotics for 1 week. All patients were discharged the same day.

In the native-tissue group, the tragal perichondrium was harvested as the graft. An additional skin incision was made over the tragus, and the perichondrium was harvested. Thereafter, the incision site was sutured with 4-0 nylon. In the MegaDerm® group, a 1.5 × 2 cm graft (thickness = 0.3-0.5 mm) was used.

Assessment of treatment outcomes

Packing materials were completely removed at 2 weeks postoperatively, and the TM was assessed at 1 and 6 months using the same device described above. Graft success was defined as closure of the TM perforation.

All patients underwent pure-tone audiography before, and at 1 and 6 months after surgery. Pure-tone air conduction (AC, 250-8,000 Hz) and bone conduction (BC, 250-4,000 Hz) thresholds were measured using clinical audiometers in a double-walled audio booth. The average hearing threshold and air-bone gap (ABG) was defined as the mean value of the measurements taken at frequencies 500 Hz, 1 kHz, 2 kHz, and 3 kHz. Postoperative hearing gain and closure of ABG were calculated by subtracting the mean preoperative AC thresholds from the mean postoperative AC thresholds, and by subtracting the postoperative ABG from the preoperative ABG in both groups, respectively. Any complications that developed during the follow-up period were analysed.

Operation time

Operation time, defined as the interval between the time of ear speculum insertion into the ear canal and time of postoperative dressing application, was analysed.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). The results of multiple experiments are presented as the mean ±standard deviation. Comparisons between continuous variables in two groups were performed using a Student's t-test or the paired t-test for evaluating differences between two groups if the normality test was passed. Otherwise, the Mann-Whitney test or Wilcoxon signed rank test were applied. Comparisons between nominal variables in two groups were performed using Fisher's exact test. A p value of 0.05 was considered as the threshold for significance.

Results

Among 60 patients, 27 (45.0 %) received MegaDerm®. Preoperative hearing level and ABGs for the two groups were not significantly different ($p > 0.05$, Table I). Age, perforation size and site of graft were not significantly different between the groups ($p > 0.05$, Table I), but the number of female patients was higher in the MegaDerm® group ($p = 0.031$, Table I).

Success in closing TM perforations

At 1 month postoperatively, 53 perforations were closed. However, six perforations in the native-tissue group (18.2%) and two in the MegaDerm® group (7.4%) remained. The success rates for the two groups at 1 month were not significantly different ($p = 0.276$).

Among six perforations in the native-tissue group, two spontaneously closed at 6 months postoperatively. Three perforations remained at 6 months; but since their sizes were small and the patients were free from any ear symptoms; revision surgeries were not necessarily performed (Fig. 1A). One patient with remnant perforation needed revision surgery. It was a small-sized perforation located on the anteroinferior quadrant of the TM preoperatively

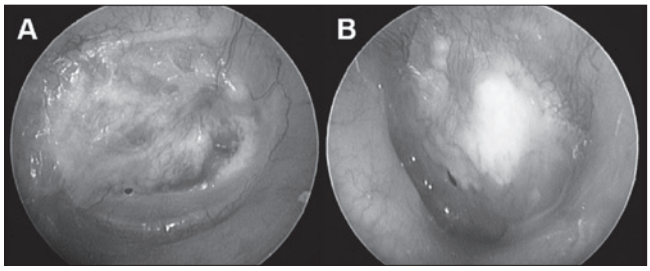

Fig. 1. Representative postoperative tympanic membrane (TM) findings. pin-point perforation developed at 1 month postoperatively and was observed without treatment in the native-tissue group (**A**) and MegaDerm® group (**B**).

(Fig. 2A), and a new perforation developed in the posterior margin of the TM after tympanoplasty (Fig. 2B). Four perforations newly developed at 6 months postoperatively. Three of these were followed up without revision surgery for the same reasons as above; however, one perforation needed revision surgery. It was initially a medium-sized perforation (Fig. 2C) and was completely closed at 1 month postoperatively. At 6 months, an otoscopic examination revealed a small-sized perforation with granulation tissue and otorrhoea growing in the middle ear space (Fig. 2D). Consequently, the graft success rate for the native-tissue group at 6 months was 75.8% (25/33), with two revision surgeries and six small pin-point perforations.

In the MegaDerm® group, two perforations were observed at 1 month postoperatively, and one needed revision surgery. One was a large-sized perforation preoperatively (Fig. 2E), and had minimally decreased in size at 1 month postoperatively (Fig. 2F); therefore, revision surgery was performed. The other perforation was observed without additional treatment (Fig. 1B). Two perforations newly developed at 6 months postoperatively, and their sizes were so small that they were not treated. Therefore, the graft success rate for the MegaDerm® group at 6 months was 85.2% (23/27), with one revision surgery and three small pin-point perforations.

Consequently, 25 perforations from the native-tissue group and 23 perforations from the MegaDerm® group were successfully incorporated into the host TM without perforation (Fig. 3). The success rates for the two groups at 6 months were not significantly different ($p = 0.519$).

We next determined if the graft success rate was dependent on the size and location of the perforation. Among the eight perforations in the native tissue group in which perforations failed to close, four were small-sized, and four were medium-sized. Among the four perforations in the MegaDerm® group, two were small-sized, one was medium-sized and

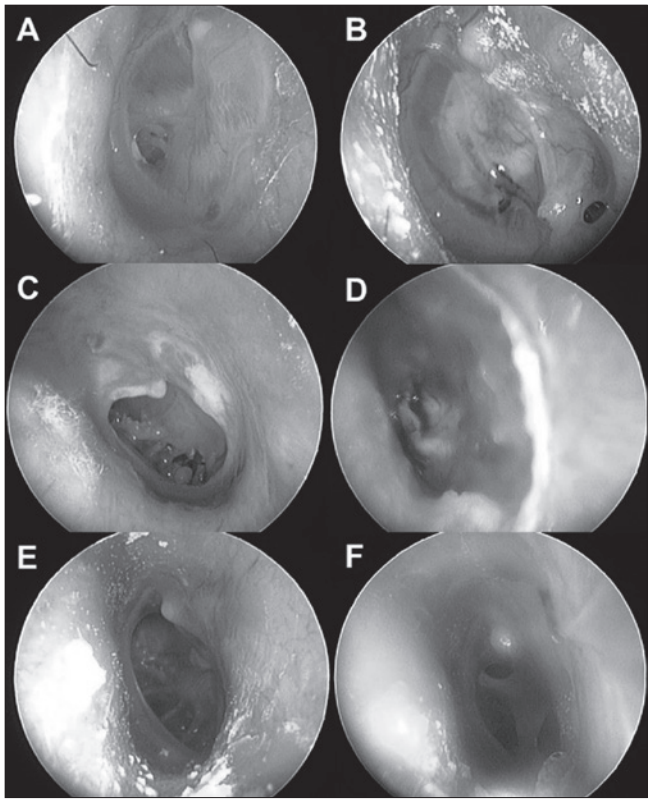

Fig. 2. Tympanic membrane (TM) photographs in patients who underwent revision surgeries. Two patients from the native-tissue group (**A-D**) and one from the MegaDerm® group (**F** and **G**) underwent revision surgeries (**A, C** and **E** represent preoperative TM findings; **B** and **F** represent TM findings at 1 month postoperatively; **D** represents TM findings at 6 months postoperatively).

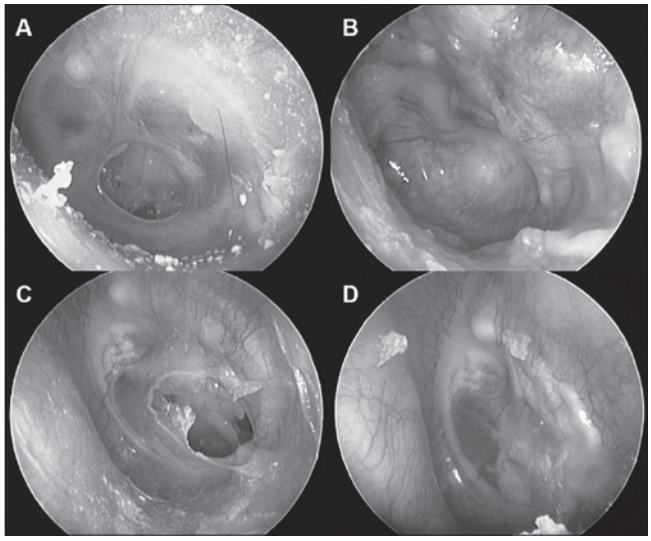

Fig. 3. Otoscopic views of the TM before and at 6 months postoperatively with complete TM closure. Approximately 75.8% of perforations in the native-tissue group (**A, B**), and 85.2% in the MegaDerm® group (**C, D**) showed successful closure, and the success rate was not significantly different between the two groups ($p = 0.519$).

Table II. Perforation size and location.

Variables	Native Tissue Group (n = 33)	MegaDerm Group (n = 27)
Small	16 (48.5%)	13 (48.1%)
• Anterosuperior	4	0
• Anteroinferior	11	11
• Posterosuperior	0	0
• Posterioinferior	0	1
• Central	1	1
Medium	16 (48.5%)	9 (33.3%)
• Anterior	7	4
• Posterior	0	1
• Inferior	6	4
• Central	3	0
Large	1 (3.0%)	4 (14.8%)
Total	0 (0)	1 (3.8%)

The proportion of perforation sites in the small-sized and medium-sized perforations did not differ significantly between groups (p = 0.215 and p = 0.528, respectively). Graft success rates did not differ based on perforation size (small vs medium, p = 0.303) or location (anterior vs posterior, p = 0.503).

one was large-sized. In the native tissue group, two of the small-sized perforations were located anterosuperior and two were anteroinferior. In the native tissue group, one of the medium-sized perforations was located centrally, one was anterior and two were inferior. Two small-sized perforations of MegaDerm® group were located at anteroinferior quadrant of the drums, and a medium-sized perforation of MegaDerm® group was located at inferior region. Proportion of size and location of the perforations did not significantly differ between groups (Table II).

The size and location of the perforation and graft success rates were analysed. Perforations were initially classified into four groups, anterior small (n = 26), posterior small (n = 1), anterior medium (n = 11) and posterior medium (n = 1); the others, such as central or inferior perforations, were excluded due to the small number of cases. Of these, six anterior small-sized perforations and one anterior medium-sized perforation failed to close. However, no statistically significant differences were found between groups (p = 0.694) in the size of the perforations (p = 0.303) or the location of the perforations (p = 0.503). The overall graft success rate was also not significantly different between the two groups (p = 0.519). There was no difference in the successful closure of TM perforation based on size, location, or graft materials (Table II).

