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Review article

Sialendoscopy in juvenile recurrent parotitis: a review of the literature

La scialoendoscopia nella parotite ricorrente giovanile: una revisione della letteratura

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SUMMARY

Juvenile recurrent parotitis (JRP) is the second most frequent salivary gland disease in childhood, defined as a recurrent non-suppurative and non-obstructive parotid inflammation. The recurring attacks actually represent the most dramatic and serious aspect of this pathology, since they significantly influence the quality of life, and there are no recognized therapies to avoid them. In recent years, there are reports of many international experiences related to the management of JRP by sialendoscopy. In this context, several authors have stressed the striking role of sialendoscopy in the prevention of JRP attacks. The objective of the current review is to overview the existing literature with particular regards to diagnostic and therapeutic outcomes after the application of sialendoscopy in patients suffering from JRP.

KEY WORDS: Sialendoscopy • Sialoendoscopy • Juvenile recurrent parotitis • Recurrent acute parotitis • Paediatric • Endoscopy

RIASSUNTO

Processo flogistico ricorrente non suppurativo e non ostruttivo della parotide, la parotite ricorrente giovanile (PRG) rappresenta la seconda patologia più frequente delle ghiandole salivari nell'infanzia. Gli attacchi ricorrenti ne costituiscono l'aspetto più serio e drammatico: incidono significativamente sulla qualità di vita e non esistono terapie preventive validate. Negli ultimi anni, la letteratura ha testimoniato la nascita di numerose esperienze internazionali correlate alla gestione della PRG con la scialoendoscopia. In questo contesto, molti autori hanno enfatizzato il ruolo cruciale della scialoendoscopia nella prevenzione degli attacchi di PRG. L'attuale revisione si propone l'obiettivo di valutare la letteratura esistente, con particolare riferimento agli aspetti diagnostici e terapeutici della scialoendoscopia applicata in pazienti affetti da PRG.

PAROLE CHIAVE: *Scialendoscopia • Scialoendoscopia • Parotite ricorrente giovanile • Parotite acuta ricorrente • Pediatrico • Endoscopia*

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Introduction

In childhood, parotid swelling is usually due to inflammation or microbial involvement of the parotid gland, although differential diagnosis includes mumps, Godwin's benign lymphoepithelial lesion, HIV, Mikulicz disease and Sjögren's syndrome [1 2]. After paramyxovirus infection (mumps), juvenile recurrent parotitis (JRP) is the second most frequent salivary gland affection [3]. Also known as recurrent acute parotitis or recurrent sialectatic parotitis, JRP is a recurrent non-suppurative and non-obstructive parotid inflammation, generally associated with intermittent painful swelling of one or both glands, often accompanied by redness and fever [4 5]. JRP usually occurs between 3 and 6 years of age and sex distribution favours males, although females are predominantly affected when the disease begins after puberty. Each episode – lasting for a few days up to a couple of weeks – may occur every 3-4 months, even though there are reports of cases with more than 10 events per year [4 6]. Symptoms are most often one-sided; in case of bilateral involvement, the disease appears to be significantly more symptomatic on one side.
Even if JRP usually vanishes spontaneously after puberty, in some cases the disease continues into adulthood, leading to a progressive loss of parenchymal function. Thus, surgery becomes unavoidable [4 5]. Lacking clear scientific evidence, the aetiology is still discussed and multifactorial causes have been suggested [4 7-9]. Diagnosis is achieved after the first attack (often ignored) and provided by careful medical history, clinical evaluation and imaging study. However, in the absence of a widely accepted consensus and universal guidelines, dissimilar diagnostic and therapeutic strategies have been described. Overall, conservative treatments provide an appropriate management of acute symptoms, through analgesics and antipyretic

drugs. The adoption of antibiotics is controversial and restricted to any potential suppurative evolution of inflammatory events. Steroids are administered only to reduce swelling, and no therapies are available to prevent recurrences [4 5 10 11].

The prevention of recurring attacks actually represents the most dramatic and serious aspect of this pathology. Recurrences not only significantly influence the quality of life, but they can also lead to progressive gland destruction, in rare cases though, and consequently to major interventions such as superficial or total parotidectomy [4 5].

In recent years, there have been many reports of international experiences related to the management of JRP by sialendoscopy. This relatively novel and promising device is designed to see inside the ductal system, and offers new perspectives for both diagnosis and treatment of benign salivary gland diseases [12]. In this context, several authors have stressed the striking role of sialendoscopy in prevention of JRP attacks.

Up to now, the emerging use of sialendoscopy in JRP has not been critically analyzed. The objective of the current review is to overview the existing literature with particular regards to diagnostic and therapeutic outcomes after the application of sialendoscopy in patients suffering from JRP.

Technical background

The need to utilize instruments with several technical features (high-resolution optical devices, resistant and easy to handle) has justified the use of different systems over the years. A valid compromise is represented by semi-rigid endoscopes, with intermediate characteristics between their flexible and rigid precursors. The presence in each endoscope of a specific irrigation channel represents the *conditio sine qua non* for ductal dilation and visualization. A working channel is required for the execution of therapeutic procedures beyond simple videoendoscopic exploration. Interventional sialendoscopy requires particular miniaturized tools as forceps, baskets, balloons, graspers, laser fibres and microdrills. Thanks to continuous technological progress, sialendoscopy is now an established procedure for salivary stones and ductal anomalies with recurrent gland inflammations in adult patients [12-15]. For all procedures, the first step is Stensen's papilla identification and dilation, using various types of dilatators. Depending on the latest manufacturers, the overall instrument diameter varies from 0.8 mm (without working channel) to 2.3 mm (with working channel), providing a resolution from 6,000 to 10,000 pixels [16]. Since the ductal paediatric diameter does not appear to be substantially different from that of adults, direct ductal visualization and interventional procedures using the latest generation endoscopes can be performed at any age [17].

Materials and methods

All existing clinical trials published in English and sourced through updated electronic databases (MEDLINE, EMBASE) were examined. The research was performed using the following keywords: "juvenile recurrent parotitis AND sialendoscopy OR sialoendoscopy OR endoscopy", "recurrent acute parotitis AND sialendoscopy OR sialoendoscopy OR endoscopy", "recurrent sialectatic parotitis AND sialendoscopy OR sialoendoscopy OR endoscopy", "paediatric AND sialendoscopy OR sialoendoscopy". Specifically, data concerning diagnostic and therapeutic outcomes in identified studies were reviewed to provide the evidence justifying sialendoscopy in JRP. Levels of evidence were assigned according to the Oxford Centre for Evidence based Medicine [18]. Searches were done at all stages, from the initial drafting of the paper to submission of the revised and final version. Review articles, letters, editorials and case reports were excluded.

Results

Ten clinical trials satisfied the research criteria. The included articles were analyzed and data were acquired to focus on the diagnostic (Table I) and therapeutic (Table II) aspects of sialendoscopy. No randomized controlled studies were found, and all outcomes were based on case series (level of evidence 4 – Table III). Two or more episodes of parotid swelling within 6-12 months were necessary to enrol patients to sialendoscopy after detailed and fully informed consent. Except for Konstantinidis and 20% of Schneider's population [19 22], each procedure was performed under general anaesthesia. The overall population was composed of 179 children (109 males, 70 females), average age 7.8 years, with a high prevalence of monolateral symptoms. The mean frequency of JRP events prior to sialendoscopy was 5.5 attacks per year. When reported, clinical examination always revealed widening of Stensen's papilla. The literature described sialectasia as the most common ultrasonographic (US) finding for diagnosis of JRP (mean 84%). Sialography confirmed sialectasis and identified kinks in one-third of Nahlieli's case series [28]. The most relevant and recognized sialendoscopic finding was the white wall appearance and lack of vascularity in the ductal layer (mean 75%). Furthermore, confined/diffused stenosis and multiple fibrinous debris/mucous plugs were noticed in a high percentage of children (mean 56% and 45%, respectively).

In all cases, interventional sialendoscopy was helpful as a treatment option through ductal irrigation with isotonic saline solution plus steroids. In anecdotic patients, the additional use of microdrills or balloon dilatation was required. A low percentage of children (mean 14%) was submitted to a second or more sialendoscopic procedures. A high rate of success was estimated for each report, with a significant complete resolution ("cured": mean 78%)

Table I. Sialendoscopy & JRP: literature review of diagnostic outcomes.

Authors	No. patients	No. parotid involvement		Mean age (years)	Sex (M:F)	Ultrasound findings (%)	Sialographic findings (%)	Sialendoscopic findings (%)
		Mono	Bi					
Schneider H[19]	15	9	6	7.5	10:5	Heterogeneous glands (100%) Sialectasia (100%)	NA	NA
Capaccio P[20]	14	8	6	7.9	8:6	Heterogeneous glands (100%) Sialectasia (100%)	NA	White ductal wall without vessels (100%) Fibrinous debris/mucous plugs (60%) Stenosis (100%) Kinks (30%)
Hackett AM[21]	12	5	7	9.7	7:5	NA	NA	White ductal wall without vessels (8%) Fibrinous debris/mucous plugs (75%) Stenosis (25%)
Konstantinidis I[22]	6	5	1	9.5	3:3	Sialectasia (100%)	NA	White ductal wall without vessels (100%) Fibrinous debris/mucous plugs (100%) Stenosis (50%)
Gary C[23]	3	3	0	9.0	3:0	NA	NA	White ductal wall without vessels (66%) Fibrinous debris/mucous plugs (66%) Stenosis (66%) Normal (34%)
Martins-Carvalho C[24]	18	NA		9.0	12:6	Heterogeneous glands (46%) Normal (27%) Lithiasis (18%) Sialectasia (9%)	NA	White ductal wall without vessels (100%) Stenosis (100%)
Jabbour N[25]	5	2	3	6.2	5:0	NA	NA	Fibrinous debris/mucous plugs (90%) Stenosis (10%)
Shacham R[26]	70	47	23	6.7	43:27	Sialectasia (100%)	Sialectasia (100%) Kinks (NA%)	White ductal wall without vessels (100%) Strictures & Kinks (NA%)
Quenin S[27]	10	3	7	5.0	4:6	Sialectasia (82%) Lithiasis (18%)	NA	White ductal wall without vessels (100%) Stenosis (100%) Fibrinous debris/mucous plugs (13%)
Nahlieli O[28]	26	20	6	7.0	14:12	Sialectasia (100%)	Sialectasia (100%) Kinks (31%)	White ductal wall without vessels (100%)

No. patients = number of patients with diagnosis of JRP submitted to diagnostic and interventional sialendoscopy
No. parotid involvement = number of monolateral (Mono) or bilateral (Bi) parotid involvement
NA = data not available

or frequency reduction ("improved": mean 22%) of JRP attacks (Table II). Mean operative time was available in only three reports. Hospital stay was noted in three articles (Table II). No major complications or side effects were observed. Hackett et al. described a possible ductal breech during sialendoscopy in a 16-year-old girl. A stent fashioned from a 3-Fr feeding tube was sutured in place with complete recovery 5 days later. The same team reported transient swelling and increased pain that resolved after antibiotic administration [21]. Another two authors reported upper airway obstruction in 11% of patients due to parotid swelling of the pharyngeal gland portion [24 27]. In all cases, such events were self-limiting and resolved spontaneously within 24 hours. Gary et al. documented a relatively high percentage of proximal duct stenosis that required papillotomy incision with subsequent complete "restitutio ad integrum" [23]. None of the published data reported follow-up times longer than 36 months (range 4-36 months). Specific details on type and size of endoscopes used are shown in Table III.

Discussion

The development of minimally invasive procedures has led to profound implications for patient management with recognized significance in the paediatric field. More specifically, sialendoscopy is a relatively novel and promising approach to salivary gland patholo-

Table II. Sialendoscopy & JRP: literature review of endoscopic treatment.

Authors	No. JRP attacks prior	Sialendoscopic treatment (%)	Mean time (min)	Repeated procedures (%)	Success (%)		Mean hospital stay (days)	Complications (%)	Follow-up (months)
					Cured	Improved (No. JRP attacks after)			
Schneider H[19]	7.2	Injection isotonic saline solution/steroids (100%)	NA	13%	NA	NA (2.4)	NA	NA	12
Capaccio P[20]	4.1	Injection isotonic saline solution/steroids/ antibiotics (100%)	20 min	21%	64%	36% (0.2)	NA	0%	30
Hackett AM[21]	5.0	Injection isotonic saline solution/steroids/ antibiotics (100%) Balloon dilatation (8%)	NA	25%	83%	NA (NA)	NA	Possible ductal breech (8%)	10
Konstantinidis I[22]	5.0	Injection isotonic saline solution/steroids (100%)	35.2 min	17%	67%	33% (NA)	0	0%	14
Gary C[23]	5.0	Injection isotonic saline solution/steroids (100%)	NA	0%	100%	0% (0)	1	Proximal duct stenosis (66%)	9
Martins-Carvalho C[24]	NA	Injection isotonic saline solution/steroids (100%) Balloon dilatation (NA%)	NA	17%	78%	NA (NA)	NA	Upper airway obstruction (11%)	24
Jabbour N[25]	7.0	Injection isotonic saline solution/steroids (100%) Balloon dilatation (10%)	NA	20%	60%	40% (2.0)	NA	0%	> 6
Shacham R[26]	6.0	Injection isotonic saline solution/steroids (100%) Balloon dilatation (6%) Microdrill (6%)	NA	7%	86%	13% (1.0)	NA	0%	6-36
Quenin S[27]	4.8	Injection isotonic saline solution/ steroids (100%)	57.0 min	10%	80%	10% (NA)	1	Upper airway obstruction (11%)	11
Nahlieli O[28]	NA	Injection isotonic saline solution/steroids (100%) Balloon dilatation (8%)	NA	8%	92%	NA (NA)	NA	0 %	4-36

No. JRP attacks prior = number of JRP attacks within 1 year prior to sialendoscopy/number of patients

No. JRP attacks after = number of JRP attacks within 1 year after sialendoscopy/number of patients

Repeated procedure (%) = Percentage of patients submitted to a 2nd or more sialendoscopic procedures

Mean time (minutes) = mean time needed for the sialendoscopic treatment

Success (%) = Percentage of patients who had complete symptoms resolution (cured), or frequency reduction of JRP attacks (improved)

NA = data not available

gies where technological advancements have allowed the valuable opportunity to see inside the ductal system. First introduced in the 1990s by Katz et al. [29] in France and Königsberger et al. in Germany [30], salivary gland videoendoscopy became an established procedure after standardization and made widely known by Francis Marchal and Oded Nahlieli [31 32]. Since then, several authors have described sialendoscopy as a suitable device for benign salivary gland disorders with validated effectiveness and safety in adults [12-15 33]. In the last 10 years, many international and authoritative experiences have assessed sialendoscopy for the diagnostic and therapeutic management of JRP [19-28]. High success rates and low morbidity seem to justify the increasing use of sialendoscopy in JRP, even if a comprehensive analysis of documented outcomes has not yet been reported [34].

JRP is the second most frequent salivary gland disease in childhood, defined as a recurrent non-suppurative and

Table III. Sialendoscopy & JRP: general features and level of evidence.

Authors	Published year	Country	Journal	Type of endoscope (outer diameter, mm)	Level of evidence*
Schneider H[19]	2013	Germany	Laryngoscope	Erlangen (0.8, 1.1)	4 (Case-series)
Capaccio P[20]	2012	Italy	J Laryngol Otol	Erlangen (0.8)	4 (Case-series)
Hackett AM[21]	2012	USA	Arch Otolaryngol Head Neck Surg	NA (1.1, 1.3)	4 (Case-series)
Konstantinidis I[22]	2011	Greece	Int J Pediatr Otorhinolaryngol	Marchal (1.1)	4 (Case-series)
Gary C[23]	2011	USA	J Indian Assoc Pediatr Surg	Erlangen (0.8, 1.1) Marchal (1.3)	4 (Case-series)
Martins-Carvalho C[24]	2010	France	Arch Otolaryngol Head Neck Surg	NA (0.9 + Sheath diameter) Marchal (1.3)	4 (Case-series)
Jabbour N[25]	2010	USA	Int J Pediatr Otorhinolaryngol	NA (1.1)	4 (Case-series)
Shacham R[26]	2009	Israel	J Oral Maxillofac Surg	Modular salivascope (0.9-1.1)	4 (Case-series)
Quenin S[27]	2008	France	Arch Otolaryngol Head Neck Surg	NA (0.9 + Sheath diameter) Marchal (1.3)	4 (Case-series)
Nahlieli O[28]	2004	Israel	Pediatrics	Nahlieli (1.3)	4 (Case-series)

NA = data not available
**A level of evidence was assigned in accordance with the study design*

non-obstructive parotid inflammation. At present, its aetiology remains unknown: genetic, infectious, allergic and immune-mediated causes have all been proposed. Diagnosis is achieved after the first attack (often ignored) and achieved by careful medical history, clinical evaluation and imaging study. Among imaging techniques, US is considered the first diagnostic step for salivary gland disorders. From the literature, it emerges that in a relevant number of cases, Martins-Carvalho et al. [24] and Quenin et al. [27], did not report any significant US findings, which were somewhat confusing and puzzling. This again highlights the disadvantages of an operator-dependent procedure. Direct endoscopic exploration permits differential diagnosis among dissimilar causes of obstruction [24 35]. Sialography has been demonstrated to be useful in detecting ductal anomalies, even though its application is limited by the presence of ionizing radiation [28]. Katz et al. published the largest study to date in JRP with an average follow-up of 5.5 years. A total of 840 children suffering from JRP were submitted to sialography with iodinated oils which provided both diagnosis and effective treatment. Complaints recurred in 98% of patients with a symptom-free interval ranging from 6 to 18 months [36]. The most relevant and recognized sialendoscopic finding was represented by a white, avascular and stenotic lining of Stensen's duct. The lack of a natural vascularisation detected sialendoscopically might constitute a possible causative agent to JRP. In particular, an abnormal pattern of vascularization may invalidate the sphincteral system of the parotid gland [28]. The reduced ability to drain saliva would then trigger an inflammatory vicious circle (salivary flow decrease, debris accumulation, obstruction, inflammation) [25], which could lead to more than 10 recurrences per year [6].