Hearing results

At 1 month postoperatively, the AC threshold improved from 41.6 ± 18.2 dB to 35.2 ± 20.1 dB (p < 0.001), and the BC threshold stabilised from 23.4 ± 17.0 dB to 22.2 ± 17.6 dB (p = 0.057) in the native-tissue group. Similar results were observed in the MegaDerm® group. The AC threshold improved from 36.4 ± 17.1 dB to 31.3 ± 8.6 dB (p < 0.001), and the BC threshold stabilised from 20.9 ± 14.9 dB to 19.7 ± 17.1 dB (p = 0.240). Hearing gain between the two groups was not significantly different (p = 0.455, Fig. 4A, 4B). ABG was significantly reduced in both groups, from 18.1 ± 6.8 dB to 13.1 ± 6.4 dB (p < 0.001) in the native-tissue group and from 15.5 ± 5.3 dB to 11.7 ± 5.7 dB (p = 0.002) in the MegaDerm® group. Therefore, ABG was reduced by 5.1 ± 7.0 dB in the native-tissue group and by 3.8 ± 5.7 dB in the MegaDerm® group, which was not significantly different (p = 0.455, Fig. 5A).

Serial pure-tone audiograms were acquired in 34 patients (17 from each group) at 6 months postoperatively. The other 26 patients referred no discomfort in subjective hearing and refused to undergo hearing tests. The AC threshold improved from 38.7 ± 15.9 dB to 30.2 ± 15.6 dB (p < 0.001) in the native-tissue group, and from 30.4 ± 12.2 dB to 24.5 ± 13.0 dB (p = 0.006) in the MegaDerm® group. The BC threshold stabilised from 20. 9 ± 15.4 dB to 18.8 ± 15.5 dB (p = 0.096) and from 16.0 ± 10.0 dB to 16.8 ± 11.1 dB (p = 0.522) in the native-tissue and MegaDerm® groups, respectively. Hearing gain was not different between the groups (p =0.31, Fig. 4C, 4D). Both groups showed significantly reduced ABGs at 6 months postoperatively: 17.8 ± 7.3 dB to 11.5 ± 7.0 (p = 0.001) in the native-tissue group and 14.3 ± 5.1 dB to 7.6 ± 4.6 dB (p < 0.001) in the MegaDerm® group. The amount of reduction in ABGs was similar between the groups (p = 0.863, Fig. 5B).

Complications

Except for the re-perforation or incomplete TM closure described above, few complications were observed.

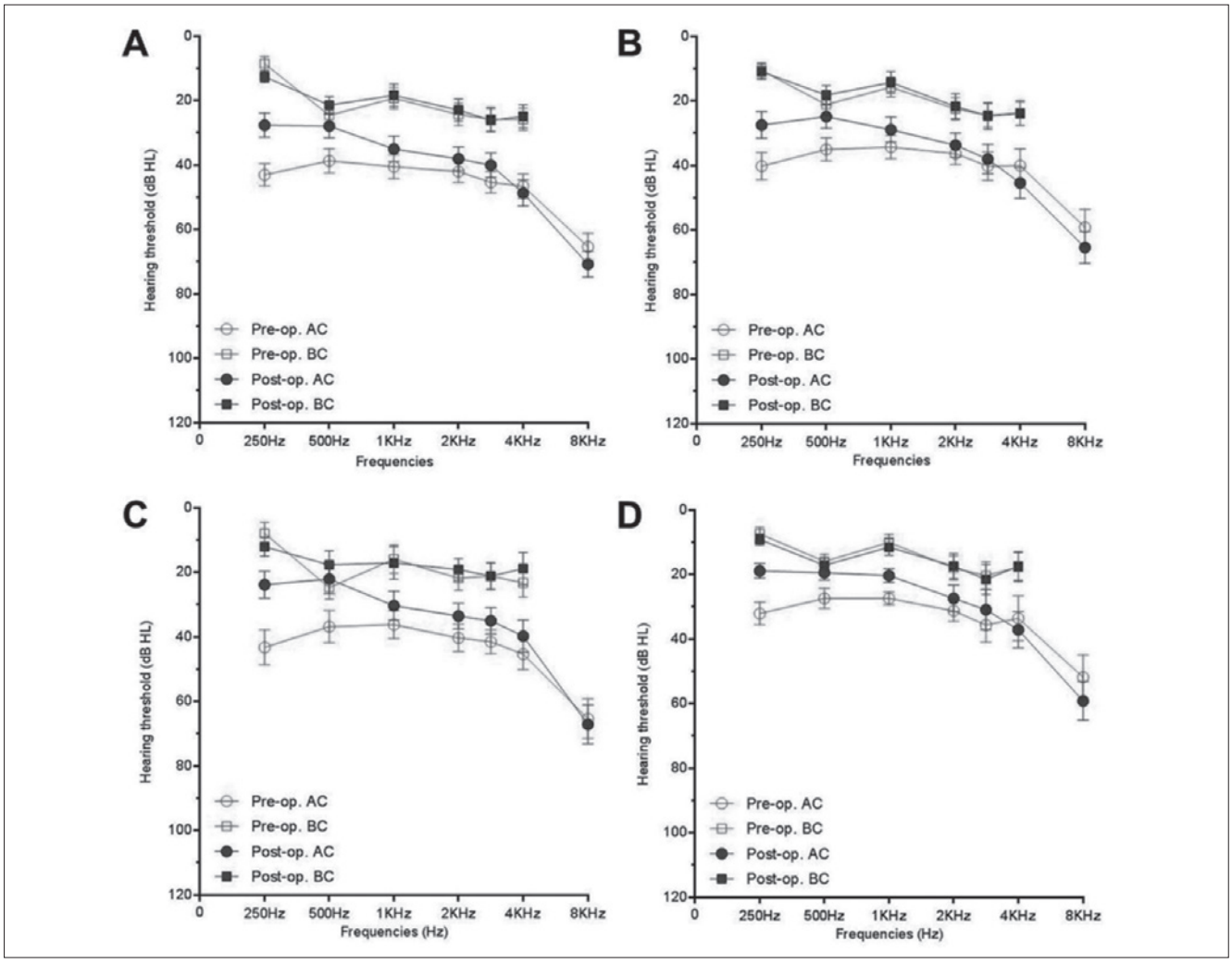

Fig. 4. Preoperative and postoperative hearing results of the native-tissue group and MegaDerm® group measured at 1 (**A**, native-tissue group, n = 33; **B**, MegaDerm® group, n = 27) and 6 months (**C**, native-tissue group, n = 17; **D**, MegaDerm® group, n = 17) postoperatively. The air-conduction thresholds significantly improved in both groups, whereas the bone-conduction thresholds remained stable. The preoperative and postoperative air- and bone-conduction thresholds were not significantly different between the two groups ($p = 0.266$ and $p = 0.445$ for preoperative and postoperative air-conduction thresholds at 1 month postoperatively; $p = 0.548$ and $p = 0.584$ for preoperative and postoperative bone-conduction thresholds at 1 month postoperatively; $p = 0.096$ and $p = 0.252$ for preoperative and postoperative air-conduction thresholds at 6 months postoperatively; $p = 0.284$ and $p = 0.682$ for preoperative and postoperative bone-conduction thresholds at 6 months postoperatively).

Myringitis was reported in one patient in each group. They were treated with otic solution and oral medication, and the myringitis resolved without re-perforation. However, another patient from the native-tissue group had middle ear infection with re-perforation, requiring revision surgery (Fig. 2B). One patient from the native-tissue group experienced donor-site perichondritis, which resolved without complications after oral medication.

Operation time

The mean operation time was 35.2 ± 15.6 min in the native-tissue group and 27.4 ± 13.2 min in the MegaDerm® group. The operation times were significantly lower in the MegaDerm® group ($p = 0.039$).

Discussion

There are several advantages to performing tympanoplasty using a human acellular dermal allograft. First, the operation time can be significantly reduced. In our study, the use of MegaDerm® helped save on average 7.8 min over the use of tragal perichondrium. The longer operation time for autologous tissue grafting was because of the harvesting and handling of the graft material. Since

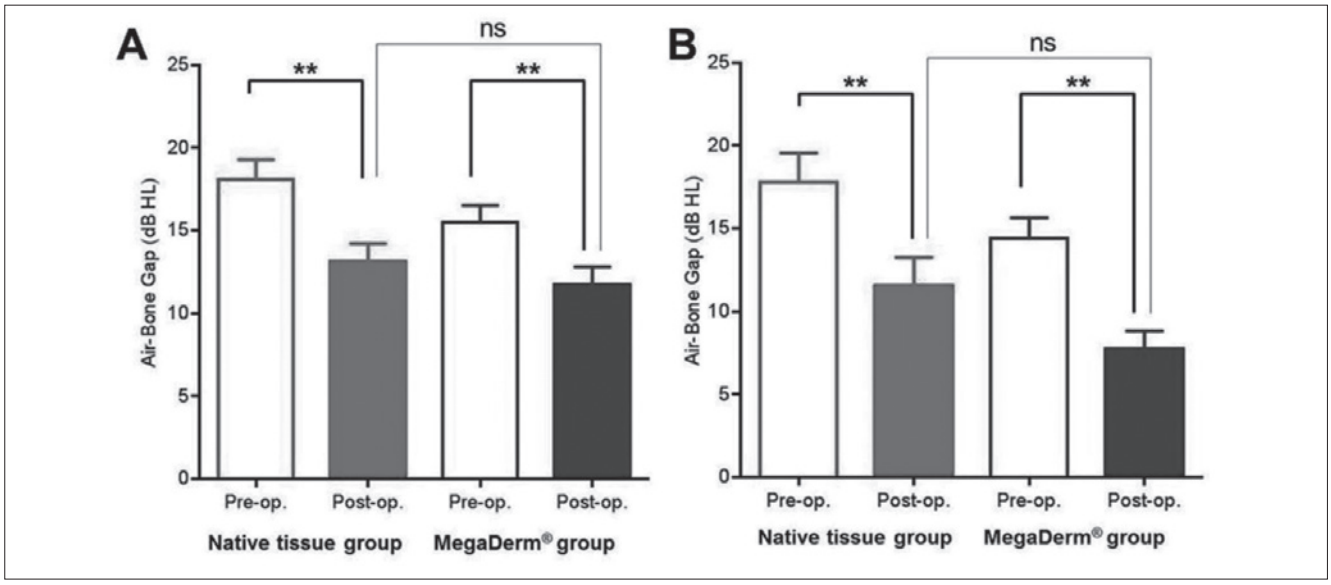

Fig. 5. Changes in air-bone gaps (ABGs) after tympanoplasty (**A**, at 1 month postoperatively; **B**, at 6 months postoperatively). Significant reductions in ABGs were observed in both groups, and the amount of reduction of ABGs and postoperative ABGs were not significantly different between the two groups (p = 0.455 at 1 month postoperatively; p = 0.863 at 6 months postoperatively).

MegaDerm® is prepared in a dried condition, surgeons do not need to wait for the material to dry as preferred, and can easily trim the material into the proper size and shape. MegaDerm® is as thick as 0.3-0.5 mm, which is generally thicker than native tissues, though still pliable, and the thickness and elasticity provide stability while handling the material.

Second, an additional incision for harvesting the graft material is unnecessary when using MegaDerm®, thus reducing donor-site morbidity. In cases in which tympanoplasty is performed via the transcanal approach, an additional incision is mandatory for harvesting the graft material unlike tympanoplasty via the retroauricular approach in which the temporalis fascia can be harvested via the same surgical site. This can reduce the probability of donor-site infection or deformity induced by injury to tragal cartilage. Reported donor-site infection is rare, but cannot be excluded [9].

Third, the limitless supply of MegaDerm® is another advantage. In cases of revision surgery, finding enough suitable fascia or perichondrium is sometimes difficult, especially if the patient has undergone multiple surgeries. Finding autogenous tissues for grafting can be another time-consuming procedure and may increase donor-site morbidity. The authors also use MegaDerm® in canal-wall-down mastoidectomy with tympanoplasty and revision surgery, and the limitless supply of graft material could contribute to stable healing.

MegaDerm® further offers an immunogenic benefit. The safety of acellular dermal matrix allografts has been well demonstrated in both animal [10 11] and clinical studies [12]. Moreover, MegaDerm® is a sterile allograft produced by removing the antigenic target of cell-mediated rejection. A previous study comparing the rate of postoperative infection between sterile allograft and aseptic allograft in breast reconstruction showed the superiority of the immunologic aspects of MegaDerm® [13]. Although a direct comparison of these two materials in tympanoplasty has not yet been performed or reported, it can be stated that at least there is no harm in utilising MegaDerm® over native tissue or conventional allografts in view of its immunogenic superiority.

In addition to the many advantages described above, MegaDerm® provides comparable functional benefits. Graft success rate varies according to materials and study designs. Success rates reported in retrospective studies were mostly higher than those reported in prospective studies, regardless of the graft material used. In 2008, Gamra et al. reported a success rate of 97.7% for cartilage from 90 tympanoplasties, and a success rate of 96.9% for temporalis fascia from 290 tympanoplasties [14]. Solmaz et al. performed 194 tympanoplasties with perichondrium-cartilage island graft, and the success rate was 91.24% [3]. A few other retrospective studies have reported similar outcomes. However, there are only two prospective studies reporting success rates for cartilage and temporalis fascia. Yung et al. reported 84.2% and 80.0% success rates and Mauri

et al. reported 86.1% and 88.2% success rates for temporalis fascia and cartilage [15 16]. The reported success rates are quite comparable to those of MegaDerm® in this study. The success rate for allografts was similar to those for autologous materials. One study that performed tympanoplasty using allografts showed an 88% success rate [17], and another reported a 78% success rate for TM closure [18]. With respect to hearing results, a prospective study with a large population of 553 patients reported 12 month follow-up data; both AC and ABG improved from 32.1 dB to 29.7 dB and from 21.2 dB to 19.1 dB at 1 year postoperatively, respectively, [19] and the improvement was comparable to that seen in our study.

Since the first commercial use of allograft in tympanoplasty in 1999, the advantages of this procedure have been widely reported [20]. Numerous studies have provided evidence for its safety and efficacy, including animal studies [21 22] and retrospective studies that compared and analysed methods and results [2 17 23]. To our knowledge, the present study is the first and only prospective randomised controlled study in human patients demonstrating the advantages of the procedure. Therefore, the present study provides stronger support for the safety and efficacy of using allograft in tympanoplasty.

Nevertheless, our study has some limitations. The function of the Eustachian tube highly affects the outcome of tympanoplasty in both disease recurrence and hearing improvement [24 25]. Age, site of graft, perforation size and hearing level were matched in both groups, but the function of the Eustachian tube was neither assessed nor compared. Although there is no available definite method that reflects the function of the Eustachian tube, information on preoperative Eustachian tube function could provide better comparison between groups and with previous reports. Second, a 6 month follow-up period is likely to be sufficient to compare the efficacy of the materials; however, for better comparison, longer-term follow-up with more subjects is needed.

Conclusions

Compared to autologous graft materials, MegaDerm® is an effective alternative as a TM graft material with similar graft success rates and postoperative hearing results, but with reduced operation times.

Conflict of interest statement

None declared.

References

1 Glasscock ME, Kanok MM. *Tympanoplasty: a chronological history.* Otolaryngol Clin North Am 1977;10:469-77.

2 Benecke JE, Jr. *Tympanic membrane grafting with alloderm.* Laryngoscope 2001;111:1525-7.

3 Solmaz F, Akduman D, Haksever M, et al. *The audiological and take results of perichondrium attached cartilage island graft in tympanoplasty: PACIT.* Acta Otorhinolaryngol Ital 2016;36:275-81.

4 Boedts D. *Tympanic grafting materials.* Acta Otorhinolaryngol Belg 1995;49:193-9.

5 Wainwright DJ. *Use of an acellular allograft dermal matrix (AlloDerm) in the management of full-thickness burns.* Burns 1995;21:243-8.

6 Livesey SA, Herndon DN, Hollyoak MA, et al. *Transplanted acellular allograft dermal matrix. Potential as a template for the reconstruction of viable dermis.* Transplantation 1995;60:1-9.

7 Lee JH, Park Y, Choi KW, et al. *The effect of sterile acellular dermal matrix use on complication rates in implant-based immediate breast reconstructions.* Arch Plast Surg 2016;43:523-8.

8 Saliba I. *Hyaluronic acid fat graft myringoplasty: how we do it.* Clin Otolaryngol 2008;33:610-4.

9 Tseng CC, Shiao AS. *Postoperative auricular perichondritis after an endaural approach tympanoplasty.* J Chin Med Assoc 2006;69:423-7.

10 Xu H, Wan H, Sandor M, et al. *Host response to human acellular dermal matrix transplantation in a primate model of abdominal wall repair.* Tissue Eng Part A 2008;14:2009-19.

11 Lucke S, Hoene A, Walschus U, et al. *Acute and chronic local inflammatory reaction after implantation of different extracellular porcine dermis collagen matrices in rats.* Biomed Res Int 2015;2015:938059.

12 Jiang DY, Chen B. *Clinical study on the immunoregulation effects of cytokines on the acellular xenogenic dermal matrix.* Zhonghua Shao Shang Za Zhi 2003;19:351-4.

13 Weichman KE, Wilson SC, Saadeh PB, et al. *Sterile "ready-to-use" AlloDerm decreases postoperative infectious complications in patients undergoing immediate implant-based breast reconstruction with acellular dermal matrix.* Plast Reconstr Surg 2013;132:725-36.

14 Gamra OB, Mbarek C, Khammassi K, et al. *Cartilage graft in type I tympanoplasty: audiological and otological outcome.* Eur Arch Otorhinolaryngol 2008;265:739-42.

15 Yung M, Vivekanandan S, Smith P. *Randomized study comparing fascia and cartilage grafts in myringoplasty.* Ann Otol Rhinol Laryngol 2011;120:535-41.

16 Mauri M, Lubianca Neto JF, Fuchs SC. *Evaluation of inlay butterfly cartilage tympanoplasty: a randomized clinical trial.* Laryngoscope 2001;111:1479-85.

17 Lai P, Propst EJ, Papsin BC. *Lateral graft type 1 tympanoplasty using AlloDerm for tympanic membrane reconstruction in children.* Int J Pediatr Otorhinolaryngol 2006;70:1423-9.

[18] Laidlaw DW, Costantino PD, Govindaraj S, et al. *Tympanic membrane repair with a dermal allograft.* Laryngoscope 2001;111:702-7.

[19] Aabenhus K, Andersen SA, Srensen MS. *Hearing results after tympanoplasty are stable short-term: a prospective database study.* Otol Neurotol 2016;37:1335-43.

[20] Youssef AM. *Use of acellular human dermal allograft in tympanoplasty.* Laryngoscope 1999;109:1832-3.

[21] Farahani F, Karimi Yazdi A, Ghasemi M, et al. *Results of acellular dermis matrix graft used for tympanoplasty in Guinea pig model.* Iran J Otorhinolaryngol 2015;27:95-100.

[22] Johnson A, Mixson C, Munday J. *Suitability of formaldehyde-treated acellular dermis for tympanic membrane repair in chinchillas.* Otol Neurotol 2007;28:778-81.

[23] Vos JD, Latev MD, Labadie RF, et al. *Use of AlloDerm in type I tympanoplasty: a comparison with native tissue grafts.* Laryngoscope 2005;115:1599-602.

[24] Bellucci RJ. *Selection of cases and classification of tympanoplasty.* Otolaryngol Clin North Am 1989;22:911-26.

[25] Vartiainen E, Nuutinen J. *Success and pitfalls in myringoplasty: follow-up study of 404 cases.* Am J Otol 1993;14:301-5.

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CASE SERIES AND REPORTS

Paroxysmal positional vertigo despite complete vestibular impairment: the role of instrumental assessment

Vertigine parossistica posizionale benigna dopo deficit vestibolare totale: quale ruolo per la valutazione otoneurologica strumentale?

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SUMMARY

Lindsay-Hemenway syndrome is characterised by a posterior canal benign paroxysmal positional vertigo following a partial unilateral vestibular loss affecting the same side. The syndrome is caused by damage of structures innervated by the superior division of the vestibular nerve and perfused by the anterior vestibular artery; the detached otoconia can cause vertigo in the still intact posterior semicircular canal. The most recent vestibular instrumental techniques allow reaching an accurate topodiagnosis in case of peripheral vestibular failure. We report on two cases of Lindsay-Hemenway syndrome despite complete vestibular failure demonstrated by vestibular instrumental assessment. After making some critical considerations on these findings, we underline the importance of not disregarding the diagnosis of paroxysmal positional vertigo in an established complete labyrinthine loss of function.

KEY WORDS: Unilateral vestibular loss • Vestibular evoked myogenic potentials (VEMPs) • video Head Impulse Test (vHIT) • Benign paroxysmal positional vertigo • Lindsay-Hemenway syndrome

RIASSUNTO

La sindrome di Lindsay-Hemenway si caratterizza per la comparsa di una sindrome vertiginosa acuta da deficit periferico monolaterale seguita da una forma recidivante di vertigine parossistica posizionale ipsilaterale da canalolitiasi del canale semicircolare posteriore. Questo quadro clinico è ricondotto ad una distruzione labirintica parziale e limitata alle sole strutture labirintiche innervate dalla branca superiore del nervo vestibolare e irrorate dall'arteria vestibolare anteriore; gli otoconi degenerati in conseguenza del danno darebbero successivamente luogo alla vertigine posizionale poiché il canale semicircolare posteriore sarebbe risparmiato. Le metodiche strumentali attualmente disponibili nella pratica clinica otoneurologica consentono di delineare una topodiagnosi in caso di deficit vestibolare acuto, identificando le strutture non funzionanti. Di recente sono giunti alla nostra osservazione due pazienti che hanno sviluppato una sindrome di Lindsay-Hemenway sebbene le metodiche strumentali avessero permesso di diagnosticare un danno labirintico completo. Provvederemo ad affrontare criticamente quanto rilevato sottolineando la necessità di non escludere una forma di litiasi conseguente ad un deficit vestibolare anche laddove venga rilevato un danno strumentale completo.