The prevention of this domino effect, being the goal of the therapeutic procedure, currently represents a genuine challenge for both surgeons and patients. Sialendoscopy breaks the cycle of inflammation by washing out intraductal debris and dilating stenosis [25]. The striking importance of early diagnosis and efficient therapy to avoid gland destruction [17 36] may justify the need for general anaesthesia in the majority of procedures. Historically, treatment of JRP included conservative or invasive methods, and no preventive therapies were available. Acute events were managed with symptomatic drugs, warmth and massages, sialogogic agents, steroids, antibiotics and duct probing. Even if no study has confirmed the benefit of prophylactic antibiotics during winter or dehydration prevention, all these measures have been attempted to obviate recurrences [4 5 10 11]. Anecdotally, oral appliance/orthotic therapy is another therapeutic effort that has been documented in a small population of children for a short follow-up time [37]. When recurrent attacks continue into adulthood with irreversible glandular damage, invasive procedures are required. Among surgical techniques, Stensen's duct ligation, tympanic neurectomy, superficial or total parotidectomy have been described, while only the latter is curative and associated with high risk including facial nerve damage [4 5 38-41]. Major operations should not

be considered exceptional however: two of the reviewed case series reported medical histories positive for parotidectomy [21 26].

In 179 children reported across 10 studies, complete evanescence of the symptoms after sialendoscopic treatment was observed in 78% of patients and partial regression in 22% of the cases. International experiences have shown the feasibility of paediatric sialendoscopy allowing Stensen's duct examination and secondary duct visualization, when possible. No major complications were documented and the low associated morbidity justified the procedure on the healthy gland [26 28]. A debated question is whether outcomes are the consequences of the natural JRP history or the effects of the procedure itself. Although the physiopathology of JRP is still poorly understood, the high success rate achieved after the first treatment in patients with a relevant number of recurrences and at an average age much far from the expected vanishing limit, supports the positive role of sialendoscopy in JRP prevention. Nevertheless, many factors weaken the strength of the evidence justifying sialendoscopy in JRP:

- all outcomes were based on case series in the absence of a control group and randomization (level of evidence 4);
- relatively small population: considering that some of the Authors belonged to the same centre (e.g. Martins-Carvalho et al. [24] and Quenin et al. [27] to Edouard Herriot University Hospital; Nahlieli et al. [28] and Shacham et al. [26] to Barzilai Medical Centre) there might be some overlap of the analyzed groups;
- results were documented without homogeneous long-term follow-up.

Overall, potential benefits also exist with respect to the limits described above, considering the diagnostic and therapeutic advantages, minimal morbidity and the lack of other recognized options for prevention. The promising impact of sialendoscopy on the quality of life remains a crucial clinical aspect that undoubtedly requires higher levels of supporting evidence.

Conclusions

The encouraging results of the diagnostic and therapeutic role of sialendoscopy emphasize the advantages of this new tool for management of JRP. However, long-term follow-up and randomized prospective studies are needed to verify these outcomes before such benefits can be fully assessed.

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HEAD AND NECK

Functional results of microvascular reconstruction after hemiglossectomy: free anterolateral thigh flap *versus* free forearm flap

Risultati funzionali delle ricostruzioni microvascolari in seguito ad emiglossectomia: lembo libero anterolaterale di coscia versus lembo libero radiale

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SUMMARY

The aim of the present study is to assess functional outcomes after hemiglossectomy and microvascular reconstruction. Twenty-six patients underwent primary tongue microvascular reconstruction after hemiglossectomy. Twelve patients were reconstructed using a free radial forearm flap and 14 with an anterolateral thigh flap. Speech intelligibility, swallowing capacity and quality of life scores were assessed. Factors such as tumour extension, surgical resection and adjuvant radiotherapy appeared to be fundamental to predict post-treatment functional outcomes. The data obtained in the present study indicate that swallowing capacity after hemiglossectomy is better when an anterolateral thigh flap is used. No significant differences were seen for speech intelligibility or quality of life between free radial forearm flap and anterolateral thigh flap.

KEY WORDS: Hemiglossectomy • Free anterolateral thigh flap • Free radial forearm flap • Functional outcomes • Microsurgery

RIASSUNTO

Lo scopo del presente studio è di valutare i risultati funzionali delle ricostruzioni linguali microvascolari in seguito ad emiglossectomia. Venti sei pazienti sono stati sottoposti a ricostruzione microvascolare primaria. Dodici di questi sono stati ricostruiti usando il lembo libero radiale e quattordici usando il lembo anterolaterale di coscia. L'intellegibilità del linguaggio, la capacità deglutitoria e la qualità della vita sono stati i parametri considerati nella valutazione dei risultati. Variabili legate all'estensione del tumore, alla resezione chirurgica ed al trattamento adiuvante sono risultati essere fondamenti nel predire i risultati funzionali post-operatori. I dati ottenuti da tale studio hanno mostrato come la capacità deglutitoria sia sensibilmente migliore nelle ricostruzioni con il lembo libero anterolaterale di coscia rispetto al lembo radiale. Non altrettanto significative sono risultate le differenze tra le due modalità ricostruttive per quanto riguarda l'intellegibilità del linguaggio.

PAROLE CHIAVE: *Emiglossectomia • Lembo libero anterolaterale di coscia • Lembo libero radiale • Risultati funzionali • Microchirurgia*

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Introduction

The most common sites of primary oral squamous cell carcinomas (OSCCs) are the tongue and the floor of the mouth [1]. Surgery remains the mainstay for oral cavity cancer treatment. Approximately 40% of all OSCC patients referred for treatment require resection of the tongue to varying degrees [2]. Immediate reconstruction should be performed after complete excision of the tumour. Quality-of-life (QoL) studies have shown that speech, chewing and swallowing are the most important factors for patients undergoing head and neck surgery [3].

With respect to these functions, significantly poorer results are achieved in patients who have undergone total or partial glossectomy than in those who have undergone resection of the soft palate [4]. The severity of functional impairment is influenced not only by the site of the tumour, but also by the extent of surgical resection. Reconstruction of the tongue is necessary when oral cavity obliteration, palatal contact and mobility will adversely affect normal swallowing and speech [5].

Owing to advancements in microsurgical techniques, more extensive resections are now possible. The aim of reconstruction is to maximize oral functions and aesthetics with less morbidity, and preserving speech, swallowing and reducing donor site morbidity [6]. The current theories about oral reconstruction advocate microsurgery as standard treatment for restoring oral functions in both young and elderly patients [7 8]. A defect orientated approach may

be helpful for deciding which type of flap should be used for reconstruction of the head and neck [9-12].

For years, the free radial forearm flap (FRFF) has been the first choice to restore soft tissue ablation in the oral cavity [13] despite several disadvantages, such as sacrifice of the most important artery of the hand [14].

Recently, the anterolateral thigh flap (ALTF) has challenged the superiority of FRFF [15]. ALTF can be thinned, it does not need a skin graft and does not risk damage to tendons or hands [16].

The heterogeneous functional data reported in the recent literature about speech and swallowing after tongue microvascular reconstruction prompted the present study. To assess differences between FRFF and ALTF, this investigation compares functional outcomes after hemiglossectomy and microvascular reconstruction.

Patients and methods

Twenty-six patients underwent primary tongue microvascular reconstruction after hemiglossectomy from June 2006 to April 2011 at the Maxillofacial Department of Bologna University. All patients were afflicted with OSCC. No bone involvement was diagnosed. Tumour excision was performed through a trans-mandibular approach or pull-through technique. The extension of the resection was hemiglossectomy or hemipelviglossectomy in all cases. With respect to the surgical procedure, hemiglossectomy was defined as resection of at least 50% of the mobile tongue. The base of the tongue was preserved in all cases. No bone resections were performed. TNM stage and defect size are listed in Table I. All patients underwent neck dissection. Neck dissection was modified neck dissection (MRND) in 20 patients and selective neck dissection (SND) in the remaining 6 patients. Bilateral neck dissection was performed in 2 patients (Table I). Neck dissection on the contralateral side was usually selective neck dissection (SND). In all patients, both hypoglossal nerves were preserved at the level of the digastric muscle above the carotid triangle.

Adjuvant therapies were required in 15 of the 26 patients. None of the patients had neo-adjuvant therapy (Table I). Twelve patients were reconstructed using a FRFF

Table I. TN classification and treatment modality.

TN classification	No. of patients (%)
T2	4 (15)
T3	16 (62)
T4	6 (23)
N0	6 (23)
N1	12 (46)
N2	8 (31)
Treatment	
Extent of resection	
Hemiglossectomy	16 (62)
Hemipelviglossectomy	10 (38)
Neck dissection	
MRDN	20 (77)
SND (SOHND)	6 (23)
Bilateral (MRND+SND)	2 (7)
Adjuvant therapy	
Radiation therapy (55-59 Gy IMRT)	11 (42)
Chemo-radiation therapy	4 (16)
No adjuvant therapy	11 (42)

MRDN: modified radical neck dissection; SND: selective neck dissection; SOHND: supraomohyoid neck dissection; IMRT: intensity-modulated radiation therapy.

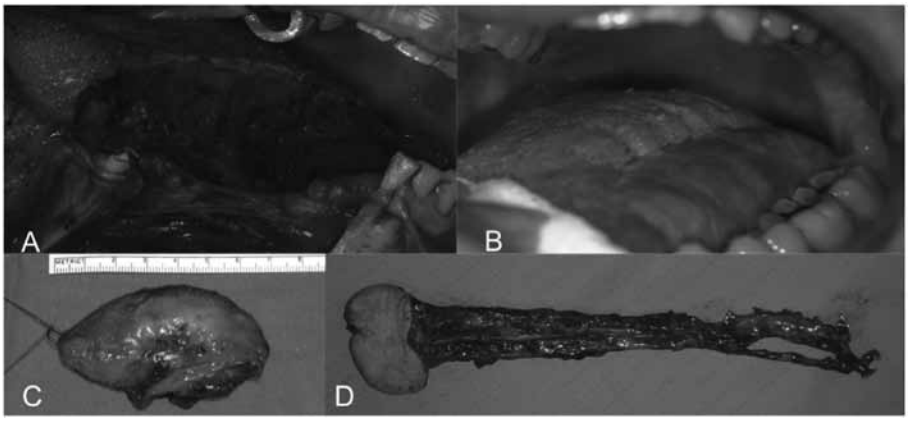

Fig. 1. A. hemiglossectomy through a trans-mandibular approach. B. Tongue appearance after microvascular reconstruction using a free radial forearm flap at 12 months post-operatively. C. Surgical specimen. D. Free radial forearm flap.

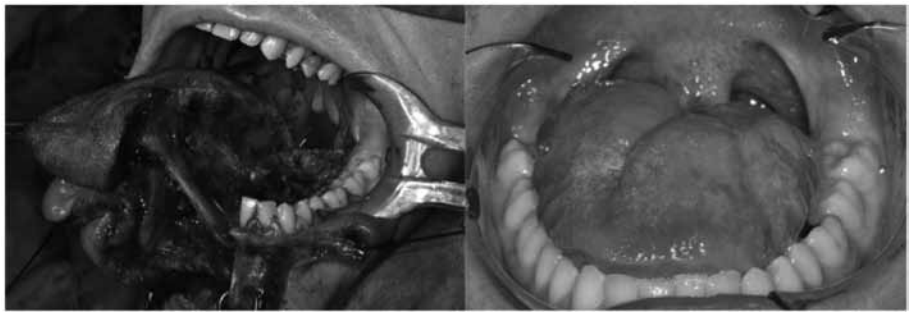

Fig. 2. Tongue reconstruction after hemiglossectomy. Left side: hemiglossectomy through a trans-mandibular approach. Right side: Tongue appearance after microvascular reconstruction using an anterolateral thigh flap at 12 months post-operatively.

(group A) (Fig. 1) and 14 employing an ALTF (group B) (Fig. 2). Microvascular reconstructions were performed by the Plastic Surgery team at the same University Hospital.

All subjects enrolled in this study were assessed by a speech therapist before and after ablative surgery. Patients started a swallowing and speech rehabilitation programme as soon as their clinical condition allowed correct receptivity, usually 1-2 weeks after surgical reconstruction. Functional outcomes were assessed 6, 12 and 24 months after reconstruction.

Functional evaluations

Information on demographic characteristics, TNM classification, stage of disease, treatment methods, microvascular and donor-site complications, postoperative recovery, speech intelligibility, swallowing capacity and quality of life scores were recorded. Speech was evaluated postoperatively by one of the authors (AT) according to the method described by Taguchi [17], in which the patient's speech was rated on a scale of 1 to 5 according to its understandability during conversation. The scores are defined as follows: 1. speech can be clearly understood; 2. speech is occasionally misunderstood; 3. speech is understood only when the context of the text is known to the listener; 4. speech is occasionally understood; and 5. speech cannot be understood at all. To grade the results and to analyze the final outcome in relation to other clinical factors, speech intelligibility was classified more broadly as either good (scores 1-2), acceptable (score 3) or poor (scores 4-5).

A swallowing ability scale system (SAS) [18] was used to assess swallowing capacity. The scoring system is based on the MTF classification: the method of food intake (M), the time required for food intake (T) and the consistency of the food that can be ingested (F). For each of these parameters, 5 subgroups are identified and scored, as given in the following. The method of food intake (M) is classified and scored as follows: M5, capacity for swallowing is unlimited (5 points); M4, capacity for swallowing anything, but care must be taken to avoid aspiration (4 points); M3, capacity to eat anything if the food is prepared in a suitable form (3 points); M2, capacity to eat small portions of food, but tube feeding is the main means of ingestion (2 points); and M1, tube-feeding is the only method of ingestion (1 point). The time required for food intake (T) is assessed according to the average time required to eat a daily meal (irrespective of its nature and consistency). This parameter is classified and scored as follows: T5, normal food intake time, < 15 min (5 points); T4, intake of food requires 15 to 25 min (4 points); T3, intake of food requires 25 to 35 min (3 points); T2, intake of food requires 35 to 45 min (2 points); and T1, intake of food requires more than 50 min, or is impossible (1 point).

The consistency of the food that a patient is able to ingest (F) is classified and scored as follows: F5, capacity to eat food of any consistency (5 points); F4, capacity to eat soft, chewable food, such as cooked rice or cooked vegetables (4 points); F3, capacity to eat gruel (3 points); F2, capacity to swallow viscous fluids (2 points); and F1, capacity to swallow only no viscous fluids (1 point). To grade the results and to analyze the final outcome in relation to other clinical factors, outcome was classified more broadly as either poor (MTF score ≤ 6 points), acceptable (MTF score 7-8 points), or good (MTF score 9-15 points).

Video-fluoroscopic examination was performed for only 6 patients in the study (5 from group B and 1 from group A). Video-fluoroscopic examinations were not considered in the results because they were partial compared to the total cohort.

Patient-reported functional outcomes and quality of life were compared between groups using the Head and Neck 35 module of the European Organisation for Research and Treatment of Cancer (EORTC H&N35) quality of life questionnaire [19]. QoL data were recorded at 6, 12 and 24 moths after surgery.

Reconstructive complications were evaluated. Complications were divided into donor-site and flap complications using Classen and Ward's [20] classification. The numbers of patients who developed donor-site complications were compared between groups. Flap complications were classified as major (requiring surgical re-exploration) or minor (all others), and frequencies were calculated for each group.

Statistical analysis

Univariate and multivariate statistical analyses were performed. Chi-square analysis with Fischer's exact test was performed to determine the influence of the reconstruction (group A or B) on speech, swallowing, QoL and patient-reported functional outcomes. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using the SPSS® Advanced Statistical™ software package (ver. 13; SPSS Inc., Chicago, IL, USA).

Results

Demographics and reconstructive outcomes

The age of patients ranged from 24 to 76 years with a median age of 50 years; 66% of patients were men. Fifteen patients had a partner, and F58% of the sample smoked at inclusion. Ten patients had no alcohol consumption at tumour diagnosis; 10 patients had a comorbidity.

Minor flap complications, which did not require surgical revision, were observed in 3 patients. Two of these were in group A and the other in group B. Total flap loss never occurred in this series.

No complications afflicted the donor site for ALTF. Two weeks was the mean time for complete healing of the thigh

donor area. Mean time for healing for the forearm donor site area was 4 weeks. Two forearm donor sites healed for second intention in approximately 30% of the grafted area, probably due to intense tendon mobility.

Speech intelligibility

All 26 patients underwent postoperative speech therapy according to the hospital's protocol. The last speech evaluation was conducted 24 months after surgery. The evaluation revealed speech intelligibility to be good in 15 patients (57.5%), acceptable in 10 (38.5%) and poor in 1 (4%).