PAROLE CHIAVE: *Deficit vestibolare unilaterale • Potenziali evocati vestibolari miogeni (VEMPs) • video Head Impulse Test (vHIT) • Vertigine parossistica posizionale benigna • Sindrome di Lindsay-Hemenway*

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Introduction

Lindsay and Hemenway [1] first described an episode of posterior canal benign paroxysmal positional vertigo (PC-BPPV) following labyrinthine ischaemic injury. They hypothesised selective damage of the vestibular structures perfused by the anterior vestibular artery, which provides the blood supply to most of the utricle, the superior and horizontal ampullae and to a small portion of the saccule, with consequent detachment of otoconia from the utricle. The otoconia could have then entered into an intact PC causing PPV. Later, Shucknecht and Kitamura [2] assumed selective viral damage of the superior vestibular nerve (VN) was the cause of the syndrome, by innervating the horizontal (HC) and anterior semicircular canal (AC), the utricle and the anterosuperior part of the saccule. The particular susceptibility to injury of the superior division of the VN is explained by a selective tropism to some viral agents or by anatomical

peculiarities of the bone auditory channel; histopathology studies of the temporal bone have shown frequent sparing of the PC [3] supporting these findings. Observing a PC-PPV after unilateral vestibular loss (UVL) implies preservation of the structures innervated by the inferior branch of the VN [4]. Nowadays, the results of ocular vestibular evoked myogenic potentials (O-VEMPs) and cervical vestibular evoked myogenic potentials (C-VEMPs) can be combined with the results of tests, such as the video head impulse test (vHIT), in order to obtain information about the state of the peripheral vestibular function of each sensory organ as well of each branch of the VN [5-7]. As Morofushi et al. reported in 1996 [8], if C-VEMPs are absent from an ear that has suffered acute UVL, PC-PPV is unlikely to develop as a consequence of the UVL because the absence of C-VEMPs imply damage to the structures innervated by the inferior VN (or of the inferior VN itself). In our ENT Unit, we have recently seen two patients presenting a PC-PPV at 8-14 days after superior and inferior vestibular neurolabyrinthitis, previously identified through an instrumental assessment. We present these cases of PC-PPV after a complete UVL because to our knowledge similar findings have not been described, which underline the necessity to consider a PC-PPV and to perform close follow-up after UVL even if a compete impairment of vestibular sense organs is identified.

Case series

A 67-year-old woman presented to our Neurotology Service (ENT Unit, Pisa University Hospital) for a standard follow-up examination 8 days after discharge for a right UVL. During hospital admission a complete clinical and instrumental vestibular assessment was performed. The caloric vestibular test (CVT) revealed a complete canal paresis (CP) on the

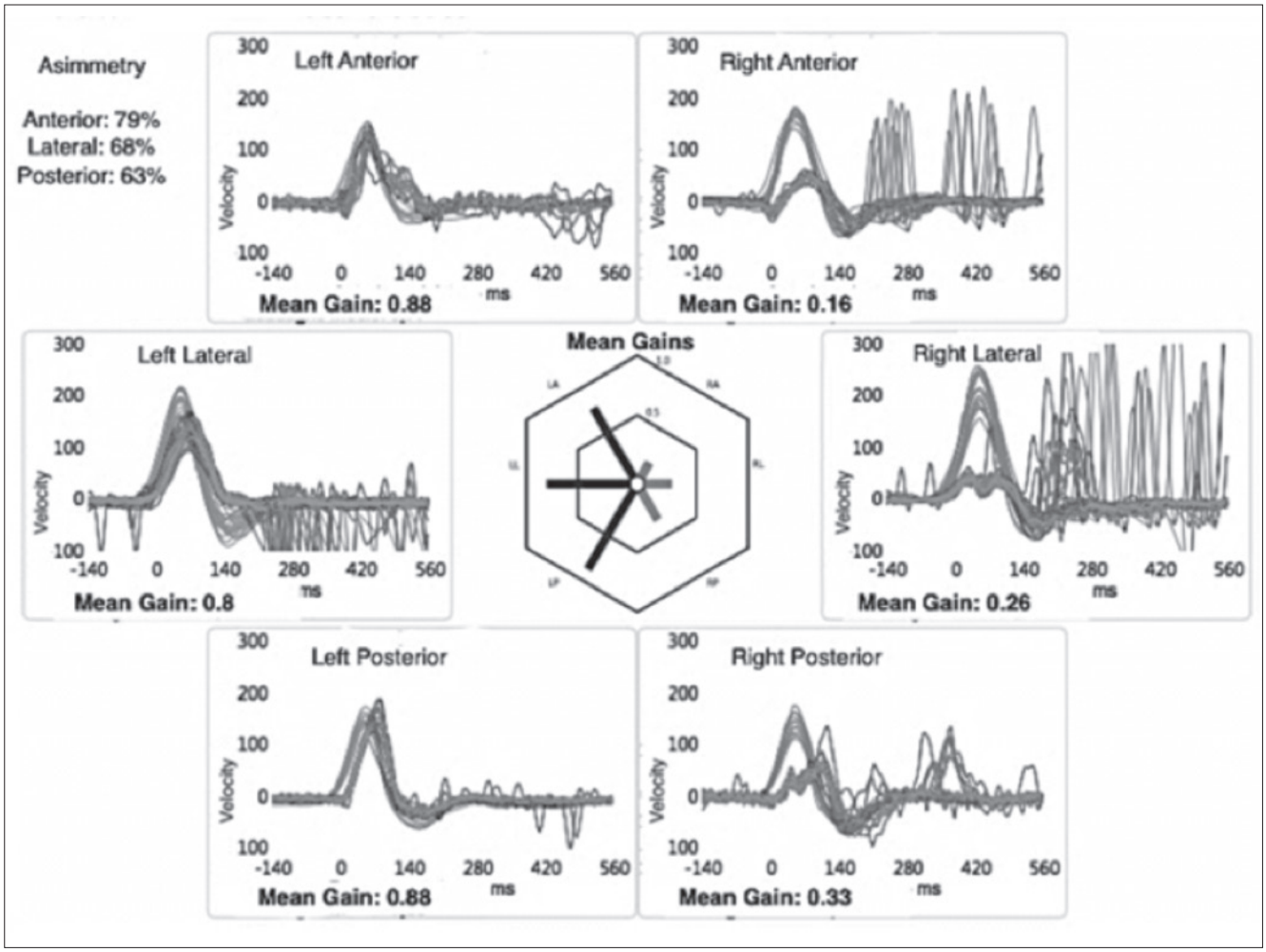

Fig. 1. Case 1, video head impulse test performed by employing a dedicated device ("ICS Impulse" system; GN Otometrics, http://www.icsimpulse.com). Right lateral canal, anterior canal and posterior canal gain are very low (0.26, 0.16, 0.33 respectively).

right side. vHIT showed a reduction in vestibulo-ocular reflex (VOR) gain values calculated on all the canals of the right side: 0.15 for HC, 0.28 for PC and 0.27 for AC (Fig. 1). Air conducted tone burst (TB) 500Hz C-VEMPs were absent on the right sternocleidomastoid muscle (Fig. 2A). Both a bone conducted 500 Hz STB stimulus at the midline forehead (Fz point) and a 500 Hz air conducted STB showed no response in the contralesional eye (O-VEMPs) (Fig. 2B). At the follow-up visit she described sudden onset and short-term spinning dizziness upon bending down and getting up, in addition to a mild sensation of unsteadiness. Clinical examination revealed the following: no spontaneous nystagmus, left-beating head-shaking and vibration-induced nystagmus and a torsional with anti-clockwise direction-up-beating nystagmus in right Dix-Hallpike positioning. The paroxysmus and the fatigability of this positional nystagmus, associated with the inversion of its direction when returning the patient to a sitting position, allowed us to make diagnosis of PC-PPV.

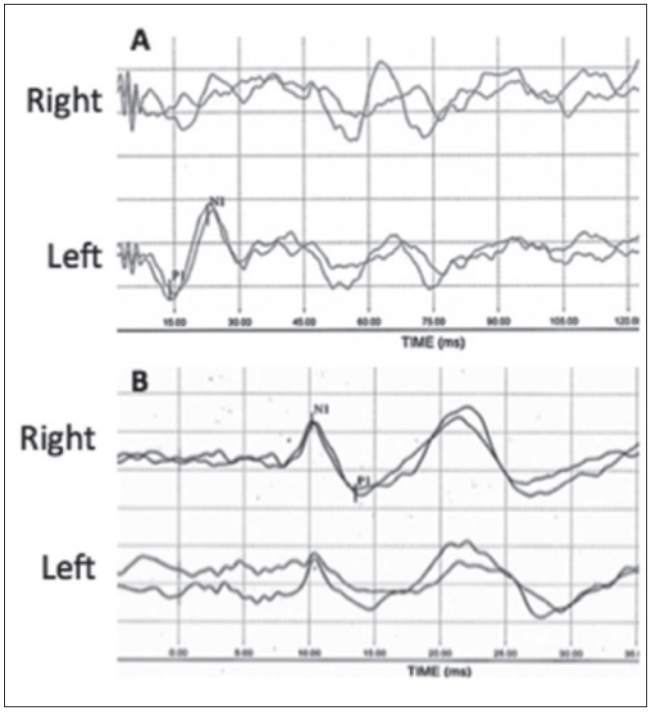

Fig. 2. Case 1, cervical vestibular evoked myogenic potentials (C-VEMPs) (A) and ocular vestibular evoked myogenic potentials (O-VEMPs) (B). C-VEMP are registered after air conducted 500 Hz TB; the response is absent on the right side (uncrossed potential). Vestibular myogenic evoked potentials for otolithic function, O-VEMPs, are registered after bone vibration (500 Hz) with a Bruel & Kjaer minishaker at the hairline (Fz); the response is abnormal on the right side/ear (crossed potential). The first component of the O-VEMP (n10) registered in the contralesional (left) eye is very small or absent and no reproducible, whereas the n10 beneath the ipsilesional (right) eye is of normal amplitude.