The relationship between free flap reconstruction, surgical resection, neck dissection, adjuvant therapy and speech intelligibility is shown in Table II. Group A had better speech intelligibility outcomes: 9 patients had a "good score", and 3 patients had an "acceptable score". The difference for speech intelligibility between groups was not statistically significant (Fischer's exact test p = 0.73). Adjuvant radiotherapy (p = 0.045) and resection extended to the floor of the mouth (p = 0.049) were predictive of worst speech intelligibility.

Patients reported functional outcomes assessed 24 months after treatment using the EORTC H&N35 quality of life questionnaire showed a better result for patients in group A. Indeed, patients reconstructed using FRFF had a score of 62, while patients reconstructed using ALTF had a score of 57. However, this difference was not statistically significant (p = 0.14).

Swallowing capacity

Swallowing therapy was initiated at the time the patients were first permitted to drink water, namely, 7 to 10 days after surgery. Feeding was initially supplemented by nasogastric intubation in all patients. Perioral ingestion without supplementary feeding was achieved in all patients. During the rehabilitation period, swallowing function and degree of aspiration were monitored using videofluoroscopy for only six patients (1 in group A and 5 in group B). The final evaluation of swallowing capacity was however based on the clinical MTF scores and the EORTC H&N35 questionnaire. The last evaluation of swallowing capacity was conducted at 24 to 36 months after surgery (average, 30 months). No patients had a poor outcome at the time of the functional evaluation. The outcome was considered to be acceptable in 7 patients. All of these were in group A. The outcome was considered to be good in 19 patients (5 in group A, and 14 in group B).

The relationship between MTF and the various treatment factors is shown in Table III. Group B had a significantly better MTF score than group A (p = 0.046).

With regard to surgical resection, multivariate analyses showed that pelvectomy (p = 0.039) and adjuvant radiotherapy (p = 0.040) were predictive factors of worse swallowing capacity at 24 months after treatment. No significant differences were recorded with regard to the type of neck dissection (p = 0.28). The EORTC H&N35 quality of life questionnaire showed better patient reported outcomes for group B (score, 65 points) compared to group A (score 59).

Table II. Speech intelligibility in relation to free flap, surgical resection, neck dissection and adjuvant therapy.

Factor	Good	Acceptable	Poor	p value
Free flap				
Group A	9	3	0	
Group B	6	7	1	p = 0.73
Surgical resection				
Hemiglossectomy	12	4	0	
Hemipelviglossectomy	3	6	1	p = 0.049*
Neck dissection				
MRND	10	9	1	
SND	5	1	0	p = 0.80
Adjuvant therapy				
Yes	5	9	1	p = 0.045*
No	10	1	0	

Statistically significant

Table III. MTF scores in relation to free flap, surgical resection, neck dissection, adjuvant therapy.

Factor	MTF Good	MTF Acceptable	MTF Poor	p value
Free flap				
Group A	5	7	0	
Group B	14	0	0	p = 0.046*
Surgical resection				
Hemiglossectomy	13	3	0	
Hemipelviglossectomy	6	4	0	p = 0.039*
Neck dissection				
MRND	13	7	0	
SND	6	0	0	p = 0.28
Adjuvant therapy				
Yes	8	7	0	p = 0.040*
No	11	0	0	

Statistically significant

Discussion

In the present study, speech intelligibility and swallowing capacity of 26 patients who had undergone hemiglossectomy either with or without pelvectomy (with preservation of base of the tongue) and free flap reconstruction using FRFF (group A) or ALTF (group B) for OSCCs were evaluated. Speech intelligibility and swallowing capacity were satisfactory (acceptable or good) in more than 90% of patients. Although not statistically significant, differences in speech intelligibility between groups were identified in favour of group A. QoL data confirmed this trend. The possible explanation of these results could be that a thinner and more pliable flap as FRFF may restore speech articulation more easily than ALTF. Both more extensive surgical resection (pelvectomy) and adjuvant radiotherapy are factors predictive of worse speech intelligibility recovery.

Swallowing capacity outcomes were better for patients reconstructed using ALTF (group B). The tongue is crucial for propelling a food bolus toward the pharynx. The role played by the anterior part of the tongue in speech is linked to the pressure it exerts on the palate. These functions call for reconstructed tissue volumes that are sufficiently large to cover the defect, ensure minimal scarring and furnish an adequate residual bulk that will compensate for long-term shrinkage. It is probable that the oral phase of swallowing can benefit from a more bulging reconstruction, which restores the physiological contact tongue-palate. Another goal of the anterior part of the reconstructed tongue is to optimize the residual "finger function". Finger function is the ability of the tongue to sweep and clear the buccal, labial and alveolar sulci, and protrude past the coronal plane of the incisors [21].

As shown by Kimata [22], the shape and the bulk of the reconstructed tongue are closely correlated with postoperative swallowing capacity. These functions were better in patients with a protuberant or semi-protuberant reconstructed tongue than in those with a flat or depressed one. On the basis of these findings, the authors advocated the use of broad, thick flaps. In clinical practice, however, it is extremely difficult to control the subsequent volume reduction and sagging of the flap, in particular when postoperative radiotherapy is performed.

More extensive surgical resections comprehensive of floor of the mouth showed poorer outcomes considering swallowing function. This occurred regardless of the type of reconstruction. The post-surgical changes in hyoid and laryngeal elevation could occur as a result of surgical detachment of the anterior attachment of the floor of mouth muscles. These muscles are generally considered responsible for the forward and upward movement of the hyoid and larynx. Cutting or damaging these muscles may have significantly changed their line of pull upward on the hyoid and larynx. This possible interpretation was also postulated by Paulosky in 1995 [23].

For both groups, radiotherapy was a predictive factor for worse functional prognosis. For patients undergoing adjuvant radiotherapy, the negative effect related to radiation also involved the oropharyngeal phase of swallowing. Movement of the tongue base and posterior pharyngeal wall toward each other until full contact is achieved is the key element in producing pharyngeal bolus driving pressure and effective bolus clearance through the pharynx [24]. When the field of postoperative radiotherapy includes the oropharynx or neck, the pharyngeal constrictors and tongue base will be included in the treatment volume. Increased fibrosis of the pharyngeal musculature after completion of radiotherapy may be expected to have a negative impact on pharyngeal bolus clearance, even in patients whose resections are limited to the anterior oral cavity.

With regard to reconstructive complications in our study cohort, we observed two minor complications for group A and one for group B. According to the recent literature [25], we observed better aesthetic results and minor donor site morbidity for ALTF. However, some modified closure techniques have recently been developed to reduce skin tension that provides subsequent improvement of the cosmetic appearance of the forearm donor site [26].

Recently, some authors have shown that the ulnar artery is dominant at the elbow, but after originating its collateral branches, the radial artery becomes the dominant artery in the distal forearm and, consequently, is the major source of vascularization to the hand [88]. Consequently, FRFF always sacrifices the major artery of the limb and leads to unattractive scars in the forearm region. This may produce not only objective complications like stiffness, pain or numbness, but also subjective complaints such as poor cosmetic intolerance.

In conclusion, functional results are difficult to assess in the heterogeneous oral cancer population. Factors such as surgical resection and adjuvant radiotherapy are fundamental to predict post-treatment functional outcomes. Data obtained in the present study indicate that swallowing capacity after hemiglossectomy or hemipelviglossectomy is better when an ALTF is used. No significant differences were seen for speech intelligibility between FRFF and ALTF. To establish the optimal treatment protocol for patients undergoing major glossectomy, however, further prospective studies and quality of life assessments involving greater numbers of patients are necessary.

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Head and neck

Cost analysis in oral cavity and oropharyngeal reconstructions with microvascular and pedicled flaps

Analisi dei costi nelle ricostruzioni orali e orofaringee con lembi microvascolari e peduncolati

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SUMMARY

Reconstructive surgery of the head and neck region has undergone tremendous advancement over the past three decades, and the success rate of free tissue transfers has risen to greater than 95%. It must always be considered that not all patients are ideal candidates for free flap reconstruction, and also that not every defect strictly requires a free flap transfer to achieve good functional results. At our institution, free flap reconstruction is first choice, although we use pedicled alternative flaps for most weak patients suffering from severe comorbidities, and for pretreated patients presenting a second primary or a recurrent cancer. From July 2006 to May 2010, 54 consecutive patients underwent soft tissue reconstruction of oral cavity and oropharyngeal defects. We divided the cohort in three groups: Group 1 (G1): 16 patients in good general conditions that received free radial forearm flap reconstruction; Group 2 (G2): 18 high-risk patients that received a reconstruction with infrahyoid flap; Group 3 (G3): 20 patients that received temporal flap (10 cases) or pectoral flap (10 cases) reconstruction. We must highlight that pedicled alternative flaps were used in elderly, unfavourable and weak patients, where usually the medical costs tend to rise rather than decrease. We compared the healthcare costs of the three groups, calculating real costs in each group from review of medical records and operating room registers, and calculating the corresponding DRG system reimbursement. For real costs, we found a statistically significant difference among groups: in G1 the average total cost per patient was € 22,924, in G2 it was € 18,037 and in G3 was € 19,872 (p = 0.043). The amount of the refund, based on the DRG system, was € 7,650 per patient, independently of the type of surgery. Our analysis shows that the use of alternative non-microvascular techniques, in high-risk patients, is functionally and oncologically sound, and can even produce a cost savings. In particular, the infrahyoid flap (G2) ensures excellent functional results, accompanied by the best economic savings in the worst group of patients. Our data reflect a large disconnection between the DRG system and actual treatment costs.

KEY WORDS: Healthcare costs • Cost analysis • Pedicled flap • Microvascular free flap • Infrahyoid flap • Head and neck reconstruction

RIASSUNTO

La chirurgia ricostruttiva del distretto testa-collo è avanzata enormemente nel corso degli ultimi tre decenni. Il tasso di successo dei lembi liberi rivascolarizzati supera il 95%. Si deve però considerare che non tutti i pazienti sono dei candidati ideali per la ricostruzione con lembi liberi; inoltre, non tutti i difetti necessitano strettamente di una ricostruzione microvascolare per ottenere buoni risultati funzionali. Presso il nostro Istituto, la ricostruzione con lembi liberi è solitamente la prima scelta, tuttavia usiamo lembi peduncolati come alternativa in pazienti con gravi comorbidità generali, e in pazienti pre-trattati nei quali ci attendiamo una compromessa affidabilità dei vasi del collo. Da luglio 2006 a maggio 2010, 54 pazienti consecutivi sono stati sottoposti a ricostruzione dei tessuti molli del cavo orale e/o orofaringe. Abbiamo diviso i pazienti in tre gruppi: Gruppo 1 (G1): 16 pazienti in buone condizioni generali che hanno ricevuto una ricostruzione con lembo libero di avambraccio; Gruppo 2 (G2): 18 pazienti ad alto rischio sottoposti a ricostruzione con lembo infraioideo; Gruppo 3 (G3): 20 pazienti che hanno ricevuto un lembo temporale (10 casi) o un lembo pettorale (10 casi). È importante sottolineare che i lembi peduncolati sono stati utilizzati in pazienti anziani, compromessi da un punto di vista generale, in cui di solito le spese mediche tendono ad aumentare piuttosto che diminuire. Abbiamo confrontato i costi sanitari dei tre gruppi, sia esaminando le cartelle cliniche e i registri di sala operatoria, sia calcolando i rimborsi previsti dal Servizio Sanitario Nazionale tramite il sistema DRG. Per quanto riguarda i costi reali, abbiamo trovato una differenza statisticamente significativa tra i gruppi: in G1 il costo medio totale per paziente è stato di € 22.924, in G2 di € 18.037, ed € 19.872 in G3 (p = 0,043). L'importo del rimborso, basato sul sistema DRG, è stato di € 7.650 per ogni paziente, indipendentemente dal tipo di intervento chirurgico. La nostra analisi mostra come l'utilizzo di lembi peduncolati alternativi, in pazienti ad alto rischio, non sia soltanto adeguato dal punto di vista funzionale ed oncologico, ma come sia in grado di produrre un risparmio economico. In particolare, il lembo infraioideo (G2) garantisce ottimi risultati funzionali accompagnati dai migliori risultati economici, questo nel gruppo di pazienti più fragili. I nostri dati riflettono un divario significativo tra il sistema DRG e i costi effettivi del trattamento.

PAROLE CHIAVE: *Costi sanitari • Analisi dei costi • Lembo peduncolato • Lembo libero microvascolare • Costo • Lembo infraioideo • Ricostruzione testa-collo*

Introduction

The application of microvascular free flaps is the most widespread method currently employed for the reconstruction of extensive defects after resection of head and neck cancer because of their versatility and reliability. The success rate of free tissue transfers has risen to greater than 95%, and fascio-cutaneous free flaps (i.e. free radial forearm flap, free antero-lateral thigh flap) are currently considered the gold standard for soft tissue reconstruction of oral cavity and oropharyngeal defects [1-3]. A recent report showed that in the United States free flap reconstruction of the head and neck is even profitable, and generates substantial revenue for the hospital [3]. Is such a scenario also valid in Italy? In fact, the complexity of modern head and neck reconstruction is paralleled by consumption of large amounts of resources, provided by both treating physicians as well as the institution. In times of increasing economic constraints, analysis of the financial value of providing these services seems worthwhile. Free flap reconstruction requires special knowledge and surgical skills, dedicated personnel and tools, careful postoperative monitoring [5 6]. Accordingly, it has been hypothesized that adopting microvascular reconstructive techniques could lead to an increase in healthcare costs [7 8]. Our interest on this subject arises from our institutional policy of treating, with alternative pedicled flaps, most weak patients suffering from severe comorbidities [9 10], pretreated patients presenting a second primary or a recurrent cancer and patients with major vessel exposure [11 12]. In fact, not all patients are ideal candidates for free flap reconstruction [13], and not every defect strictly requires a free flap transfer to achieve good functional results [14 15], thereby minimizing medical complications and mortality [16].

DRG is the acronym of "Diagnosis-Related Group", and indicates the remuneration system to the hospital based on healthcare activities. The system was created in the early 1980s by Professor Fetter of Yale University [17], and has been utilized in Italy since 1995. In Fetter's prototype, the hospital is defined as a company that provides numerous products. The first step is to classify each clinical case in one of 467 groups. Next, starting from inputs represented by the available resources, the hospital develops a defined number of outputs for each patient that are fitted on the starting health status. All these outputs are directed to obtain a final product: diagnosis and/or treatment (defined as the evaluation and/or any change in the state of health of the patient). Fetter developed a classification system for discharged patients, identifying subgroups of patients receiving a similar pattern of outputs, and assuming that similar diseases, treated in similar institutions, need a similar consumption of human and material resources. With this system, the hospital is remunerated using predetermined rates. Each resigned patient is attributed to a specific DRG, calculated using a Software Grouper that, through a process of hierarchical combination of information contained in the hospital discharge card (in Italy called *Scheda di Dimissione Ospedaliera*, SDO), automatically assigns each group. The SDO contains: the main discharge diagnosis (encoded with ICD9-CM, a classification system in which diseases and traumas are ordered with an epidemiological aim), any received treatment or procedure and the patient's general information.

The DRG code assignment is based on three steps:

- assignment to one of 25 "Major Diagnostic Categories" (MDCS), based on the ICD9-CM encoded main discharge diagnosis;
- assignment to a subgroup after surgical "Medical" or "Surgical".

Then consider:

- type of intervention (for surgical DRG);
- age;
- further disorders and/or complications related to the main discharge diagnosis;
- discharge status (alive, deceased, resigned against the advice of physicians, transferred to another Department).

Once codified, each DRG will have its weight, and the software will provide the fraction of DRG's value compared to a full DRG. Each DRG corresponds to a tariff.

To calculate the total reimbursement of a DRG, it is therefore necessary to apply the following formula:

Cost = (fraction of DRG's value) × DRG's point

It must be specified that the DRG's point value, in Italy, varies from region to region, and that for each DRG there is a threshold value, expressed in days, which is the length of hospitalization considered outside the threshold. Outside this limit, the applied additional remuneration per day is much less consistent than within the threshold. In this study, we compared the real costs of microvascular *vs.* alternative pedicled flap reconstructions, and we calculated the reimbursement based upon the DRG system.

Materials and methods

From July 2006 to May 2010, 86 consecutive patients with oral cavity or oropharyngeal squamous cell carcinomas underwent head and neck reconstruction by a single operator (AD), using microvascular free flaps or alternative pedicled flaps. We selected cases where the surgical defect (resulting from pull-through or transmandibular approaches) put the oral cavity and/or the oropharynx in communication with neck spaces, and we excluded reconstructions after segmental bony resections (mandibular resections/maxillectomy), thus result-

Table I. Functional analysis.

Score	Diet	Speech
1	regular diet without restrictions	always understandable
2	moist or soft diet	usually understandable, but with frequent repetition or face to face contact required
3	liquid diet	difficult to understand, even with face to face contact
4	tube-dependent intake	never understandable, with written communication required

ing in a study population of 54 patients. After analysis of medical records and surgical registers, we recorded the following for each patient: all examinations and visits carried out during pre-operative evaluation; tumour site, clinical and pathological staging (in accordance with the 7th edition of TNM classification system) [18]; type of reconstructive procedure, surgical and reconstructive time, materials and drugs used during surgery; days of hospitalization in intensive care; global hospitalization time, consultations, medications, blood transfusions, and examinations performed in post-surgery or in protected resignation; time of tracheotomy closure, time of oral feeding restoration. The pre-operative risk of each patient was evaluated using the Classification of the American Society of Anesthesiology (ASA) [19]. Postoperative functional results were assessed by the physician at outpatient follow-up consultation and at 6 months after surgery using a score system; the type of diet was assessed in all cases. Options were numerically weighted from 1 to 4 as shown in Table I.

Patients

We divided patients into three groups. In Group 1 (G1), 16 patients in good general conditions receiving free radial forearm flap reconstruction; in Group 2 (G2), 18 high risk patients who received a reconstruction with infrahyoid flap; in Group 3 (G3), 20 patients who received temporal flap (10 cases) or pectoral flap (10 cases) reconstruction.

G1 comprised 12 male and 4 female patients; 9 patients received a free radial forearm flap to reconstruct a defect of the oral cavity, while 7 patients had reconstruction of the oropharynx. The mean age in G1 was 58.2 years (median 58, range 45-70 years), and all patients were classified ASA I-II.

G2 included 12 male and 6 female patients, 12 receiving infrahyoid flap for oral cavity and 6 for oropharyngeal reconstruction. All flaps were harvested from the same neck side of the primary tumour during homolateral neck dissection; 10 patients had bilateral neck dissection. The mean age in G2 was 69.6 years (median 72, range 55-83 years), 3 patients were classified ASA II, and the remaining ASA III. Contraindications for free flap reconstruction in G2 were: severe comorbidities (diffuse atherosclerosis, diabetes mellitus, heart failure) in 15 cases, and age exceeding 80 years with moderate comorbidities in 3 cases.

G3 had 16 male and 4 female patients, 11 reconstructions of the oral cavity (7 pectoralis major flaps and 4 temporal flaps) and 9 reconstructions of the oropharynx (3 pectoralis major flaps and 6 temporal flaps). The mean age in G3 was 69.6 years (median 70, range 64-81 years); 3 patients were classified ASA I, 14 patients ASA II, 2 patients ASA III and 1 ASA IV. The contraindications for free flap and infrahyoid flap in G3 were: age exceeding 80 years with severe comorbidities and contraindications for infrahyoid flap reconstruction in 3 cases; post surgical vessel-depleted neck and previous radiation in 10 cases, and previous chemoradiation in 7 cases. Ten patients with vessel-depleted neck had no neck dissection. However, even in these cases, tumour resection created a communication between the oral cavity or oropharynx and neck spaces.

Costs

We compared the healthcare costs of the three groups in two different ways:

- calculating the reimbursement following the DRG system;
- calculating real costs in each group from review of medical records and operating room registers.

To assess actual costs for each patient, we looked at:

- the cost of main materials and drugs actually consumed during diagnostic and therapeutic procedures, provided by the regional administrative institution for human and financial medical resources of Tuscany, Italy (ESTAV-Centro);
- the standard cost per hour of the physician and nurse (obtained by dividing the average salary per contractual hours, € 55 and € 23 respectively);
- the cost of each diagnostic procedure, retrieved from the regional tariff list (including personnel expenditure);
- the average hospital stay, according to the Institutional Business Accounting (€ 420 per day, all inclusive);
- the average cost of hospital intensive care unit stay, according to Institutional Business Accounting (€ 1,300 per day, all inclusive);
- the cost of operating theatre, estimated according to the Institutional Business Accounting (€ 200 per hour including all fees except those of the medical/paramedical staff).

Costs were divided into three categories: preoperative, operative and postoperative. Preoperative costs include only those required by the anesthesiologist for undertaking the surgical procedure. All diagnostic procedures requested

by the surgeon to determine the specific characteristics of the disease (CT, MRI) were excluded, since these belong and are charged within the outpatient path. Postoperative costs were calculated until discharge.

Statistical analysis

Differences among groups were tested with the ANOVA; for categorical variables we used a chi-square test of Pearson: P values less than 0.05 were considered statistically significant.

Results

Clinical results

Patient characteristics and results are shown in Table II. All reconstructions were successful. In all cases, a separation between oral cavity or oropharynx and neck spaces was obtained and none of the patients was re-admitted within 6 months from surgery. The mean operative time in G1 was 9 hr (range 7 h-12 h 40 min), in G2 it was 6 hr 40 min (range 5 hr 20 min-8 h), and in G3 it was 7 hr (range 5 hr 10 min-8 hr 30 min).

Table II. Patient characteristics and statistical analysis.

	Group				Total (54)
	G1 (16)	G2 (18)	G3 (20)	p*	
Age (yrs), mean (SD); Range	58.2 (6.32); 45-70	69.6 (9.41); 55-83	69.6 (6.8); 64-81	p < 0.01	64.7 (9.5); 45-83
Gender, n (%) male Female	 12 (75) 4 (25)	 12 (66) 6 (34)	 16 (80) 4 (20)	 p = 0.88	 40 (74) 14 (26)
Tumour Site	9 OC 7 OP	12 OC 6 OP	11 OC 9 OP	p = 0.61	32 OC 22 OP
Primary Tumour Recurrent Tumour Second Primary	12 2 2	15 2 1	3 7 10		30 11 13
pT 1 2 3 4a	 - 7 8 1	 - 5 9 4	 4 5 8 3	 p < 0.01	 4 17 25 8
pN (10 G3 patients had no neck dissection) 0 1 2a 2b 2c 3	 4 2 1 5 4 -	 8 2 - 6 2 -	 2 - - 3 2 3	 p = 0.07	 14 4 1 14 8 3
Skin Paddle Surface (cm^2) mean (SD) range	 44.7 (15.5) 20-63	 22.7 (4.5) 18-40	 44 (16.9) 32-56	 p < 0.01	 34.7 (15.9) 18-63
Operating time, (h), mean (SD); range	9.5 (1.6); 7-12.4	6.6 (0.8); 5.2-8	7.4 (0.9); 6.1-8.3	p = 0.14	8 (1.8); 5.2-12.4
Blood loss (Hb g/dl), mean (SD); range	3.25 (1.4); 1.1-6.2	2.6 (1); 0.4-3.5	3.6 (2.6); 1.7-5.5	p = 0.59	3.04 (1.4); 0.4-6.2
Patients blood-transfused, n (%) Yes No	 3 (19) 13 (81)	 3 (17) 15 (83)	 4 (20) 16 (80)	 p = 0.96	 10 (19) 54 (81)
Tracheotomy closure, mean (days)	6 (4.2); 3-9	7.4 (2.7); 4-11	7 (2.1); 5-10	p = 0.83	7.3 (2.8); 3-11
Oral intake restoration, mean (days)	14.8 (10); 8-40	11.5 (5.9); 6-25	12.6 (4.7); 9-18	p = 0.63	13.2 (7.9); 6-40
Discharge, (days), mean (SD) range	23.2 (7.5); 16-39	21.8 (12); 12-61	26.5 (9.9); 16-38	p = 0.63	23.2 (9.8); 12-61
Diet score, n, mean (SD); range	1.33 (0.4); 1-2	1.28 (0.4); 1-2	1.6 (0.7); 1-3	p = 0.29	1.42 (0.6); 1-3
Speech score, mean, n	1 (0); 1-1	1.07 (0.2); 1-2	1.2 (0.4); 1-2	p = 0.28	1.06 (0.2); 1-2

*SD: Standard deviation; ChT: Chemotherapy; RT: Radiotherapy; Hb: Haemoglobin; OC: Oral Cavity; OP: Oropharynx; * Differences in mean values among groups were tested with ANOVA, for categorical variables chi-square Pearson test was used.*

Table III. Real costs in euro.

	Groups			
	G1	G2	G3	p*
Pre-operative	333	458	393	0.23
Operative	9,673	5,751	6,172	0.034
Post-operative	12,919	11,828	13,307	0.065
Total cost	22,924	18,037	19,872	0.043

** tested using ANOVA; for categorical variables, chi-square test of Pearson.*

Postoperative intensive care recovery was used in 4 patients in G1 with a mean stay of 3.7 days, in 4 G2 patients with a mean stay of 3 days and in 3 G3 patients with a mean stay of one day.

All patients were discharged with complete restoration of oral intake (mean time 15 days, range 7-18) and tracheotomy closure (mean time 7 days, range 3-11). Mean discharge time after surgery was 23 days (range 12-39) with no differences among groups (23.2 days G1; 21.8 days G2; 26.5 days G3). No significant differences were found with regards to verbal intelligibility and diet score among groups. Nevertheless, patients in G3 receiving TMF had minimal diet restrictions, while all patients with PM flap reconstruction required soft or liquid diets.

Economic results

The DRG system has assigned all 54 patients to the main diagnostic category (MDC) #3 "Diseases and disorders of the ear, nose, mouth and throat", and class number 482: "Surgical tracheotomy for diagnosis concerning the face, the mouth and the neck". Since our Hospital is a tertiary referral centre, it receives a 3% increase on 1st tariff level for DRG high specialty (weight > 2.5). The amount of the refund, based on the DRG system, was € 7,650 for each patient. In fact, none of the patients had a hospital stay beyond the threshold of 72 days.

Looking at the real costs, we found a statistically significant difference among groups: in G1 the average total cost per patient was € 22,924, in G2 it was € 18,037, and € 19,872 in G3, (p = 0.043; Table III). Surgical expenses for G1 patients were significantly higher than those for G2 and G3 patients: € 9,673, € 5,751 and € 6,172 respectively (p = 0.034; Table III). No statistically significant differences were found for preoperative and postoperative costs among the 3 groups: € 333 and € 12,919, € 458 and € 11,828, € 393 and € 13,307, in G1, G2 and G3 respectively (p values were 0.23 and 0.065 respectively; Table III).

Discussion

The main goals in modern head and neck reconstructive surgery are restoration of form and function [20]. In oral cavity and oropharyngeal reconstructions, the surgeon is faced with several challenges: ensuring optimal healing; increasing residual function; preventing scar formation and anchylosis of mobile structures; ensuring effective deglutition, intelligible speech, and airway patency. Failure in some of these aspects, in addition to jeopardizing the patient's quality of life, produces an increase in health care costs. In the present study, we analyzed reconstructions performed by a single surgeon (AD) to avoid inter-operator differences, and focused on soft tissue reconstructions to obtain a homogeneous cohort. We selected oral cavity and oropharyngeal defects in communication with neck spaces to represent a similar level of complexity. In fact, transoral resections are mostly performed for small tumours, where the reconstruction in these cases is less difficult, employing primary closure, local flaps or skin grafts. Furthermore, since we focused our study on head and neck surgery, we excluded the costs of adjuvant therapies, since these are independent of the type of reconstructive procedure and could have created a bias (i.e. pre-irradiated patients). In recent years, at our Institution, the free radial forearm flap has represented the main reconstructive option for soft tissue reconstruction of oral cavity and oropharyngeal defects following cancer ablation. In fact, microvascular reconstructions represent a major advancement in the management of head and neck tumours; nevertheless, our philosophy of carefully considering all anatomical and general conditions for each patient drove us to reconsider pedicled alternative flaps in selected cases. With this study, we wanted to verify our preliminary impression that this philosophy was not only oncologically sound, but also cost effective. Indeed, the infrahyoid flap has proven to be a valuable alternative in elderly patients suffering from severe comorbidities (G2 patients), ensuring excellent functional results [9 10 21 22]. The temporal flap and pectoralis major flap can still be useful in patients with a vessel depleted neck or when the expected quality of the recipient vessels is questionable (G3 patients) [11 23]. Looking at our data, and calculating the total real costs in the three groups, we immediately realized the inadequacy of the DRG system, which always assigned the highest hierarchical remuneration to the tracheotomy, rather than any other accompanying demolition/reconstruction.

The advantages of the DRG system should consist in fixing an anticipated "price" for hospitalizations, but the DRG miserably fails when dealing with major head and

neck oncologic resections and reconstructions. In our series, the obtained refund per patient, based on the DRG, was € 7,650; the gap between the real costs and the refund has been as high as € 15,274 for G1 patients, € 10,387 for G2 and € 12,222 for G3 patients. These data reflect a large disconnection between the DRG system and true treatment costs; the DRG seems undeniably unsuitable to calculate and compare healthcare costs, and therefore to be used as a parameter for policy choices. The results of our analysis showed a significantly increased cost for microvascular procedures *vs.* pedicled alternatives. We must highlight that pedicled alternative flaps were used in elderly, unfavourable and weak patients, where medical costs usually tend to rise rather than decrease. In fact, the average preoperative costs for the more "fragile" patients of Group 2 and Group 3, requiring specific additional preoperative assessments were higher than preoperative costs in Group 1 (Table IV). These data show that our philosophy is not only valid from a medical point of view, but it is also economically sound. Nevertheless, our findings warrent further confirmation in a larger cohort of patients. It seems difficult to conduct a comparison with other studies because there are significant differences due to: the different criteria for choosing the type of reconstruction, the diverse systems of remuneration and the various costs of human and material supplies among different institutions and countries.

Kroll [24] in 1997 compared 145 oral cavity and oropharyngeal free flap reconstructions (using free radial forearm flaps or rectus abdominis free flaps) with 33 pectoralis major flap reconstructions. The operative costs were slightly higher for free flaps, but the total costs were lower: $ 37,314 for free flaps and $ 48,917 for pectoralis major flaps.

Table IV. Pre-operative costs in euro.

	Group		
	G1	**G2**	**G3**
Patient admission time			
Medical time (10 min)	6	6	6
Paramedical time (10 min)	2	2	2
Pre-operative exams			
Routine blood screenings	126	126	126
Extra blood screenings	36	113	102
Urinalysis	3	3	3
Chest X-ray	45	45	45
ECG	20	20	20
Paramedical time (15 min)	4	4	4
Pre-operative evaluations from various professionals			
Head and neck surgeon	22	11	11
Anaesthesiologist (20 min)	11	11	11
Nurse	9	4	6
Specific additional preoperative assessments	6	53	6
Other costs 15% direct and indirect costs	43	60	51
Total	333	458	393

Ten years later, de Bree [25] matched 40 oral cavity/oropharyngeal reconstructions with free radial forearm flap with 40 patients receiving the pectoralis major flap for similar defects; total costs were lower for the free radial forearm flap group: € 38,709 *vs.* € 42,733. However, in both these studies, free flaps were tested against the pectoralis major flap, which unfortunately is known to cause some healing delay for frequent necrosis of the most distal edge of the skin paddle; this usually doesn't require further interventions, but it does increase hospital stay and costs. In fact, where conservative transmandibular approaches are employed, the bulkiness of the pectoralis major flap produces less than ideal functional outcomes, because the mandible presses upon the flap favouring hypovascularization and necrosis of the distal portion, and because the thickness and bulkiness of the flap hinders the motility of the preserved structures. According to previous studies, the incidence range of total necrosis and partial necrosis for the pectoralis major flap has been reported to be from 0-2.7% and 4-29%, respectively [26-34].

It is our policy, however, to use the pectoralis major flap for defects mainly lying below an imaginary line between the labial commissure and tragus; instead, the temporal flap is chosen for defects mainly lying above this line. Furthermore, for reconstructions following mandibular sparing procedures, we prefer to use the pectoralis major flap as myofascial transposition, reducing its bulk, and consequently reducing the pressure of the mandible. These two specific indications decrease the occurrence of distal marginal necrosis and the related costs.

In our series, the mean length of hospitalization was 23.2 days in G1, 21.8 days in G2 and 26.5 in G3, which was not significantly different ($p = 0.63$). The intraoperative costs for G1 patients were significantly higher ($p = 0.034$) than costs for G2 and G3 patients: € 9,673, € 5,751, and € 6,172 respectively (Table V). The highest intraoperative costs for G1 patients are due to longer operative time, and, above all, to the simultaneous work of a double medical and paramedical team (flap harvest during tumour resection; Table V). Longer operative times in G1 were mainly dependent on the microvascular reconstruction times, not only technically related to preparation of the recipient vessels under microscopic magnification and revascularization times, but also to "meticulous" and "patient/delayed" surveillance of microanastomosis patency prior to definitive skin closure (of course this step could be omitted or quickened, but we feel that "it is better to be safe than sorry"). On the other hand, higher operative costs in G1 were less dependent on operative times and mainly related to personnel-related costs (medical and paramedical).

The analysis of postoperative expenses (Table VI) showed a substantial parity between G1 and G3, with slight best performance again for G2. The inappropriate use of post-

Table V. Operative costs in euro.

	Group		
	G1	G2	G3
Materials			
Intubation kit	5	5	5
Sterile gloves	288	96	96
Thread	73	52	57
Microsurgical kit	22	-	-
Gauze	24	16	12
Scalpel	2	1	1
Tracheal cannula	75	75	63
Syringe	5	4	4
Sterile drape	12	8	8
Surgery disposable mask and cuff	4	1	2
Drugs			
Anaesthesia (fluids included)	232	188	196
Sodic heparin	7	-	-
Antibiotics	6	6	6
Histology			
Frozen sections	320	344	315
Definitive pathological report	880	865	846
Transfusions	70	62	7
Blood gases analysis	97	55	70
Operative room costs	1,900	1,320	1,546
Personnel			
Surgeons	3,008	1,091	1,223
Anaesthesiologist	523	364	408
Paramedical staff	858	447	502
Other costs			
15% direct and indirect costs	1,262	751	805
Total	9,673	5,751	6,172

Table VI. Postoperative costs in euro.