In a second case we evaluated a 48-year-old woman that complained of brief episodes of spinning dizziness associated with head movements. Fourteen days prior she reported a long lasting spinning vertigo diagnosed as right UVL. Instrumental findings performed 5 weeks before were the following: complete CP on the right side and high frequency VOR gain studied with vHIT on the right side equal to 0.56, 0.31 and 0.31 for the HC, AC and PC, respectively (Fig. 3). C-VEMPs were absent on the right side and evocable on the left side (Fig. 4A); O-VEMPs showed no response only on the left side (same methodology illustrated above) (Fig. 4B). During the follow up visit we performed a bedside examination that revealed a left-beating head shaking and vibration-induced nystagmus, but no spontaneous nystagmus. The right Dix-Hallpike manoeuvre revealed a torsional (with anti-clockwise direction) up-beating nystagmus. Magnetic resonance imaging (MRI) brain scan, performed on both patients, showed no abnormalities. No audiological impairment and, in particular, no air-bone gap was detected. The examination revealed a PC-PPV affecting the same side of superior and inferior neurolabyrinthitis. Both patients underwent a successful therapeutic Semont's maneuver to treat the PC-PPV [9].

Discussion

The combined use of new diagnostic tools like C-VEMP, O-VEMP and vHIT allows to assess impairment of the otolith organs and semicircular canals, and therefore to differentiate involvement of the vestibular receptor in UVL patients [5-7]. CVT and vHIT allow examining HC function with a low (0.03 Hz) and high (5-7 Hz) frequency range of the stimulus; in turn, both tests provide information about superior VN function. The most recent vHIT devices even allow testing of the AC and PC; a normal VOR gain on the PC suggests that the function of the inferior VN is preserved. Moreover, saccular and inferior VN function can be studied with C-VEMPs, and utricular and superior VN function with O-VEMPs. Despite the large number of studies that have attempted to clarify the proper pathway of O-VEMPs, these potentials reflect mainly utricular and superior VN function. Moreover, the efferent branch of the reflex seems to be independent with respect to the stimulus employed; however, bone conducted stimulus administered to the midline Fz is considered the most efficient [10 11]. Both O-VEMPs and C-VEMPs have been employed to diagnose cases of UVL with selective involvement of the inferior VN [12].

Although the aetiology has not yet been understood, BP-PV is classified as idiopathic in most cases; however, its

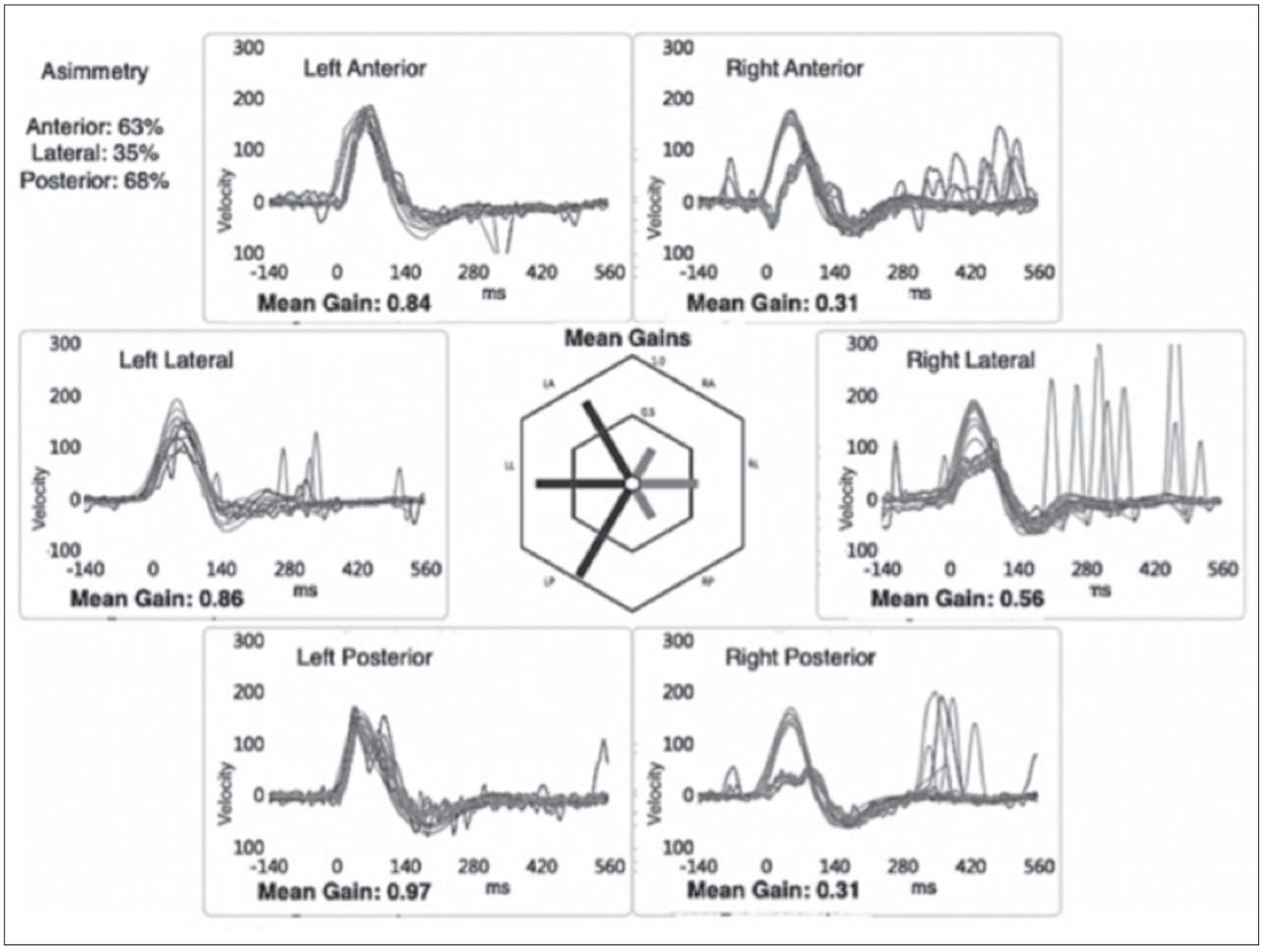

Fig. 3. Case 2, video head impulse test performed by employing a dedicated device ("ICS Impulse" system; GN Otometrics, http://www.ics-impulse.com). Right lateral canal, anterior canal and posterior canal gain are very low (0.56, 0.31, 0.31 respectively).

pathogenesis is almost certain and attributable to detachment and displacement of otoliths in one semicircular canal. Since the results of our vestibular tests indicated functional impairment of the structures innervated by the inferior VN (or of the inferior VN itself), it is hard to understand how a stimulus on the PC could reach vestibular nuclei and then oculomotor nuclei. Since normal MRI excluded a central origin of the positional nystagmus, some hypotheses can be formulated. PC loss of function can be caused by PPV itself: the literature shows that HC-PPV can affect the results of both CVT and HIT [13]; we did not consider this theory because our tests were performed before finding any sign of PPV. A simpler explanation is that sufficiently preserved function in the PC and inferior VN allows a severe PPV to manifest itself despite instrumental findings. Differently, if we assume that neurolabyrinthitis is caused by a loss of inputs from PC ampulla (pathological PC-VOR gain) and from the saccule (absent C-VEMPs), how can the PC-PPV be explained? We can hypothesise that a type 2 cell preservation in PC would be able to make the cupula respond to low-frequency stimuli such as free-floating otoconia, whereas the damaged type 1 cells would not allow the cupula to respond to high frequency stimuli like vHIT. A different theory implies the inferior VN fibres to be the site of the lesion: in this case, the intact PC ampulla receptors would respond to otoconia. However, it would be harder to explain how residual neural activity would make the VN reactive only to positioning manoeuvres (slow displacement of the cupula), but not to the vHIT. A role in this sense could be played by vestibulo-cochlear anastomoses first described by Von Oort in 1981 [14]. This would explain the presence of PPV and the absence of C-VEMPs in case of complete VN impairment; however, it still implies a stimulus-dependent

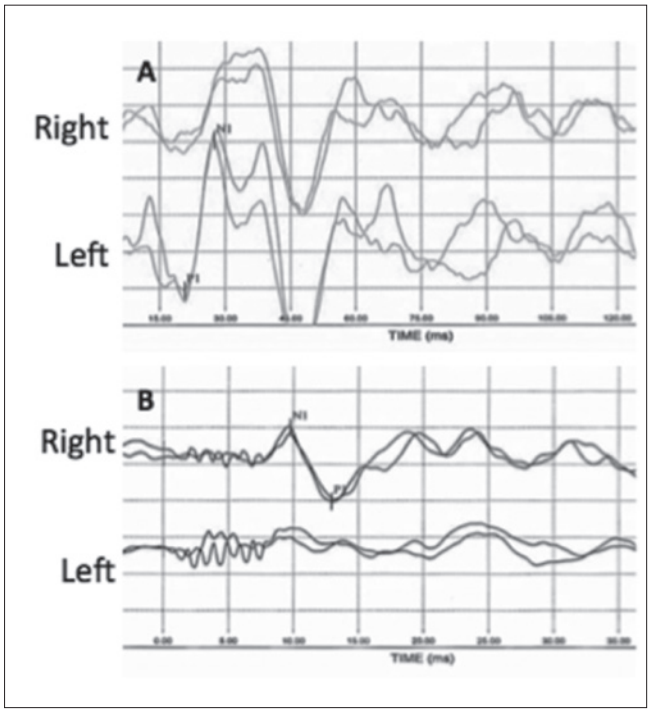

Fig. 4. Case 2, air conducted cervical vestibular evoked myogenic potentials (C-VEMPs) (A) and bone conducted ocular vestibular evoked myogenic potentials (O-VEMPs) (B). C-VEMP are registered after air conducted 500 Hz TB; the response is absent on the right side (uncrossed potential). Vestibular myogenic evoked potentials for otolithic function, O-VEMP, are registered after bone vibration (500 Hz) with a Bruel & Kjaer minishaker at the hairline (Fz); the response is abnormal on the right side/ear (crossed potential). The first component of the O-VEMP (n10) registered in the contralesional (left) eye is absent, whereas the n10 beneath the ipsilesional (right) eye is of normal amplitude.

transmission of the afferent inputs by the anastomoses. One should also take in account that the amplitude of the potential is extremely dependent on sternocleidomastoid muscle contraction and on the age of the patient: sometimes the lack of reliability of C-VEMPs does not necessarily imply the presence of pathology [15]. It is also possible that our findings might be due to artefacts. However, the standardised methodology used and the presence of a reliable p1-n1 complex (with normal amplitude and latencies) on the healthy side make this possibility less plausible. Finally, because of the neural pathway of VEMPs, it is also possible that there are aspects that are still not completely understood.

Conclusions

The present cases show that a clinical entity attributable to Lindsay-Hemenway syndrome is possible even though vestibular instrumental assessment shows complete labyrinthine impairment. Therefore, even in this case, a diagnosis of PPV should be considered and close follow-up is recommended. Some hypotheses about the findings can be made, even if further studies are needed for better comprehension.

Acknowledgements

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Conflict of interest statement

None declared.

References

1 Lindsay J, Hemenway W. *Postural vertigo due to unilateral sudden partial loss of vestibular function*. Ann Otol Rhinol Laryngol 1956;65:692-706.

2 Schuknecht HF, Kitamura K. *Second Louis H Clerk lecture. Vestibular neuritis*. Ann Otol Rhinol Laryngol 1981;90:1-19.

3 Proctor L, Perlman H, Lindsay J, et al. *Acute vestibular paralysis in herpes zoster oticus*. Ann Otol Rhinol Laryngol 1979;88:303-10.

4 Büchele W, Brandt TH. *Vestibular neuritis, a horizontal semicircular canal paresis?* Adv Oto-Rhino-Laryngol 1988;42:157-61.

5 Curthoys IS. *The interpretation of clinical tests of peripheral vestibular function*. Laryngoscope 2012;122:1342-52.

6 Taylor RL, McGarvie LA, Reid N, et al. *Vestibular neuritis affects both superior and inferior vestibular nerves.* Neurology 2016;87:1704-12.

7 Magliulo G, Gagliardi S, Ciniglio Appiani M, et al. *Vestibular neurolabyrinthitis: a follow-up study with cervical and ocular vestibular evoked myogenic potentials and the video head impulse test*. Ann Otol Rhinol Laryngol 2014;123:162-73.

8 Murofushi T, Halmagyi GM, Yavor RA, et al. *Absent vestibular evoked myogenic potentials in vestibular neurolabyrinthitis. An indicator of inferior vestibular nerve involvement?* Arch Otolaryngol Head Neck Surg 1996;122:845-8.

9 Albera A, Boldreghini M, Canale A, et al. *Vertigo returning to the sitting position after the Semont manoeuvre. Is it a prognostic symptom?* Acta Otorhinolaryngol Ital 2018;38:145-150.

10 Rosengren SM, Kingma H. *New perspectives on vestibular evoked myogenic potentials*. Curr Opin Neurol 2013;26:74-80.

11 Curthoys IS, Iwasaki S, Chihara Y, et al. *The ocular vestibular-evoked myogenic potential to air-conducted sound; probable superior vestibular nerve origin*. Clin Neurophysiol 2011;122:611-6.

12 Manzari L, Burgess AM, Curthoys IS. *Ocular and cervical vestibular evoked myogenic potentials in response to bone-*

conducted vibration in patients with probable inferior vestibular neuritis. J Laryngol Otol 2012;126:683-91.

[13] Strupp M, Brandt T, Steddin S. *Horizontal canal benign paroxysmal positioning vertigo: reversible ipsilateral caloric hypoexcitability caused by canalolithiasis?* Neurology 1995;45:2072-6.

[14] Oort H. *Über die verästelung des nervus octavus bei Säugetieren. (Modell des utriculus und sacculus des kaninchens).* Anat Anz 1918;51:272-80.

[15] Welgampola MS, Colebatch JG. *Vestibulocollic reflexes: normal values and the effect of age*. Clin Neurophysiol 2001;112:1971-9.

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CASE SERIES AND REPORTS

Defect-oriented reconstruction after transoral robotic surgery for oropharyngeal cancer: a case series and review of the literature

La ricostruzione dei difetti dopo chirurgia robotica transorale per i tumori dell'orofaringe: casi clinici e review della letteratura

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SUMMARY

Transoral robotic surgery (TORS) is a fascinating new technique that has been shown to be a safe and feasible treatment for selected oropharyngeal cancers. Furthermore, TORS might offer some advantages in selected locoregionally advanced cancers. Thus, the patient selection is the keypoint for the useful application of TORS. However, the reconstruction of large oropharyngeal defects is challenging due to the restoration of velopharyngeal competency and swallowing. Moreover, the absence of mandibular splitting increases the difficulties faced by reconstructive surgeons. The paradigm for oropharyngeal reconstruction has undergone changes paralleling reflecting the overall change in the trend of the treatment alternatives over the last few decades. Flap choice and harvesting should be tailored to obtain significant advantages both in functional terms and for easy insetting. In this review, we analyse the strengths and weaknesses of the various flaps used in TORS framework with particular regards on our preliminary experience.

KEY WORDS: Transoral robotic surgery • Reconstruction • Oropharyngeal carcinoma • Minimally invasive surgery • Flap

RIASSUNTO

La chirurgia transorale robotica (TORS) rappresenta una potenziale modalità di trattamento dei tumori dell'orofaringe. Sebbene la radiochemioterapia rivesta un ruolo di primaria importanza nel trattamento delle forme localmente avanzate, la TORS in casi selezionati permette di ottenere una resezione nel rispetto dei canoni della chirurgia oncologica evitando la mandibulotomia e conseguentemente le complicanze da essa derivate. Tuttavia, gli ampi difetti chirurgici che possono derivare abbisognano necessariamente di una fase ricostruttiva che consenta, oltre a ricoprire strutture nobili un discreto ripristino delle funzionalità deglutitorie. In letteratura sono stati descritti diversi approcci ricostruttivi per lesioni di piccole e grandi dimensioni con lembi peduncolati o liberi. La difficoltà maggiore potenziale nella ricostruzione dell'orofaringe in assenza di una mandibulotomia è l'inserimento del lembo ricostruttivo nella cavità, soprattutto quando si utilizzano lembi liberi. Lo scopo di questo articolo è di analizzare pregi e difetti delle opzioni ricostruttive (già descritte in letteratura) in base al difetto creatosi con particolare riguardo anche alla nostra esperienza preliminare.

PAROLE CHIAVE: *Chirurgia robotica transorale • Ricostruzione • Carcinoma orofaringeo • Chirurgia mini-invasiva • Lembi ricostruttivi*

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Introduction

Primary chemoradiation therapy (CRT) and transoral robotic surgery (TORS) with or without adjuvant CRT are competing therapeutic approaches with similar oncologic outcomes in the management of oropharyngeal squamous cell carcinoma (OPSCC) [1]. However, CRT may also result in significant functional impairments such as severe dysphagia and feeding tube dependence [2]. On the other hand, TORS may lead to debilitating post-ablative defects depending on the size and anatomic location of the defect. TORS may benefit the patients through pathologic downstaging as well as the potential for improvement in oncologic outcomes, identifying the primary tumour, or reducing the toxicity of definitive chemoradiation therapy [3]. From this point of view, TORS might offer some advantages in select-

ed locoregionally advanced patients (i.e. early T3 lesions, cN2-3). Moreover, The National Comprehensive Cancer Network guidelines recognise transoral surgery as a potentially useful tool in the treatment of selected patients in this setting [4]. The paradigm for oropharyngeal reconstruction has undergone changes reflecting the overall change in the trend of the treatment alternatives over the last few decades. The aim of this study is to highlight the reconstruction options for oropharyngeal defects after TORS and to analyse the particular characteristics that guide the surgeon towards the best tailored reconstruction.

Case #1

A 65-year-old male patient with a cT2N1 OPSCC p16- tumour, involving the left anterior pillar extending to the homolateral soft palate (Fig. 1A), was referred to our Institution. The history revealed smoking and light drinking habits, and no significant comorbidities. The patient was scheduled for TORS and selective neck dissection (SND) of levels I-IV. A tracheostomy was performed prior to robotic surgery. Next, a Feyh-Kastenbauer retractor (Gyrus Medical Inc., Maple Grove, MN) was used to expose the operative field. The tumour margins were observed intraoperatively with a 0° or 30° 8 mm Hopkins scopes (Karl Storz, Germany) using white light and a narrow band imaging (NBI) high-definition video- endoscopy system (CV-260SL processor, CVL-260SL light source, Olympus Optical Co., Ltd., Japan). The edges of surgical excision were marked with monopolar cautery and controlled with NBI (Fig. 1B). The daVinci® Surgical Robotic System (Intuitive Surgical, Sunnyvale, CA) was positioned 30° angled on the right side of the patient. 0° or 30° 8.5 mm endoscopes were used with two 5 mm side arms Maryland dissectors and cautery (Fig. 1C). All vessels encountered during the resection were clipped prior to transaction. The entire surgical specimen was oriented and submitted to the pathologist for intraoperative assessment of the margin status with frozen sections. Next, the SND was performed. Once neck dissection was completed and clear margins confirmed by the pathologist, the temporalis muscle flap (TMF) was easily harvested and transposed to resurface the defect (Fig. 2). A nasogastric tube was placed. Tracheotomy was closed on postoperative day 5 and the patient resumed oral feeding on day 7 and discharged on day 9 with normal diet. The pathological report was consistent with a pT2N0 R0 OPSCC p16-. No indications for adjuvant treatment was posed at multidisciplinary tumour board. No swallowing disorders were reported after 6 months of follow-up.

Case #2

A 61-year-old male patient with a cT3N2c OPSCC p16- (Figure 3) tumour, involving the left soft palate, tonsil and homolateral base of tongue (BOT), was referred to our Institution. The history revealed heavy smoking and drinking habits, and no other significant comorbidities. CT and PET scan did not demonstrate distant metastasis. The patient was scheduled for TORS and bilateral modified radical neck dissection (MRND) with tracheostomy. The edges of surgical excision were marked in the same way as previously described as well as the robotic setting. The margin status with frozen sections were assessed. During the neck dissection, an antero-lateral thigh flap (ALT) was harvested with a three-petal shape skin paddle (Fig. 4). A nasogastric tube was placed. Tracheotomy was closed on postoperative day 8 and the patient resumed oral feeding on day 15 and discharged on day 20 with normal diet. The pathological report was consistent with a pT3N2c R0 OPSCC p16- lesion with extracapsular spread in one of the left cervical lymph nodes. The multidisciplinary tumour board posed indication for adjuvant CRT. No experience of loco-regional relapse or swallowing impairment were recorded after 3 months of follow-up.