	Group		
	G1	G2	G3
Ordinary hospital stay	9,744	9,156	11,130
Hospital stay in ICU	1,219	867	195
Medications (hospital ward)			
Materials	97	79	81
Medical time	31	14	22
Paramedical time	16	7	19
Other specialists in consultation	63	98	38
Exams			
Imaging, ECG	30	26	38
Rehabilitation			
Speech therapy	27	24	31
Physiotherapy	8	14	16
Other costs	1,684	1,543	1,737
Total	12,919	11,828	13,307

operative intensive care recovery (ICU) in 4 G1 patients did deny a saving in this group of healthier patients, and instead raised postoperative costs (Table VI). Postoperative ICU monitoring was not related to protracted operative times, but only for the lack of the appropriate sub-intensive facility and it was no longer used for the 12 more recent cases.

Our reconstructive philosophy has provided successful results in functional terms, also in terms of "cost-effectiveness". The use of alternative pedicled flaps in high-risk patients probably reduced the risk of flap failure, with consequent expenditure restraints. The use of microvascular techniques for these patients might have led to an increase in production costs linked to the increase of indirect costs arising from possible complications. The limits of our study are mainly represented by the retrospective setting and the small cohort. It would be beneficial, for subsequent analyses, a perspective evaluation with a larger cohort, possibly multi-institutional. In our opinion, satisfaction and quality of life of the patient must, however, precede any economical concern [35-38].

Conclusions

Our analysis shows that the use of alternative non-microvascular techniques in high-risk patients, does not affect the result in oncologic and functional terms, and can even produce a cost saving. In particular, the infrahyoid flap ensures excellent functional results accompanied by the best economic performance in the most fragile patients.

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Head and neck

Is there a role for video-assisted parathyroidectomy in regions with high prevalence of goitre?

Il ruolo della paratiroidectomia video-assistita nelle regioni ad elevata endemia gozzigena

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SUMMARY

Minimally-invasive procedures for parathyroidectomy have revolutionized the surgical treatment of primary hyperparathyroidism (pHPT). Co-existence of goitre is considered a major contraindication for these approaches, especially if unilateral. A specific advantage of video-assisted parathyroidectomy (VAP) compared to other endoscopic techniques is the possibility to combine it with thyroidectomy when necessary and when the selection criteria for video-assisted thyroidectomy (VAT) are met. We evaluated the role of VAP in a region with a high prevalence of goitre. The medical records of all patients who underwent parathyroidectomy and concomitant thyroid resection in our Division, between May 1998 and June 2012, were reviewed. Patients who underwent VAP and concomitant VAT were included in this study. Overall, in this period, 615 patients were treated in our Division for pHPT and 227 patients (36.9%) underwent concomitant thyroid resection. Among these, 384 patients were selected for VAP and 124 (32.3%) underwent concomitant VAT (lobectomy in 26 cases, total thyroidectomy in 98). No conversion to conventional surgery was registered. Mean operative time was 66.6 ± 43.6 min. Transient hypocalcaemia was observed in 42 cases. A transient recurrent nerve lesion was registered in one case. No other complications occurred. Final histology showed parathyroid adenoma in all but two cases of parathyroid carcinoma, benign goitre in 119 cases and papillary thyroid carcinoma in the remaining 5 patients. After a mean follow-up of 33.2 months, no persistent or recurrent disease was observed. In our experience, a video-assisted approach for the treatment of synchronous thyroid and parathyroid diseases is feasible, effective and safe at least considering short-term follow-up.

KEY WORDS: Video-assisted parathyroidectomy • Endemic goitre • Parathyroid surgery • Video-assisted thyroidectomy

RIASSUNTO

L'introduzione delle tecniche di paratiroidectomia mini-invasiva ha rivoluzionato il trattamento chirurgico dell'iperparatiroidismo primitivo (pHPT). La presenza di un gozzo voluminoso è stata generalmente considerata una delle principali controindicazioni agli approcci mini-invasivi di paratiroidectomia, soprattutto se unilaterali. Uno dei principali vantaggi della paratiroidectomia video-assistita (VAP) è la possibilità di eseguire resezioni tiroidee concomitanti, laddove i criteri di inclusione delle tiroidectomia video-assistita (VAT) siano rispettati. In questo studio abbiamo valutato il ruolo della VAP in una regione di endemia gozzigena. Sono state analizzate tutte le cartelle cliniche dei pazienti sottoposti a paratiroidectomia e concomitante tiroidectomia tra Maggio 1998 e Giugno 2012, presso la nostra Unità Operativa. Sono stati inclusi nello studio tutti i pazienti sottoposti a VAP e concomitante VAT. Durante il periodo considerato, su un totale di 615 pazienti trattati per pHPT, 227 casi (36,9%) sono stati sottoposti a concomitante tiroidectomia. Tra questi, 384 pazienti sono stati selezionati per l'approccio video-assistito. In 124 di questi 384 pazienti (32,3%) è stata associata una VAT: una lobectomia in 26 casi e una tiroidectomia totale in 98 casi. La conversione a chirurgia convenzionale non si è resa necessaria in nessun caso. Il tempo operatorio medio è stato 66,6 ± 43,6 min. In quarantadue casi è stata rilevata un'ipocalcemia transitoria. Nella serie riportata è stato osservato un solo caso di lesione ricorrenziale transitoria. L'esame istologico definitivo ha dimostrato 122 adenomi paratiroidei, 2 casi di carcinoma paratiroideo, uno struma colloideo-cistico in 119 casi e un carcinoma papillare della tiroide in 5 casi. A un follow-up medio di 33,2 mesi, non sono stati registrati casi di persistenza né di recidiva di malattia. I risultati del nostro studio dimostrano che, in casi selezionati, l'approccio video-assistito rappresenta un'opzione terapeutica efficace nel trattamento di una significativa percentuale di pazienti affetti da pHPT associato a gozzo.

PAROLE CHIAVE: *Paratiroidectomia video-assistita • Gozzo endemico • Chirurgia paratiroidea • Tiroidectomia video-assitita*

Acta Otorhinolaryngol Ital 2013;33:388-392

Introduction

The last two decades have seen a revolution in the field of surgical treatment of sporadic primary hyperparathyroidism (pHPT), at least in part due to advances in technology [1 2]. The evolution of preoperative imaging studies, the availability of the quick parathyroid hormone assay (qPTHa) and the introduction of cervicoscopy gave great impulse to the application of several variants of minimally-invasive techniques for parathyroidectomy. To date, a minimally-invasive approach to parathyroidectomy emerged as a valid and validated option to treat selected cases of sporadic pHPT, at least in referral centres [3], and are assuming an increasingly important role [4].

Nonetheless, the diffusion of the minimally-invasive parathyroidectomy has resulted in several controversies regarding the indications for these approaches [5]. One of the criticisms regards the role of minimally-invasive parathyroid access in the treatment of a concomitant thyroid pathology [6-8], which could represent a relevant limit for the diffusion of these approaches, especially in regions with a high prevalence of goitre. Indeed, in countries with endemic goitre, concomitant thyroid disease is found in 35-78% of patients with pHPT [7].

Miccoli [9] first described video-assisted parathyroidectomy (VAP), and in 1998 our department adopted the procedure [10]. Early after its first description, this technique encountered large, worldwide acceptance [10-15] as it is easy to reproduce in different surgical settings. Indeed, it reproduces all the steps of a conventional procedure, with the endoscope representing a tool that allows performing the same operation through a smaller skin incision [10]. Thanks to its central access, VAP, in selected cases, allows performing bilateral neck exploration and thyroid resection when necessary through the same central access [3 10 16].

The aim of this study was to evaluate the role of VAP in a region with a high prevalence of goitre.

Materials and methods

The medical records of all patients who underwent parathyroidectomy for pHPT and a concomitant thyroid lobectomy (TL) or total thyroidectomy (TT), between May 1998 and June 2012, at our institution were reviewed. Patients who underwent VAP and concomitant video-assisted thyroidectomy (VAT) were included in this study. Demographic, clinical, surgical, pathologic and follow-up data of these patients were evaluated. Statistical analysis was performed using a commercially available software package (SPSS 10.0 for Windows; SPSS Inc., Chicago, Ill). The χ^2 test was used for categorical variables, and a *t* test was used for continuous variables. A p value < 0.05 was considered statistically significant.

Preoperative work-up

Preoperative high-resolution ultrasound (US) and ^{99}mTc-sestamibi (MIBI) scans were performed in all patients with sporadic pHPT to localize hyperfunctioning glands. All patients had normal renal function (serum creatinine value ranging from 0.7 to 1.2 mg/dl).

Indications

Ideal candidates for VAP are those with sporadic pHPT in whom a single adenoma is suspected basing on preoperative MIBI-scan and ultrasonography. Parathyroid adenomas larger than 3 cm in their maximum diameter should not be selected for VAP, because a difficult dissection can lead to dangerous capsular rupture. Patients with concomitant nodular goitre requiring surgical removal can be selected for VAP if the inclusion criteria for the video-assisted thyroidectomy (VAT) are respected [10 17]. Basing on the surgeons' experience, in selected cases, patients with previous contralateral neck surgery or intrathymic/retrosternal adenomas can be selected for VAP. In case of suspected multiple gland disease, a video-assisted bilateral exploration can be planned.

Intraoperative-PTH (IOPTH) monitoring

All patients underwent IOPTH monitoring. Blood samples were collected peripherally pre-incision (preoperative baseline concentration – PTH), pre-excision (after dissection and just before clamping the blood supply of the suspected affected gland – PTH) and at 10 min (PTH-10) and 20 min (PTH-20) after gland excision. A point of care chemiluminescence immunoassay system (Stat-IntraOperative-intact PTH – Future Diagnostics, Wijchen, The Netherlands) was used for IOPTH measurements and set up in the recovery room. Blood specimens were collected and analyzed following the manufacturer's indications [18].

Surgical technique

The surgical technique we use has been previously described elsewhere in detail [19]. The patient, under general or loco-regional anaesthesia with cervical block [20 21], is positioned supine with the neck in slight extension. A small (1.5 cm) horizontal skin incision is made between the cricoid cartilage and the sternal notch, in the midline. The cervical linea alba is opened as far as possible. The technique is completely gasless. The endoscope (5 mm, 30°) and the dedicated small surgical instruments are introduced through the skin incision without any trocar utilization (Fig. 1). After identifying the inferior laryngeal nerve in the involved side, a targeted exploration is usually carried out to identify the abnormal gland. The magnification (2-3 folds) of the endoscope permits a easy identification of the nerve and the parathyroid glands, if the principles of blunt and bloodless dissection are respected. In case of suspicion of multiglandular disease, bilateral parathyroid exploration can be accomplished. The gland should not be grasped, in order to avoid any capsular rupture. After cutting the pedicle, the adenoma is extracted through the skin incision.

When video-assisted thyroidectomy is required, dissection of the thyroid gland is safely performed under endoscopic vision according to the technique previously described [17-19].

Follow-up schedule

During follow-up, calcium levels combined with intact PTH (iPTH) values were examined at 1, 3 and 6 months after the operation, and the following classification criteria for post-surgical resection outcome at 6 months were used:

group 1: cured patients/operative success: normal or low serum calcium levels for at least 6 months after parathyroidectomy; group 2 – patients with disease persistence/operative failure: persistent hypercalcaemia and elevated iPTH levels (> 65 pg/ml; 6.89 pmol/l) within 6 months after surgery.

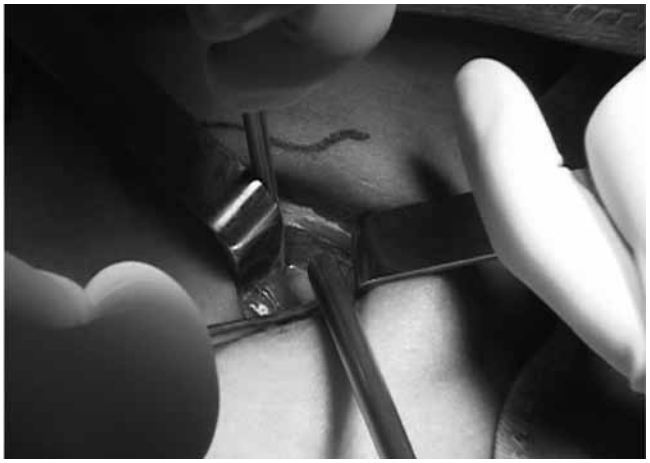

Fig. 1. Video-assisted parathyroidectomy: two small conventional retractors are used to medially retract the thyroid lobe and laterally retract the strap muscles to maintain the operative space. The endoscope (5 mm, 30°) and dedicated small surgical instruments are then introduced through the skin incision without any trocar utilization.

Results

Between May 1998 and June 2012, at our institution 615 patients underwent surgery for primary HPT. Among these, 227 patients (36.9%) underwent concomitant thyroid resection.

Three hundred and eighty four patients with PHPT who fulfilled the inclusion criteria were selected for VAP. Among these, concomitant VAT was carried out in 124 patients (32.3%): 105 females and 19 males, with a mean age of 60.8 ± 10.3 years (range: 38-84). Indications for concomitant thyroid resection were indeterminate nodule within bilateral goitre in 31 cases and multinodular goitre (MNG) with compressive symptoms in the remaining 93 cases. The mean diameter of the dominant nodule of the 93 cases of MNG was 20.3 ± 9.8 mm (range: 2-46 mm). Video-assisted TL was performed in 26 cases and video-assisted TT in 98 cases. No conversion to conventional surgery was necessary. The mean operative time of all procedures was 66.6 ± 43.6 min (range: 30-175). In particular, the mean operative time of VAP associated to video-assisted TL was 63.19 ± 38.1 min (range: 30-170); the parathyroid lesion was ipsilateral to the side of the thyroid lobectomy in 19 cases and contralateral in the remaining 7 cases. The mean operating time for VAP associated with video-assisted TT was 68.27 ± 32.5 min (range: 40-175). Transient hypocalcaemia was observed in 42 cases (32.8%), transient recurrent lesion in one case (0.8%). No other complications occurred. Mean postoperative hospital stay was 3.4 ± 1.7 days (range: 3-7). Most patients (93%) considered the cosmetic result as excellent as evaluated by a verbal response scale (Fig. 2a-b).

Final histology showed parathyroid adenoma in all but two cases of parathyroid carcinomas.

In particular, in these latter two cases, no signs and/or suspicions of malignancy were present on the basis of preoperative evaluation; in both cases simultaneous video-assisted total thyroidectomy for a concomitant bilateral thyroid disease was performed.

Final histology of thyroid specimens revealed benign goitre in 119 cases and papillary thyroid carcinoma in 5 cases. The preoperative cytological examination of the five cases of papillary thyroid carcinoma was consistent with indeterminate nodules. After a mean follow-up of 33.2 ± 20.0 months (range: 3-110), no persistent recurrent parathyroid or thyroid disease was observed.

Discussion

The results of VAP in terms of cure and complication rates are similar and rival those of conventional surgery. This has been extensively demonstrated in the international literature [3 4 16], and it is also confirmed in our personal experience [10 18 19].

Some criticisms about the technical aspects for MIVAP have concerned the operating time. However, it has been demonstrated in large retrospective series [10 14] as well as in small comparative, randomized trials [3 22] that the operating time does not represent a limit. A prospective, randomized, small comparative study (level II evidence) showed that the operating time for MIVAP was significantly shorter than conventional bilateral exploration and similar to open minimally-invasive parathyroidectomy [22].

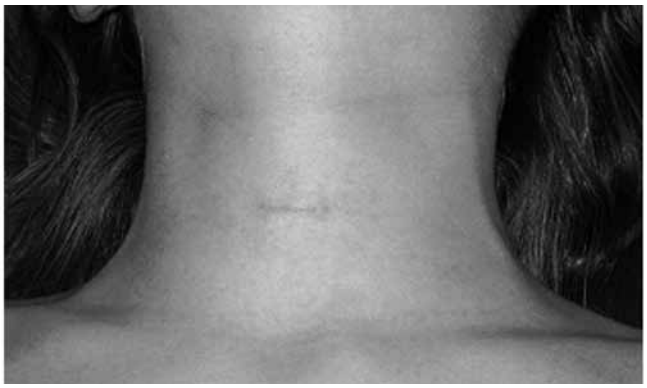

Fig. 2a. Cosmetic result of a VAP at two weeks after surgery.

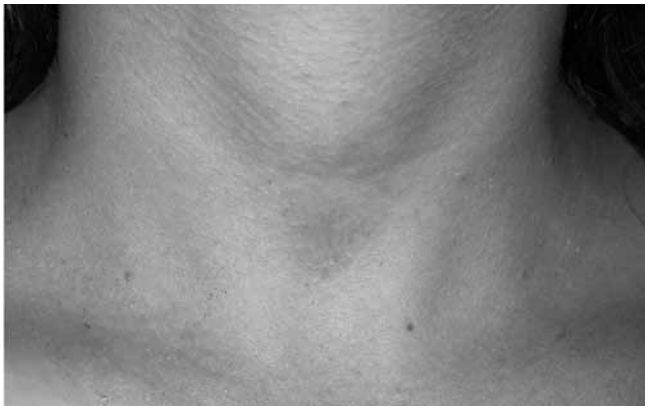

Fig. 2b. Cosmetic result of a VAP at six months after surgery.

In addition, in our overall experience with exclusive VAP and IOPTH the mean operating time was 42.6 ± 18.1 min (range: 15-95).