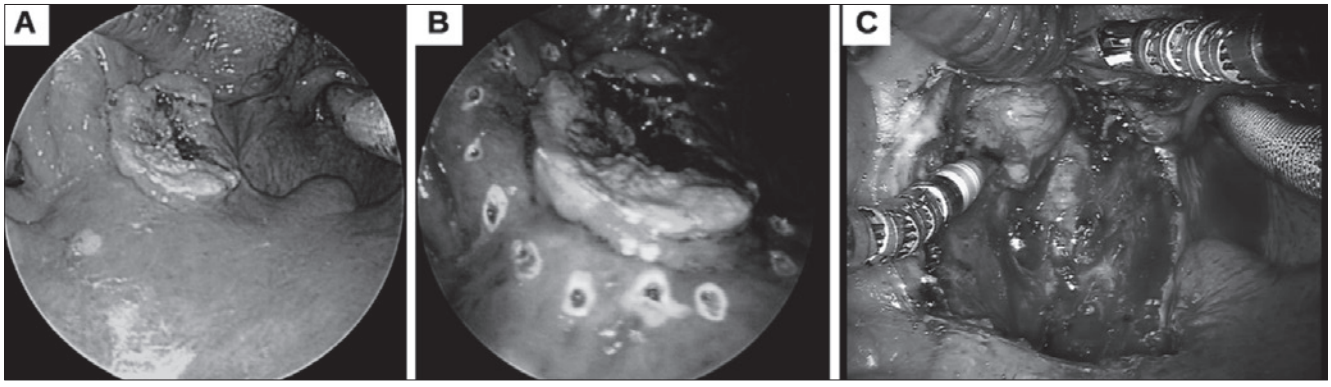

Fig. 1. A) Endoscopic view of the tumour. **B)** Checking the surgical edges with NBI. **C)** Endoscopic view of surgical field after completed tumour resection.

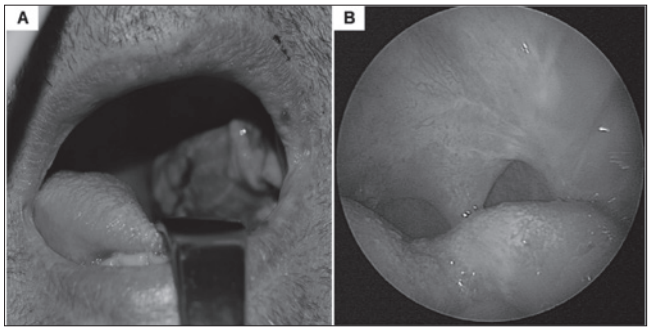

Fig. 2. A) The temporalis muscle flap on the fifth postoperative day. **B)** Endoscopic view of the left lateral pharyngeal and soft palate reconstructed with temporalis muscle flap after one month.

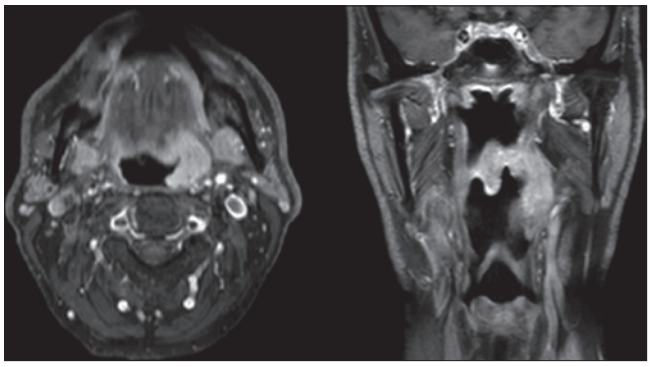

Fig. 3. Magnetic resonance imaging showing the extension of lesion: left base of tongue, tonsil and soft palate.

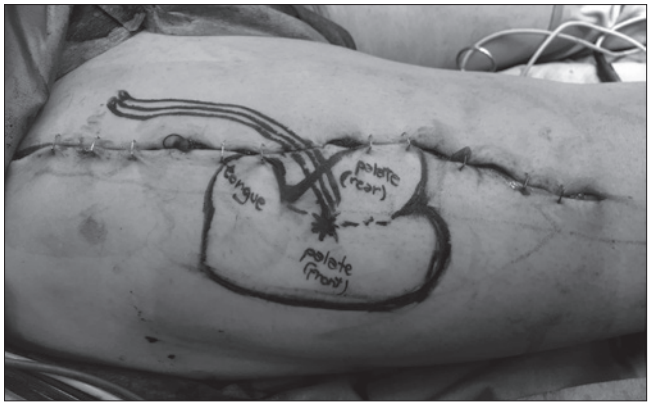

Fig. 4. Modified skin paddle of antero-lateral thigh flap according to Caliceti et al.

Case #3

A 51-year-old male patient with a cT3N0 OPSCC p16- tumour, involving the left tonsil, base of tongue and partially the soft palate, was referred to our Institution. The history revealed moderate smoking and heavy drinking habits, and no other significant comorbidities. MRI and CT scan did not demonstrate regional or distant metastasis. The patient was scheduled for TORS and SND levels II-IV with tracheostomy. The robotic resection and the reconstruction were performed in the same fashion described above. A nasogastric tube was placed. Tracheotomy was closed on postoperative day 6 and the patient resumed oral feeding on day 15 and discharged on day 17 with normal diet. The pathological report was consistent with a pT3N0 R0 OPSCC p16- lesion. The multidisciplinary tumour board posed indication for adjuvant radiotherapy on the oropharynx due to extension of the primary tumour. At 3-month follow-up, the patient did not experience any swallowing impairment or local relapses (Fig. 5).

Discussion

Currently, the majority of robotic surgeons favour leaving to heal by secondary intention the oropharyngeal defects following TORS for early OPSCC (cT1-2). However, the resection of smaller tumours involving the soft palate may result in velopharyngeal insufficiency. In fact, surgical resection inevitably affects the native function of the oropharynx; therefore, our group advocates the use of NBI in order to obtain free margins and to reduce over-resections, consequently minimising the risk of functional impairments [5].

Among existing classification schemes for oropharyngeal defects, the reconstructive algorithm developed by de Almeida et al [6] seems to be easier to apply in the robotic surgery framework. Local flap or regional flaps are amenable for class I/II defects. In exclusive resection of the soft palate , the restoration of the velopharyngeal competency may be obtained with a posteromedially based musculomucosal flap (PMM) [6] as well as with a facial artery musculomucosal flap (FAMM) [7 8] . Theoretically, the combination of PMM and FAMM might provide a valuable solution in concomitant non-extensive lateral pharyngeal wall and soft palate defects.

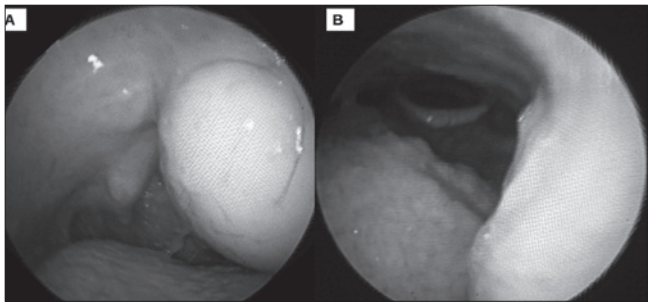

Fig. 5. Endoscopic view of insetted antero-lateral thigh flap. **A)** anterior view; **B)** retropalatal view.

An interesting application of the nasoseptal flap in covering tonsillar fossa resection is described by Pinheiro et al [9]. This flap may be considered a valid option either alone or in combination with previously described local flaps.

Regarding the BOT, our group advocates healing by secondary intention even in T3 tumours according to our experience in sleep apnoea robotic surgery [10]. Furthermore, extensive BOT resections did not lead to swallowing disorders in the post-operative course. Our experience is in accordance with de Almeida et al [6]. Obviously, in the case of the resection involving an extensive deeper muscular part of the tongue, restoration of bulk is needed and often requires soft tissue free flaps, although an infrahyoid flap may be a valuable option [11].

Class III/IV defects constitute a variable challenge for an effective functional reconstruction. Recent studies continue to demonstrate favourable functional outcomes following free tissue transfer [7 12-17], although in the vessel-depleted neck or in the presence of severe comorbidities flap failures are noted to be higher given the quality of the recipient vessels.

The radial forearm free flap (RFFF) and the ALT are the two types of reconstruction most commonly used for pharyngeal defects after TORS [7 12-17]. Perhaps the easiest of these flaps to harvest is the RFFF. However, the possibility of resulting in a reduction in dexterity and hand's grip strength of the donor's arm should be explained and discussed with the patient.

Many recent studies have been published that support an expanding role for the ALT for use in reconstruction of large pharyngeal defects [7 14 17]. In our experience (see Table I), we used the ALT for reconstructing class IV defects involving part of BOT and thoroughly the soft palate harvesting the skin paddle with a three petal shape (Fig. 4). This strategy has been described by Caliceti et al. [18] insetting the flap after transmandibular approaches. This particular shape allows one petal to replace the rear side of the palate, one for the front side of the palate and the tonsillar fossa and the third petal to reconstruct the tongue base. The dimensions of the template can be adjusted to the resected specimen before starting the flap dissection in order to optimise the precision. Flap insetting is the most challenging phase due to severely restricted physical access and visualisation. However, in our experience, the accurate shape and measure of the flap allow to thoroughly perform a manual inset, although the robot might be used for suturing parts of flap in deeper and narrower spaces. We strongly suggest to achieve the best exposure as much as possible (even modifying the position of the mouth gag after resection) and to start suturing the posterior wall between nasopharyngeal mucosa and the rear surface of the new palate (1st petal). Next, the flap is folded onto itself and sutured to the mucosa of the anterior face of the palate and the lateral pharyngeal wall (2nd petal), and the third petal is sutured to the tongue base (Fig. 4). In case of expected excessive bulky of ALT, Ghanem suggested to use the vastus lateralis free flap (VLFF) [16]. This flap might be used as rescue option in case of accidental damage of ALT perforator arteries.

Table I. Overview of published studies on oropharyngeal reconstruction in TORS framework and our experience.

Author	Year	Tumour site (T classification)	Flap	Complication
Selber et al. [7]	2010	1 RMT involving tonsil, BOT, soft palate	1 RFFF	-
		1 tonsil (T2)	1 FAMM	
Garfein et al. [13]	2011	1 BOT	1 RFFF	-
Ghanem [15]	2011	1 tonsil (T2) 1 BOT/oral tongue (T1) 1 tonsil, BOT, oral tongue (T4a)	3 RFFF	-
		1 tonsil (T4a)	1 vastus lateralis free flap	
Genden et al. [16]	2011	6 lateral pharyngeal wall involving BOT and soft palate	6 RFFF	1 partial flap necrosis
Bonawitz & Duvuuri [8]	2013	5 soft palate	5 FAMM	-
Park et al. [14]	2013	1 soft palate (T3)	1 ALT	-
		1 tonsil (T2)	1 RFFF	
Mukhija et al. [12]	2016	1 soft palate and tonsillar fossa (T3) 1 soft palate, lateralpharyngeal wall, RMT (T3)	2 RFFF	-
Pinheiro et al. [9]	2016	1 tonsil	1 nasoseptal flap	-
Forlì experience	-	2 lateral pharyngeal wall involving BOT and soft palate (T3)	2 ALT	-
		1 anterior tonsillar pillar involving soft palate (T2)	1 TMF	

RFFF: radial forearm free flap; ALT: antero-lateral thigh flap; TMF: temporalis muscle flap; FAMM: facial artery musculomucosal flap; BOT: Base of Tongue; FOM: Floor Of Mouth; RMT: Retro Molar Trigone

In the free flap era, regional flaps are often overlooked albeit they still represent a valid alternative especially in patients with severe comorbidities or vessels-depleted necks. In terms of cost-effectiveness, the use of alternative pedicled flaps in TORS framework probably reduce the risks of postoperative complications, with consequent expenditure restraints and reducing treatment costs arising from operating room duration and a double surgical team [19 20]. Our group successfully adopted the TMF restoring a competent velopharyngeal sphincter and a watertight seal between the pharynx and neck in a case of OPSCC involving part of soft palate and the anterior tonsillar pillar [21].