Besides its reproducibility, VAP also seems to offer significant advantages over conventional surgery in terms of patient satisfaction with the cosmetic result and postoperative recovery [3]. Moreover, it has been demonstrated that in selected cases of pHPT, VAP is curative and safe considering short- and medium-term outcome and complications [10-14 22 23].

The association between benign and malignant thyroid disease with pHPT has been previously described [5-8]. Indeed, the presence of concomitant thyroid disease has been reported in 15%-70% of patients with pHPT [24 25]. In a surgical series of 51 patients with pHPT, Kösem described 43 cases (84.3%) of coexistent thyroid diseases. Among these, 9 patients (17.6%) had papillary thyroid cancer [26].

The association between pHPT and goitre seems to be more much relevant in areas with iodine deficiency. It has been reported that in an endemic goitre region, 67 of 137 patients with PHPT (49%) had concomitant thyroid disease [7].

In a large retrospective analysis involving a population living in a geographical area with an average-mild iodine deficiency, such as the mixed Italian regions, a total of 124 of 241 patients (51.5%) with pHPT showed concomitant thyroid disorders [27].

It has been pointed out that a head and neck endocrine surgeon needs to be aware of the possible coexistence of thyroid and parathyroid disease so that, when encountered, they can be safely and effectively managed in a single procedure [24 25]. However, some authors have argued that concomitant thyroid disease requiring surgical management represents an exclusion criteria for minimally-invasive parathyroidectomy [5 6]. Perrier [5] reported that 17% of patients referred to parathyroidectomy were considered ineligible for localized parathyroid surgery because of a coexisting thyroid pathology. However, a relevant advantage of central access is the possibility to perform thyroid resection, even bilateral, when necessary. This introduces an important difference when compared to other minimally-invasive techniques, as conversion to a conventional approach is usually required when bilateral thyroid resection is needed [28]. Because of the high prevalence of multinodular goitre in some countries, the central approach of VAP can allow experienced surgeons to increase the number of patients eligible for a video-assisted procedure. Indeed, in our experience in a region of high prevalence of goitre in Italy, the video-assisted approach was successful accomplished in the treatment of both parathyroid and thyroid disease during the same procedure in a significant percentage of patients (32.3%).

Moreover, concomitant thyroid diseases with pHPT may result in more difficult preoperative localization of the pathological parathyroid gland. Indeed, in these cases, one of the main problems is the accuracy of preoperative imaging studies. It has been reported that the coexistence of pHPT and thyroid disease may reduce the sensitivity of sestaMIBI from 81% to 75%, and of US from 73% to 55% [29]. However, the combined use of sestaMIBI and US seems to be more effective in patients with pHPT for localization of an enlarged parathyroid gland even in the case of concomitant thyroid disease [29]. This would make it possible to perform a focused parathyroidectomy in the most of patients suffering from pHPT even in an endemic goitre region [7].

Moreover, it might be stressed that even if preoperatively, well-documented single adenoma is a prerequisite for any type of focused parathyroidectomy [1 30], the concept that preoperative localization studies are mandatory when performing a minimally-invasive approach remains valid only for procedures that imply a unilateral approach. Among these, the lateral approach (VAP-LA) described by Henry which is the most diffuse, has been shown to be effective and safe, with a minimal complication rate [31]. Nonetheless, due to its unilateral approach, the rate of contraindications for VAP-LA appears fairly high (43%) compared to that of large series of VAP [23]. This may depend on the need of stricter eligibility criteria, due to the unilaterality of the approach, which implies the strong demonstration of a single enlarged parathyroid gland on preoperative imaging studies and excludes bilateral thyroid disease. The main technical limitation of the technique is, indeed, that a unilateral approach prevents the possibility to accomplish bilateral exploration when necessary without conversion to an open conventional procedure [28 30 31].

On the other hand, a relevant merit of VAP is the possibility of performing bilateral neck exploration when necessary through the same central access. This characteristic in part explains the lack of conversion in the present series and the very low conversion rate generally reported for VAP [10 16]. Moreover, the possibility of performing a bilateral neck exploration produces two main effects on the restrictive inclusion criteria. First, at least from a theoretical point of view, VAP can be performed if IOPTH monitoring is not available or in the case of inadequate preoperative localization, given the ability to explore all parathyroid sites through this approach [10 23 32].

In our experience in an endemic goitre area, 62.4% of patients with PHPT were eligible for VAP. The possibilities given by central access allowed us to treat a significant percentage of patients with concomitant thyroid disease who fulfilled the indication criteria of VAT. No conversion to conventional surgery was necessary and no definitive complications occurred. After a mean follow-up of 33.2 months, no persistent or recurrent parathyroid or thyroid diseases was observed.

Conclusions

When selection criteria are followed, the treatment of synchronous thyroid and parathyroid disorders can be accomplished using a minimally-invasive procedure. In our experience, a video-assisted approach is feasible, effective and safe for the treatment of synchronous thyroid and parathyroid disorders, at least considering short-term follow-up.

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Salivary glands

Warthin's tumour of the parotid gland: our experience

Tumori di Warthin della ghiandola parotide: nostra esperienza

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SUMMARY

Benign tumours account for approximately 60-80% of parotid neoplasms and among these, Warthin's tumour is the second most common benign neoplasm accounting for approximately 15% of all parotid epithelial tumours. The medical records of 100 consecutive patients with Warthin's tumour of the parotid gland admitted for treatment at the Department of Head and Neck Surgery and Otorhinolaryngology, Hospital A.C. Camargo, São Paulo, Brazil, between 1983 and 2011 were retrospectively analyzed. The surgical procedures included 104 (96%) subtotal parotidectomies and 4 (3.7%) total parotidectomies. One hundred and eight parotidectomies were performed in 100 patients with Warthin's tumour. Postoperative complications occurred in 67 (62.3%) of surgical procedures, and facial nerve dysfunction was the most frequent complication, occurring in 51 of 108 surgeries (47.2%). The marginal mandibular branch of the facial nerve was affected in 46 of the 48 cases (95.8%) of facial nerve dysfunction. Frey's syndrome was diagnosed in the late postoperative period in 19 patients (17.6%). We conclude that either superficial or total parotidectomy with preservation of facial nerve are the treatment of choice for Warthin's tumour with no case of recurrence seen after long-term follow-up. Facial nerve dysfunction and Frey's syndrome were the main complications associated with this surgery. Thus, if on one hand total parotidectomy is an appropriate radical resection of parotid parenchyma reducing, in theory, the risk of recurrence, on the other hand superficial parotidectomy is also a radical and efficient method with lower morbidity in terms of facial nerve dysfunction and Frey's syndrome.

KEY WORDS: Warthin's tumour • Treatment • Complications • Recurrence • Parotid • Parotid tumours

RIASSUNTO

Le neoplasie benigne rappresentano circa il 60-80% dei tumori della ghiandola parotide e fra questi, il tumore di Warthin è il secondo istotipo più frequente con una prevalenza del15% circa dei tumori epiteliali della parotide. Abbiamo analizzato retrospettivamente le cartelle cliniche di 100 pazienti affetti da tumore di Warthin trattati fra il 1983 e il 2011 presso il dipartimento di chirurgia della testa e del collo dell'ospedale di San Paolo "A.C. Camargo" (Brasile). Nei 100 pazienti analizzati furono effettuate 108 parotidectomie di cui 104 parotidectomia subtotale (96%), e 4 parotidectomia totali (3,7%). Complicanze post operatorie si sono verificate nel 62,3% delle procedure chirurgiche e in particolare la disfunzione del nervo facciale fu la più frequentemente osservata (51/108 procedure effettuate – 47,2%). Una disfunzione del ramo marginalis mandibulae del nervo facciale eè stata riscontrata in 46 dei 48 casi (95,8%) con disfunzione del facciale. La sindrome di Frey's fu riscontrata invece tardivamente in 19 pazienti (17,6% dei casi). Nella nostra casistica anche ad un follow-up a lungo termine non sono state apprezzate recidive di tumori di Warthin dopo parotidectomia esofacciale o totale con preservazione del nervo facciale. La disfunzione del nervo facciale e la sindrome di Frey erano le principali complicanze osservate dopo la chirurgia. Benché la parotidectomia totale rappresenti l'approccio chirurgico più radicale i nostri dati dimostrano che la parotidectomia superficiale non solo consente di ottenere una buona radicalità chirurgica ma allo stesso tempo si associa ad una bassa moribidità in termini di disfunzione del nervo facciale e sindorme di Frey.

PAROLE CHIAVE: *Tumore di Warthin • Complicanze • Recidive • Parotide • Tumori della parotide*

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Introduction

Benign tumours account for approximately 60-80% of parotid neoplasms and comprise a heterogeneous group with distinct clinical and histological features and biological behaviour [1]. Among these, Warthin's tumour, also known as adenolymphoma or papillary lymphomatous cystadenoma, is the second most common benign neoplasm and accounts for approximately 15% of parotid epithelial tumours [2-4].

Warthin's tumour is most common in male patients (4:1 male:female ratio) during the sixth and seventh decades of life [5]. Unlike other benign neoplasms of the salivary glands, this tumour has a tendency towards bilateral involvement, and approximately 90% of lesions occur in the superficial lobe of the parotid gland [6]. Histologically, the tumour has an oncocytic epithelial component forming uniform rows of cells surrounded by cystic spaces associated with a lymphoid stroma often showing the presence of germinal centres (Figs. 1, 2) [7]. Treatment consists of partial, subtotal or total parotidectomy with preservation of the facial nerve [8]. Malignant transformation is described in only 0.1% of cases, and usually arises in the epithelial component of the lymphoid tissue tumour [9]. The incidence of recurrence after surgical treatment is extremely rare [5].

The aim of this study is to describe the outcomes of patients with Warthin's tumour of the parotid gland considering clinical and demographic characteristics, type of surgery, complications and the incidence of recurrence.

Patients and methods

The medical records of 100 consecutive patients with Warthin's tumour of the parotid gland admitted for treatment at the Department of Head and Neck Surgery and Otorhinolaryngology, Hospital "A.C. Camargo", São Paulo, Brazil, between 1983 and 2011 were retrospectively analyzed. One hundred and thirteen tumours were diagnosed in 100 patients with a median age of 58 years (range 32-84 years). There were 72 males and 28 females. Of these, 75 patients (75%) were Caucasian. Tobacco use was reported at diagnosis by 72 patients and 11 reported a previous history of smoking. Four patients had bilateral synchronous tumours and 9 had bilateral metachronous tumours. The treatment employed was surgery in all cases. The surgeries were performed by several surgeons from the same department, mostly residents directly supervised by specialists in head and neck surgery. The surgical procedures included 104 (96%) subtotal/superficial parotidectomies, defined by the resection of tumours located in the superficial portion of the gland (above the nerve) and 4 (3.7%) total parotidectomies, indicated for those tumours located in the deep lobe of gland. The facial nerve was identified and preserved in all cases. In three of the four patients with bilateral synchronous tumours, surgery was performed only on the side where the tumour was larger. Otherwise, in 9 patients with metachronous bilateral tumours, contralateral parotidectomy was performed in 7 cases. All eight contralateral parotidectiomies in patients with bilateral tumours were performed at different times. In five patients with bilateral tumours, the second side was not operated because of patient refusal or for clinical reasons (small tumours and few symptoms).

Routinely, the facial nerve trunk is identified before making the identification and dissection of its branches. No devices were used to identify the nerve in primary surgeries. In two patients, the mandibular branch of facial nerve was sacrificed because of reported tumour involvement, and these cases were not included in the analysis of postoperative nerve dysfunction. Rotation of sternocleidomastoid muscle flap (SMF) was performed in the last 10 years to fill the parotid bed after resection and to reduce the incidence of Frey's syndrome. The type of drain used varied during the study period. The Penrose drains that were originally used were replaced in 1994 by vacuum drainage Hemovac (Por-

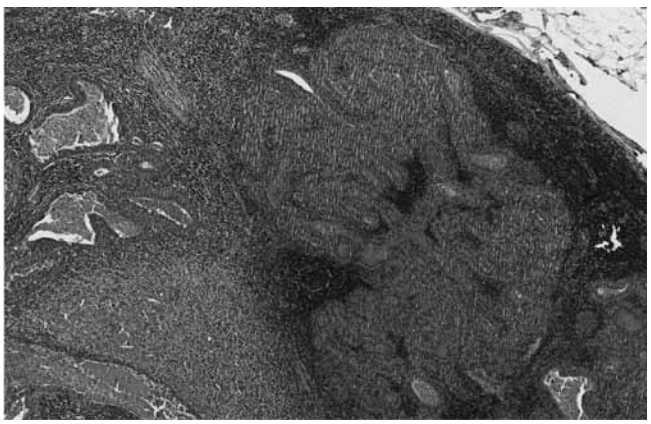

Fig. 1. Histological section stained with HE with 40x magnification, showing the interface between the salivary gland and the tumor.

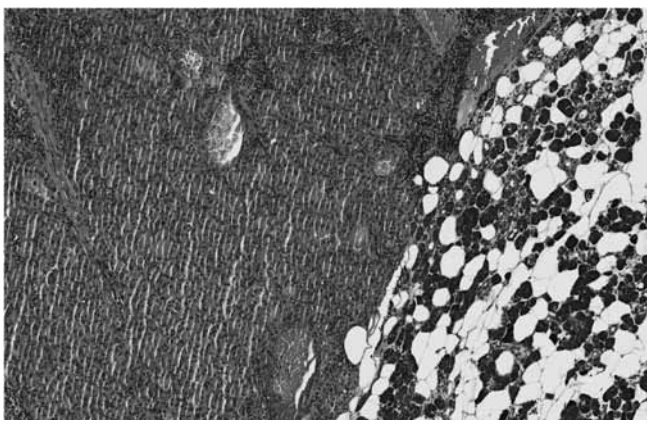

Fig. 2. Histological section stained with HE with 40x magnification, demonstrating the neoplasm characterized by cystic and solid areas, cells with abundant granular and eosinophilic cytoplasm with central nuclei. The stroma is rich in lymphocytes.

tovac), and in the last decade we have used silicone drains (Jackson-Pratt and Blake) to facilitate postoperative care and allow early hospital discharge.

SPSS 17.0 was used for statistical analysis. The association between variables with the occurrence of complications was evaluated by chi-square or Fisher's exact test, as appropriate. The Mann-Whitney test was used to evaluate the difference between the mean length of hospitalization. A p value < 0.05 was considered statistically significant.

Results

One hundred and eight parotidectomies were performed in 100 patients with Warthin's tumour. The time of hospitalization varied from 1 to 19 days (median, 2 days). Postoperative complications occurred in 67 (62.3%) surgical procedures, and facial nerve dysfunction was the most frequent complication, followed by other less frequent complications such as seroma and infection (Table I). There was no total facial nerve dysfunction or postoperative mortality. The mean and median days of hospitalization between the patients who did or did not have postoperative complications were similar and not statistically different. Similarly, the incidence of postoperative complications did not show statistically significant correlation with gender, age, smoking and alcohol, type of parotidectomy, nodule size and use of the sternocleidomastoid muscle flap.

Postoperative facial nerve dysfunction occurred in 51 of 108 surgeries (47.2%) (Table I). In 43 cases (84.3%), dysfunction was transitory with recovery of function occurring in a period ranging from 1 to 19 months (median, 4 months). Unfortunately, in eight cases there was no detailed report in the clinical chart regarding recovery from facial mobility. The marginal mandibular branch of the facial nerve was affected in 46 of the 49 cases (93.8%). Six cases (12.2%) had dysfunction of other associated branches. Only one patient had postoperative dysfunction of all branches of the facial nerve.

Seroma and haematoma were found in 2 of 108 (1.9%) procedures. All were treated conservatively with aspiration. Wound infection was observed in 10 of 108 (9.2%) procedures. There was no statistically significant correlation with the incidence of wound infection and the type of drain used. Two cases of fistula occurred.

Frey's syndrome was diagnosed in the late postoperative period in 19 patients (17.6%) (Table II). There were no reports of bilateral Frey's syndrome in patients with surgery on both sides. Frey's syndrome occurred less frequently in patients who underwent rotation of the sternocleidomastoid muscle flap (SMF) to fill the parotidectomy field (10 of 67; 14.9%) compared with cases that did not undergo flap reconstruction (9 of 41; 22%), but this difference was not statistically significant.

Table I. Complications in 108 parotidectomies for Warthin's tumour.

Complication	n	%
Number*	44	40.7
Facial nerve dysfunction	51	47.2
Infection	10	9.2
Seroma	2	0.9
Haematoma	2	0.9
Fistula	2	0.9

** Some patients had more than one complication.*

Table II. Incidence of Frey's Syndrome.

		Frey's Syndrome	
		No	Yes
Parotidectomy	Partial	78	19
	Total	4	0
SMF	No	21	9
	Yes	56	10
Follow-up	Min	6 m	
	Max	20 y	
	Mean	4.13 y	
	Median	2 y	

SMF: sternocleidomastoid muscle flap; m: month; y: years.

Discussion

Warthin's tumour is a benign neoplasm, first described by Aldred Warthin in 1929, which occurs predominantly in the parotid gland and represents approximately 15% of parotid tumours [5 9]. Fewer than 10% of cases occur outside this gland [5]. Furthermore, bilateralism is described in 5-15% of cases and multifocality in 6-20% [9-12]. In our series, we studied only tumours of the parotid gland, and bilateral Warthin's tumours were observed in 13 (13%) patients, (4 synchronous cases and 9 metachronous cases). Although the occurrence of bilateral Warthin's tumour is relatively common in this group of patients, the presence of a bilateral synchronic tumour is rare [11-14].

The origin of Warthin's tumour is unknown and its classification as cancer is controversal [15 16]. Surgery is the main mode of therapy used and is associated with a low recurrence rate [15]. Several authors have correlated recurrence rate with the extent of surgery, which ranges from 0-13% [5 11 17]. In our study, superficial parotidectomy with facial nerve preservation was used in 97% of cases, and there were no cases of recurrence after a median follow-up of 31 months. Although superficial parotidectomy is the treatment of choice for patients with benign tumours of the parotid gland, it is associated with both early and late complications [18 19].

The main complications associated with surgery of the parotid gland are facial nerve dysfunction and Frey's syndrome. Postoperative dysfunction of the facial nerve may be total or partial (some branches), and transient or perma-

nent [20 21]. On the other hand, Frey's syndrome is detected later, may be symptomatic or asymptomatic and its diagnosis is performed with the Minor test that is based on application of a solution containing 1.5 g of iodine, 10 g of castor oil and 88.5 g of absolute alcohol that must be applied to the skin of the parotid region. After drying, starch powder should be applied, which together with local sweating, will produce a blue iodine-starch reaction [22 23].

In the literature, the incidence of transient dysfunction of the facial nerve has been reported in 10-68% of cases, while permanent dysfunction occurs in 0-19% [20 24]. In our series, the incidence of postoperative dysfunction of facial nerve was 47.2%. The marginal mandibular branch was the most affected with 90% of cases of nerve dysfunction, although total dysfunction (all branches) was detected in only 1 patient. Classification regarding the degree of facial nerve dysfunction could not be done since this was a retrospective study, and this data was not evaluated in most cases.

Dysfunction of the marginal mandibular branch is a major problem and has been reported in 48-59% of cases in the literature [21 25]. Several factors have been described to be associated with an increased incidence of postoperative dysfunction of the facial nerve after parotidectomy [26]. Yuan, in 2009, studied 626 patients undergoing surgery for benign disease of the parotid and found that the factors associated with increased postoperative dysfunction of the facial nerve were the extent of parotidectomy and diabetes mellitus [21]. Similarly, Koch in 2010 observed facial nerve dysfunction in 32.7% of cases, and the main factor was the extent of surgery [19]. In another study of 162 patients who underwent parotidectomy for benign disease, the presence of facial nerve dysfunction was observed in 40% of cases. In this study, the presence of inflammation and parotidectomy for Warthin's tumour were the factors that were most relevant to dysfunction [27]. In our study, there were no factors that significantly correlated with postoperative dysfunction of the facial nerve.

Frey's syndrome has been described as a main complication related to surgery of the parotid gland. The incidence of this syndrome varies widely according to the diagnostic investigation. It is reported spontaneously for about 10% of patients, but when questioned actively about the existence of gustatory sweating, approximately 30-40% of patients report the presence of such symptoms. Moreover, when under diagnostic investigation, Frey's syndrome is seen in up to 95% of patients undergoing parotidectomy [23]. In our study, the diagnosis of Frey's syndrome was made based on spontaneously clinical complaints of the patient or after being questioned by the attending physician about symptoms during follow-up, and was seen in 17.6% of patients. This occurred more often in patients in whom a SMF was not used to fill the parotid space (22% *vs.* 14.9%). However, this difference was not statistically significant. When symptomatic, Frey's syndrome was treated with botulinum toxin injection in the most severe cases, and by applying deodorants or antiperspirants in milder cases. Queiroz Filho, in 2004, studied the occurrence of Frey's syndrome in 2 groups of patients according to the presence or absence of SMF and found that 47.4% (9/19) of patients in the group who did not receive the flap had complaints of gustatory sweating, and in 36.8% (7/12) of patients the Minor test was positive. Otherwise, in the group that received the flap, complaints or a positive test for Minor were not found [28]. In a systematic literature review, Sanabria concluded that there is not sufficient clinical evidence to determine that the use of SMF in preventing Frey's syndrome is an effective procedure in preventing Frey's syndrome [29].

We conclude that either superficial or total parotidectomy with preservation of the facial nerve are the preferred treatments for Warthin's tumour with no case of tumour recurrence seen during long-term follow-up. Facial nerve dysfunction and Frey's syndrome were the main complications associated with this surgery. Thus, if in one hand, total parotidectomy is an appropriate radical resection of parotid parenchyma reducing, in theory, the risk of recurrence, on the other superficial parotidectomy is also a radical and efficient method with low morbidity in terms of facial nerve dysfunction and Frey's syndrome. Currently, resections such as those of the lower extremity of the superficial pole of parotid should not be ruled out, as they can be performed safely in lower tumours, allowing lower manipulation of cranial branches of the facial nerve with less morbidity. However, further prospective and randomized studies are needed to reach a more definitive conclusion.

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Rhinology

LPS may enhance expression and release of HMGB1 in human nasal epithelial cells in vitro

Espressione e rilascio della proteina HMGB1 da coltura di cellule epiteliali nasali dopo stimolazione con LPS

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SUMMARY

Chronic rhinosinusitis with nasal polyps is a common disease with still unclear pathophysiologic mechanisms. The airway epithelial barrier has been shown to be involved in different chronic disorders, including rhinitis, nasal polyposis and asthma. High mobility group box 1 (HMGB1), a primarily nuclear protein, is involved in the induction of airway inflammation in patients with chronic rhinosinusitis, allergy, asthma and COPD. Pathogen-derived lipopolysaccharide is widely used as a trigger for inflammation. However, the molecular dialogue between LPS and HMGB1 in the delayed inflammatory processes remains to be explored, and the regulation of HMGB1 release through LPS from epithelial cells has not been extensively studied in patients with chronic rhinosinusitis and nasal polyps. The objective of the present study was to investigate the relocation of HMGB1 in LPS-induced human nasal epithelial cells in vitro. We obtained epithelial cells of nasal polyps from 10 patients requiring surgery for sinusitis at the ENT Department of the Chinese PLA General Hospital. The primary cultured human nasal epithelial (HNE) cells were stimulated with LPS. The expression and translocation of HMGB1 in intracellular and culture supernatants were determined using Western blot and immunofluorescence assay. HMGB1 protein was released in a time-dependent fashion in culture supernatants: in fact, expression of HMGB1 protein in HNE cells showed no significant changes at 0-24 h after exposure to 100 μg/ml LPS, but increased significantly at 48 and 72 hr. Immunofluorescence analysis revealed the transfer of HMGB1 from nuclei to cytoplasm in response to LPS exposure after 24 hr. These data reveal a hitherto unrecognized association between HMGB1 and LPS in human nasal epithelial cells. LPS can affect HMGB1 translocation and release, suggesting the involvement of HMGB1, through inflammatory mediators, in chronic rhinosinusitis with nasal polyps.

KEY WORDS: HMGB1 protein • Lipopolysaccharides • Nasal polyps • Human nasal epithelial cells • Primary cell culture

RIASSUNTO

La rinosinusite cronica e la poliposi nasale sono patologie frequenti con un meccanismo fisiopatologico non del tutto chiarito. La barriera epiteliale delle vie respiratorie sembra essere coinvolta in diverse patologie croniche come la rinite, la poliposi nasale e l'asma. HMGB1, proteina espressa originalmente a livello nucleare, è coinvolta nell'induzione dell'infiammazione delle vie aeree nei pazienti affetti da rinosinusiti croniche, rinite allergica, asma e COPD. I Lipopolisaccaridi batterici sono ampiamente utilizzati come trigger dell'infiammazione. Tuttavia, il dialogo molecolare tra LPS e HMGB1, nella fase tardiva del processo infiammatorio, resta da approfondire. La regolazione del rilascio di HMGB1 dopo stimolazione con LPS dalle celle epiteliali non è ancora stata studiata in modo esaustivo in pazienti con diagnosi di rinosinusite cronica con poliposi nasale. L'obiettivo di questo studio è stato quello di analizzare in vitro la localizzazione di HMGB1 in colture di cellule epiteliali nasali umane dopo stimolazione con LPS. Abbiamo prelevato cellule epiteliali di polipi nasali da 10 pazienti sottoposti a chirurgia per sinusite cronica presso il Dipartimento di O.R.L. del PLA General Hospital di Pechino. Abbiamo stimolato la coltura primaria di cellule epiteliali nasali umane con LPS. L'espressione di HMGB1 e la traslocazione intracellulare e nel surnatante della coltura sono stati determinati usando la tecnica Western Blot e la determinazione in immunofluorescenza. L'espressione della proteina HMGB1 nelle cellule epiteliali nasali umane non ha mostrato variazioni significative a 0-24 h dall'esposizione a 100 μg/ml di LPS, ma è aumentata significativamente a 48 e 72 h. HMGB1 è rilasciata nel surnatante in modo tempo-dipendente. Le analisi di lmmunofluorescenza hanno mostrato il trasferimento di HMGB1 dal nucleo al citoplasma in risposta all'esposizione ad LPS dopo 24 ore. I nostri risultati hanno evidenziato un'associazione tra HMGB1 e LPS a tutt'oggi non dimostrata. I LPS possono pertanto ritenersi implicati nella traslocazione e nel rilascio di HMGB1 dalle cellule epiteliali nasali umane, suggerendo il coinvolgimento di HMGB1 come mediatore infiammatorio tardivo nelle rinosinusiti croniche associate o meno a poliposi nasale.

PAROLE CHIAVE: *Proteina HMGB1 • Lipopolisaccaridi • Polipi nasali • Cellule epiteliali nasali umane • Coltura cellulare primitiva*

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Introduction

Inflammatory cytokines are important factors that mediate inflammation, and have the potential to initiate and maintain nasal and sinus mucosa responses [1 2] to different kinds of stimuli. Nasal polyps are the consequence of persistent inflammatory and remodeling responses in several chronic inflammatory diseases. Current treatments relieve symptoms, but do not resolve the high incidence of recurrences [3 4], which underlines the need for specific research correlating novel molecular targets, inflammation and nasal mucosa function.

Previous studies have shown that high mobility group box 1 (HMGB1) protein, as the class of "alarmins", participates in the innate and adaptive immune responses such as chronic obstructive pulmonary disease (COPD), asthma, sepsis, cystic fibrosis (CF) and systemic lupus erythematosus [5-9]. There is evidence that the release of damage associated molecular patterns (DAMPs) in the epithelium, such as HMGB1, may evoke inflammatory responses in the lower airways and local nasal mucosa [10-12]. The initial phase of HMGB1 secretion requires an inflammatory signal such as lipopolysaccharides (LPS), IL-1 or TNF-α for monocytes or macrophages. LPS, a component of the outer membrane of Gram-negative bacteria, is suggested to participate in interacting and activating immune cells where it translocates nuclear HMGB1 to the cytoplasm and extracellular space [8 12 13]. In turn, these cells respond to HMGB1 by increasing their migration, proliferation and activating downstream cytokines release. Until now, the role of HMGB1 release and related molecular mechanisms have not been elucidated completely.

Recently, our studies have demonstrated that nasal polyps augment HMGB1 expression both in the epithelium and extracellular matrix, which indicates that HMGB1 may play an important role in CRSwNP [14 15]. However, the mechanism of HMGB1 protein in CRSwNP remains unclear. We designed a study to further understand the relationships between LPS and HMGB1 in human nasal epithelial (HNE) cells. In primary culture, HNE cells are able to differentiate into ciliated cells [16]. In this study, we stimulated epithelial cells with LPS in vitro and observed the expression and translocation of HMGB1 by immunofluorescence assay and Western blot.

Table I. Culture medium composition.

Culture medium	BEBM	H-DMEM+BEBM (1:1)
Insulin (μg /ml)	5	5
Transferrin (μg/ml)	10	10
Hydrocortisone (μM)	1.4	1.4
Epidermal growth factor (ng/ml)	0.5	0.01
Epinephrine (μM)	2.7	2.7
Triiodothyronine (nM)	9.7	9.7
Bovine pituitary extract (%)	0.26	0.26
Retinoic acid (nM)	0.3	50
Penicillin G+ streptomycin sulphate	100 U /ml+100 μg/ml	100 U/ml+100 μg /ml
Gentamicin b+amphotericin b	50 μg/ml+0.25 μg/ml	-

Materials and methods

Sample collection and cell culture

We obtained epithelial cells of nasal polyps and paranasal sinus mucosa from 10 patients requiring surgery for their sinusitis, excluding cases with non-invasive fungal sinusitis, chronic obstructive pulmonary disease, cystic fibrosis, primary ciliary dyskinesia (PCD) or severe asthma. This study was approved by the ethics committee of Chinese PLA General Hospital, and all patients gave their informed consent before recruitment in the study.

Freshly removed tissue was placed in Dulbecco's phosphate buffer (Ca^{2+} and Mg^{2+} free) before transfer to the laboratory. We digested the tissue in DMEM/F12 containing 0.1% protease type XIV (Sigma-Aldrich Corp), 0.1 mg/ml of deoxyribonuclease (Sigma-Aldrich Corp), 100 U/ml penicillin, 100 μg/ml streptomycin, 50 μg/ml gentamycin and 0.25 μg/ml amphotericin B for 18-24 hours. 10% foetal bovine serum (FBS) was added to neutralize the protease. After centrifuging, cells were counted and then plated on collagen type IV (Sigma) coated tissue culture 24- or 48- well plates in 10% FBS+BEGM (Gibco) (Table I) for 2 to 3 days. Next, we cultured the cells in serum-free modified medium (H-DMEM+BEBM 1:1). Cells were grown submerged until almost confluent in a humidified chamber with 95% air and 5% CO_2 at 37 °C. The culture medium was changed every day. LPS was added during mucociliary differentiation (continuous treatment). For observing mucociliary differentiation, cells were also directly seeded on 6.5 mm transwell plates and maintained in air–liquid interface culture (ALI).

LPS solution and stimulation

LPS (*Escherichia coli* O111:B4; Sigma, St. Louis, MO) was dissolved in BEBM medium at stock concentrations of 5 mg/ml, stored at -80 °C. Immediately before each experiment, an aliquot of LPS was thawed and diluted to working concentrations of 10 μg/ml, 50 μg/ml and 100 μg/ml. At 85-95% confluence, cells were treated with the three indicated LPS concentrations. The levels of HMGB1 protein in epithelial cells and supernatants were assessed after 0, 12, 24, 48 and 72 hr by Western blot.

Scanning electron microscopy

The air-liquid interface membranes were dehydrated in a progression of increasing ethanol, dried in CO_2, sputter-coated with gold palladium and then examined in a scanning electron microscope (SEM).

Cell viability assay

Because HMGB1 is not only secreted by activated innate immune cells, but also leaked by necrotic cells, prior to immunofluorescence and Western blot experiments the viability of cells used for experiments was assessed by 4% trypan blue exclusion and the live/dead viability determined. Only population of cells with a viability > 95% were used for experiments.

Immunofluorescence microscopy

Cell cultures were perfused with DPBS to remove the dead cells, and fixed in 4% paraformaldehyde for at least 20 min. Nonspecific staining was blocked with 5% goat serum, 3% bovine serum albumin (BSA) and 0.3 Triton® X-100 at room temperature for 30 min. Next, cells were incubated in 1% BSA-HMGB1 rabbit polyclonal antibody (Abcam, dilution 1:300) or β-tubulin mouse monoclonal antibody (Sigma, dilution 1:200) overnight at 4 °C. After three washes with PBS, the cells were incubated in alexa fluor® 488 goat anti-rabbit IgG and alexa fluor® 594 goat anti-mouse IgG (Invitrogen, dilution 1:1000) at room temperature for 60 min. Nuclear staining was performed using 4',6-diamidino-2-phenylindole (DAPI). Negative controls were processed in parallel without a primary antibody incubation step. Immuofluorescent photographs were taken with Leica fluorescence microscope.

HMGB1 protein Western blot analysis

Total protein extracts were prepared from epithelial cells in RIPA lysis buffer containing 1 mM phenylmethylsulphonyl fluoride (PMSF). Cell culture supernatants were collected after elimination, filtration (0.22 μm filter) and concentration using Amicon Ultra centrifugal filter devices (Millipore). Protein samples were quantified using the BCA assay kit (DingGuo). Briefly, equal amounts of cellular proteins were boiled and then loaded onto a 12% SDS-PAGE gel and transferred to polyvinylidene difluoride (PVDF) membranes. After blocking with 5% non-fat milk in TBST, the membrane was incubated with primary antibodies specific for HMGB1 mouse monoclonal antibody (Abcam, dilution 1:500) and β-actin mouse monoclonal antibody (Santa Cruz, dilution 1:1000) overnight. Subsequently, the membrane was incubated with the appropriate secondary antibody (Jackson ImmunoResearch Laboratories, dilution 1:3000) for 2 hr, and immunoreactive bands were visualized using a chemiluminescence ECL kit (Pierce). The relative band intensity was quantified by using Quantity One analyzer software.

Statistical analysis

All statistical analysis was performed using SPSS13.0 statistical analysis software. Results are presented as the means ± SD of 5 independent experiments. Those without significantly deviation from the normally distributed population were selected for one-way ANOVA analyses to determine significant differences among groups. When the ANOVA was significant, post hoc testing of difference was performed using Tukey's test. A p value < 0.05 was considered statistically significant.