From the therapeutic point of view, TORS may be a valuable method of de-intensification for the locoregionally advanced patient in at least three ways: (1) decreasing the dose of radiotherapy; (2) obviating the need for chemotherapy; (3) decreasing the radiotherapy target volume [3]. Concurrent neck dissection allows to stage the lymph node involvement, and consequently to determine laterality of adjuvant radiotherapy without increasing risks of complications or delaying the adjuvant treatments [22]. Percutaneous endoscopic gastrostomy (PEG) tube dependency rates are important data that reflect on the toxicity of adjuvant treatment, functional outcomes and quality of life. Published rates of acute PEG tube dependence after definitive CRT range from 9% to 39% with median time to PEG tube removal ranging from 3.3 to 5.9 months and up to 37% of patients still PEG tube dependent at 1 year. Albeit the PEG tube insertion rate is almost similar after TORS, the dependency rate at one year is reported around 1% [2].

Conclusions

The introduction of TORS has led to a resurgence in the role of surgery in the management of patients with OPSCC. The available reconstructive options allow an expanding role of this minimally invasive surgery, even in locally advanced tumours. Given the rapidly increasing application of robotic surgery in the treatment of OPSCC, prospective comparisons of TORS versus CRT are critical to resolve the pressing clinical and cost-effectiveness issues in this disease.

Conflict of interest statement

None declared.

References

1 Sher DJ, Fidler MJ, Tishler RB, et al. *Cost-effectiveness analysis of chemoradiation therapy versus transoral robotic surgery for human papillomavirus-associated, clinical N2 oropharyngeal cancer*. Int J Radiat Oncol Biol Phys 2016;94:512–22.

2 Carpenter TJ, Kann B, Buckstein MH, et al. *Tolerability, toxicity, and temporal implications of transoral robotic surgery (TORS) on adjuvant radiation therapy in carcinoma of the head and neck.* Ann Otol Rhinol Laryngol 2014;123:791-7.

3 Ward MC, Koyfman SA. *Transoral robotic surgery: the radiation oncologist's perspective.* Oral Oncol 2016;60:96-102.

4 Pfister DG, Ang KK, Brizel DM, et al. *Head and neck cancers, version 2*.2013. Featured update to the NCCN guidelines. J Natl Comp Canc Netw 2013;11:917-23. Erratum in: J Natl Compr Canc Netw 2013;11:1458.

5 Vicini C, Montevecchi F, D'Agostino G, et al. *A novel approach emphasising intra-operative superficial margin enhancement of head-neck tumours with narrow-band imaging in transoral robotic surgery.* Acta Otorhinolaryngol Ital 2015;35:157-61.

6 de Almeida JR, Park RCW, Villanueva NL, et al. *Reconstructive algorithm and classification system for transoral oropharyngeal defects.* Head Neck 2014;36:934-41.

7 Selber JC. *Transoral robotic reconstruction of oropharyngeal defects: a case series.* Reconstr Surg 2010;126:1978-87.

8 Bonawitz SC, Duvvuri U. *Robotic-assisted FAMM flap for soft palate reconstruction.* Laryngoscope 2013;123:870-4.

9 Pinheiro CD, Galati LT. *Nasoseptal flap for reconstruction after radical tonsillectomy.* Head Neck 2016;38:E2495-8.

10 Eesa M, Montevecchi F, Hendawy E, et al. *Swallowing outcome after TORS for sleep apnea: short- and long-term evaluation.* Eur Arch Otorhinolaryngol 2015;272:1537-41.

11 Perrenot C, Phulpin B, Mastronicola R, et al. *Infrahyoid myocutaneous flap for reconstruction after robotic transoral surgery for oropharyngeal tumors.* Plast Reconstr Surg 2014;133:236e-7e.

12 Mukhija VK, Sung C-K, Desai SC, et al. *Transoral robotic assisted free flap reconstruction.* Otolaryngol Head Neck Surg 2016;140:124-5.

13 Garfein ES, Greaney PJ, Easterlin B, et al. *Transoral robotic reconstructive surgery reconstruction of a tongue base defect with a radial forearm flap.* Plast Reconstr Surg 2011;127:2352-4.

14 Park YM, Lee WJ, Yun IS, et al. *Free flap reconstruction after robot-assisted neck dissection via a modified face-lift or retroauricular approach*. Ann Surg Oncol 2013;20:891-8.

15 Ghanem TA. *Transoral robotic-assisted microvascular reconstruction of the oropharynx*. Laryngoscope 2011;121:580-2.

16 Genden EM, Park R, Smith C, et al. *The role of reconstruction for transoral robotic pharyngectomy and concomitant neck dissection*. Arch Otolaryngol Head Neck Surg 2011;137:151-6.

17 Meccariello G, Montevecchi F, Sgarzani R, et al. *The reconstructive options for oropharyngeal defects in the transoral*

robotic surgery framework. Oral Oncol 2017;66:108-11.

18 Caliceti U, Piccin O, Sgarzani R, et al. *Surgical strategies based on standard templates for microsurgical reconstruction of oral cavity and oropharynx soft tissue: A 20 years' experience.* Microsurgery 2013;33:90-104.

19 Deganello A, Gitti G, Parrinello G, et al. *Cost analysis in oral cavity and oropharyngeal reconstructions with microvascular and pedicled flaps.* Acta Otorhinolaryngol Ital 2013;33:380-7.

20 Montevecchi F, Cammaroto G, Meccariello G et al. *Transoral robotic surgery (TORS): a new tool for high risk tracheostomy decannulation*. Acta Otorhinolaryngol Ital 2017;37:46-50.

21 Meccariello G, Montevecchi F, Deganello A et al. *The temporalis muscle flap for reconstruction of soft palate and lateral oropharyngeal wall after transoral robotic surgery.* Auris Nasus Larynx 2018;45:162-4.

22 Kucur C, Durmus K, Gun R, et al. *The safety and efficacy of concurrent neck dissection and transoral robotic surgery.* Head Neck 2015;38:E519-2.

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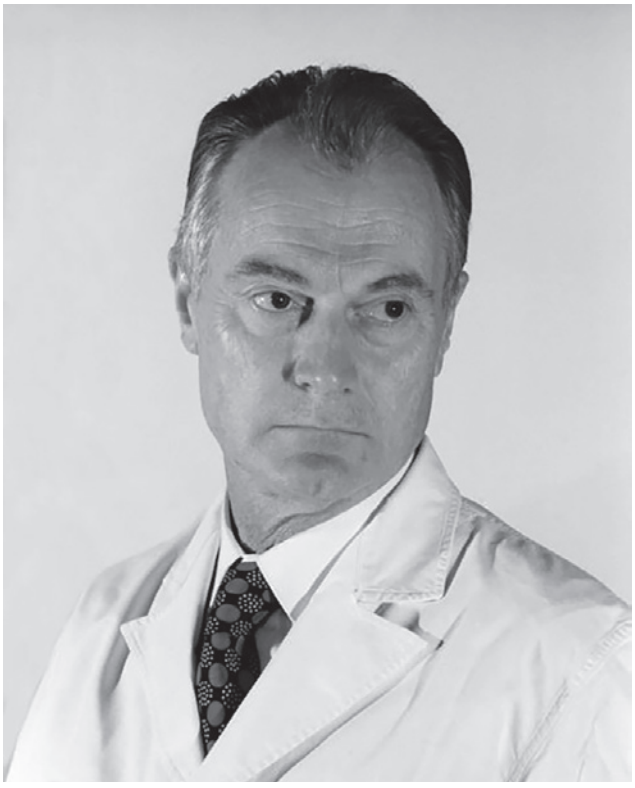
In Memoriam of Giancarlo Zaoli

(27 November 1925 - 31 July 2018)



Another member of the group of distinguished colleagues who contributed decisively in reforming and re-launching our Society during 1970-1990 has left us. Giancarlo Zaoli was born in Forlì on November 27, 1925, and in Bologna undertook his studies in Medicine, graduating in 1949. He immediately became interested in ENT under the guidance of a great teacher, Pietro Caliceti. After the death of the latter, he moved to the ENT Clinic at the University of Perugia, then directed by Domenico Filipo, and gave an active contribution to the Institute's scientific activities. He continued his clinical experience at the Hospital of Forlì, in the Unit then directed by Prof. Fabio Fabbi, and subsequently managed to independently form a new ENT unit at Forlimpopoli. In 1968, his professional career took a radical turn and he returned towards a hospital environment. In that year, in fact, an important ENT Department had been established at the Hospital of Rimini (before there was only a consultancy service) and Zaoli was made Head of the Department, a position that he maintained until his retirement in 1991. In those 20 years, he was able to advance the activities of this Department in a very significant manner. He was able to stimulate his colleagues by directing each of them to deepen and cultivate with particular dedication at least one of the various disciplines that make up our specialty (from imbalance disorders to allergology, from phoniatrics to plastic surgery, etc.).

During those years, Zaoli also knew how to bring his own active contribution to the life and evolution of our Society, exactly in the period of its renewal, and was President of the AOOI from 1984-1986 and of the SIO from 1990-1991. From a professional and scientific point of view, I remember that the greatest passion of Giancarlo Zaoli, the sector in which he gave the most important contributions, was plastic surgery, a subject that he, along with Valerio Micheli-Pellegrini, began, in Italy, to transferring ENT skills into routine practice, at high levels and publishing articles and monographs of national and international relevance. Of fundamental importance was the Official Report SIO "Reconstructive surgery in cervico-cephalic district tumours" that Zaoli presented, in collaboration with Giovanni Motta, at the 1978 congress in Modena.

What I have described above gives a fairly comprehensive picture of the professional life of Giancarlo Zaoli, a dutiful remembrance of his work, intended above all for those who did not know it directly. For me and for all the others who were his friends, his human qualities were exceptional. He was a good, friendly man who knew how to deal with life with extreme gentleness. A man who loved fast sports cars and refined clothes, but for this he certainly could not be considered a fatuous individual. Indeed, he was extremely practical and generous as shown by the work he carried out for many years for an association of laryngectomised patients. If, ultimately, we need a single definition that can sum up the human qualities of Giancarlo Zaoli, I think that the best is that he was a very great gentleman.

Giorgio Sperati

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