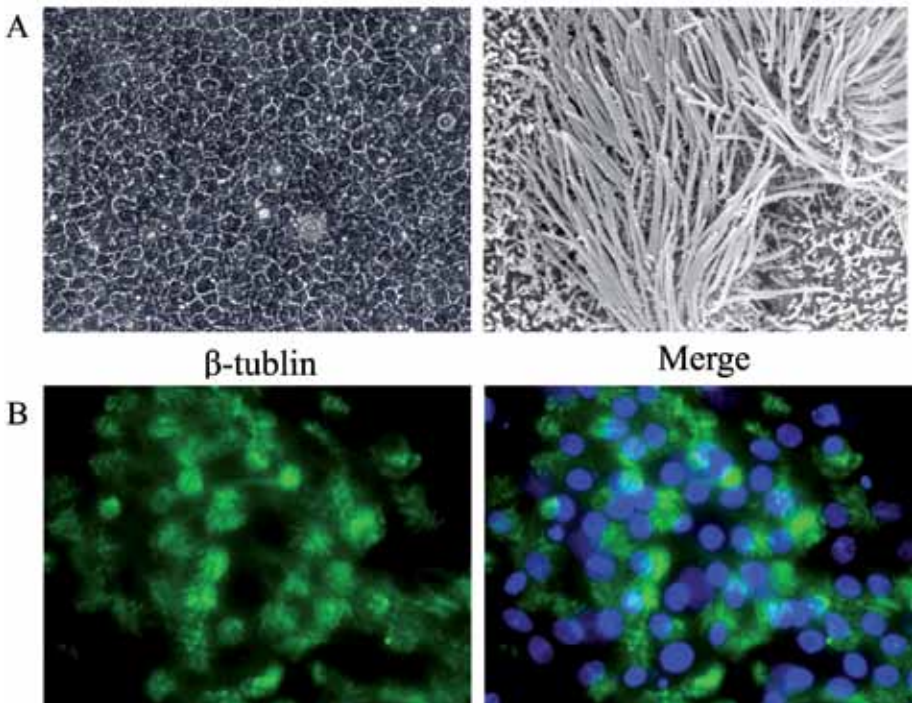

Fig. 1. Morphologic features of cultured HNE cells. A: Phase contrast image of epithelial cells in submerged culture (left); microstructure of the epithelial cells with cilia and microvilli in ALI culture (right ×5000); B: Fluorescence image of ciliated epithelial cells. Cilia are stained with β-tubulin (green). Original magnification: A left ×200; A right ×5000; B×400.

Results

Morphological characterization of HNE cells in vitro

To characterize the effect of inflammatory mediator LPS on HMGB1 expression in HNE cells, we first established primary cultures of human nasal epithelial (HNE) cells, which has greatly facilitated the study of upper airway diseases. HNE cells remained in a differentiated state (Figs. 1A

left, 1B) in submerged cultivation. Demonstration of β-tubulin by immunofluorescence indicated an intact monolayer with a differentiated cell population. On the other hand, with SEM the epithelial surface showed ciliated cells and microvilli cells for an ALI cultivation (Fig. 1 A right), which was similar to that reported in the literature [17].

LPS alters HMGB1 protein localization in HNE cells

Immunofluorescence and fluorescence microscopes were used to confirm the location of intracellular HMGB1 protein in LPS-induced HNE cells. The nuclei stained strongly, while no cytoplasm stained with red at 0 or 12 h, indicating that HMGB1 is distributed mainly in the nuclei (Fig. 2A-B). After stimulation, the cytoplasmic stain increased gradually from 24 hr and enhanced from 48 to 72 hr, and nuclear staining decreased gradually at the same time (Fig. 3C-E). These indicated that LPS induced HMGB1 translocation to the cytoplasm and extracellular release.

LPS stimulated a time-dependent production of HMGB1 protein in HNE cells

Although HMGB1 location changed following stimulation with LPS, it is still unknown if the LPS stimulus affects HMGB1 production in HNE cells. To explore this possibility, HNE cells were stimulated with 100 μg/ml LPS. The result was confirmed in Western blot. LPS induced an increase level of HMGB1 in HNE cells in a closely related time-dependent manner (Fig. 3). The level of HMGB1 protein in HNE cells showed no significant change at 0-24 hr, but HMGB1 protein levels at 48 hr were higher than at 0 hr, as well as for HMGB1 level at 72 hr.

Release of HMGB1 protein from HNE cells

Secreted HMGB1 in the cultured supernatant of the LPS-treated HNE cells was detectable after 12 hr, and the concentration of HMGB1 significantly increased at 24 hr after onset of treatment and continued to increase steadily (Fig. 4). The HMGB1 concentration in the culture supernatant was significantly higher at 48 hr and 72 hr compared to 0, 12 and 24 hr ($p < 0.001$ for each time point).

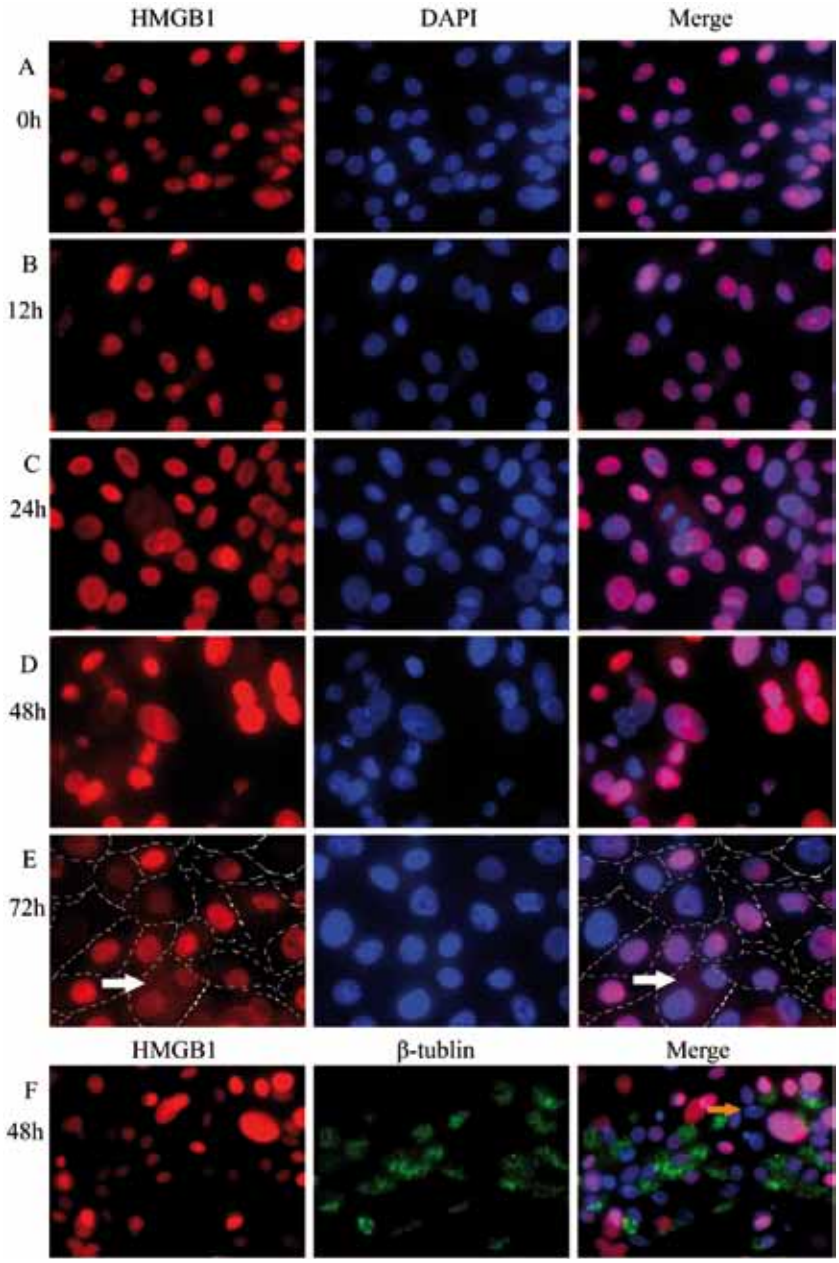

Fig. 2. Immunofluorescence detection of LPS-induced HMGB1 expression translocation in nasal epithelial cells at different times. A: 0 hr, B: 12 hr, C: 24 hr, D: 48 hr, E: 72 hr; F: HMGB1 (red) and β-tubulin (green) localization. White arrow: HMGB1 expression in cytoplasm of epithelial cells, yellow arrow: nuclei stained with DAPI. White dotted line: contour of epithelial cell

Discussion

Infections (viral, bacterial and fungal) under physiological conditions are readily eliminated without involvement of the adaptive immune system at the mucosal lining of the upper airways which is the first-line defense mechanism against pathogens and antigens [18]. Airway diseases such as rhinosinusitis and asthma are characterized by impaired airway epithelium immune barrier function [19 20]. LPS has emerged as a key regulator of inflammation; its exposure level is implicated in airway epithelium integrity, and in initiation of airway disease and development [21 22]. It is

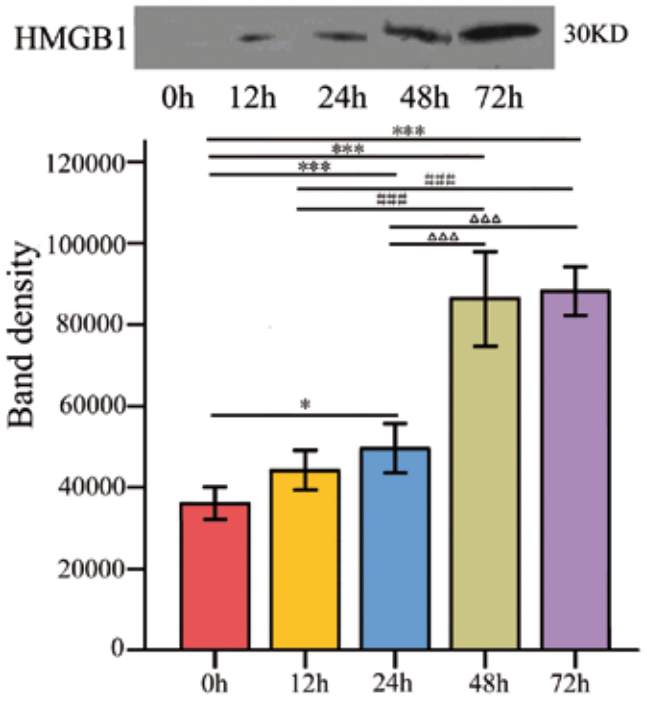

Fig. 3. HMGB1 expression in epithelial cells in vitro exposed to 100 μg/ml LPS from 0 to 72 hr.
The band density values are quantified by Quantity One software.
Data represent means ± SD; bars are presented as the relative ratio of HMGB1 to β-actin.
* as compared with 0 h group; # as compared with 12 h group; △ as compared with 24 h group; * $p < 0.05$; *** $p < 0.001$; ### $p < 0.001$; △△△ $p < 0.001$.

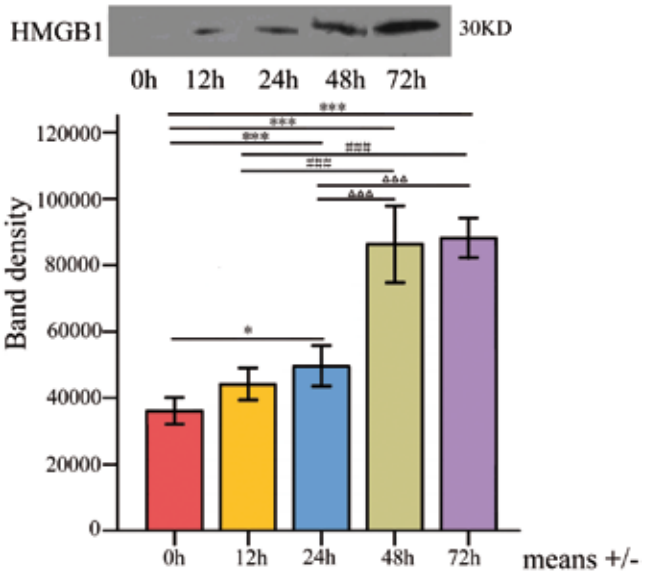

Fig. 4. Levels of released HMGB1 from HNE cells exposed to 100 μg/ml LPS from 0 hr to 72 hr by Western blot analysis (n = 5 for each group).
Data represent means ± SD. * as compared with 0 h group; # as compared with 12 h group; △ as compared with 24 h group; * $p < 0.05$; *** $p < 0.001$; ### $p < 0.001$; △△△ $p < 0.001$.

already known that DAMPs, such as HMGB1, may induce the selective recruitment of immune cells and lead to airway inflammation, and as such are important events in the progression of the inflammation response. To better understand the pathophysiological role of HMGB1 in inflammation, we used primary cultures of human nasal epithelial (HNE) cells, and demonstrated LPS-induced active translocation and release of HMGB1 in a time dependent manner.

In the present study, to ensure that HMGB1 protein was secreted from viable HNE cells, we used trypan blue exclusion to evaluate cell viability after LPS stimulation. When exposed to 10-100 μg/ml LPS, the viability of cells was not affected. This study documented for the first time the presence of HMGB1 immunostaining in the nuclei of HNE cells from nasal polyps; after LPS stimulation, translocation of HMGB1 from nuclei to cytoplasm occurred, suggesting that HNE cells represent a potential source of the secreted form of HMGB1 in the airways. This finding was in agreement with the results of Western blot analysis. In line with our results, the level of intracellular HMGB1 protein did not change in the early stages (0-24 hr) of stimulation with LPS, but increased significantly at 48 hr and maintained a higher level for up to 72 hr. Furthermore, HMGB1 protein was also released in the culture supernatant from viable HNE cells in a time-dependent fashion. The extracellular HMGB1 protein was significantly elevated at 24-72 hr. These findings are consistent with prior reports, indicating that HMGB1 is a late proinflammatory cyokine and differs from the early release of proinflammatory cyokines, such as TNF (1-2 hr), IL-1 (4-6 hr) and IFN-γ (4-6 hr) by LPS [23-25]. Our results suggest that after the export of cytoplasmic HMGB1 to the culture medium, intra-nuclear HMGB1 is re-synthesized and relocated, keeping its level high.

Alternations in the structure and function of the nasal epithelial cells change the mechanical properties of the airway barrier and might also drive inflammation.

Nasal epithelial cells are a major target for LPS, and toll-like receptors (TLR) -2, -4 and -9, members of the larger family of TLRs, have been demonstrated to play a role in nasal epithelial cells and related nasal mucosa diseases [26-28]. They belong to pattern- recognizing receptors (PRPs) and directly recognize PAMP on pathogens. Via TLR-4 signaling, bacterial products (e.g. LPS) may subsequently trigger the intracellular signaling pathway, including the MAPK-p38 and NF-κB pathways [29 30]. Many inflammatory responses to LPS are mediated by activation of the two pathways and enhance the transcription of HMGB1 products of the activated macrophage [31 32].

The mechanism of HMGB1 transfer from the nuclei to special cytoplasmic organelles, namely secretory lysosomes, is related to acetylation of specific lysine residues [28 29]. Following this, HMGB1 accumulates in the cytoplasm with its nuclear reentry blocked. Once released

into the extracellular medium, HMGB1 may exert its effects by binding to its receptors, RAGE, TLR-2, TLR-4 and TLR-9 [31-33]. Since HMGB1-induced activation of NF-κB is known to involve TLR-2 and TLR-4, we hypothesize that HMGB1 may activate the NF-κB signaling pathway to cause cytokine production and thereby indirectly promote dysfunction of the epithelial cell barrier. We have previously observed that cytokines IL-5, IL-8 and TNF-α may interfere with the expression and the localization of HMGB1 in nasal polyps. Clearly, more experimental investigations will be required to increase our understanding of these interacting networks, and especially the regulatory pathways of HMGB1 in HNE cells.

Taken together, the nasal epithelium is more than a physical barrier, and is critical in regulating nasal and sinus mucosa homeostasis. This study demonstrated that HNE cells are a source of HMGB1 and that LPS triggers active release of HMGB1. Our findings suggested that LPS plays a potentially important role in the induction and prolongation of inflammatory processes by inducing HMGB1 release and "recycle" of injurious proinflammatory mediators. Understanding the mechanisms of infection- or injury-elicited inflammatory responses directly or indirectly through HMGB1 may provide important insights into the pathogenesis associated with rhinosinusitis and are instrumental in identifying new targets for therapy.

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Sleep disorders

The role of drug-induced sleep endoscopy in the diagnosis and management of obstructive sleep apnoea syndrome: our personal experience

Ruolo dell'endoscopia delle prime vie aeree durante il sonno indotto farmacologicamente nella diagnosi e nel trattamento della sindrome delle apnee ostruttive durante il sonno: la nostra esperienza personale

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SUMMARY

Nowadays, drug-induced sleep endoscopy (DISE) is performed widely and its validity and reliability has been demonstrated by several studies; in fact, it provides clinical information not available by routine clinical inspection alone. Its safety and utility are promising, but still needs to be improved to reach the level of excellence expected of gold standard tests used in clinical practice. Our study compares the results of clinical and diagnostic evaluation with those of sleep endoscopy, evaluating the correlation between clinical indexes of routine clinical diagnosis and sites of obstruction in terms of number of sites involved, entity of obstruction and pattern of closure. This study consists in a longitudinal prospective evaluation of 138 patients who successfully underwent sleep endoscopy at our institution. Patients were induced to sleep with a low dose of midazolam followed by titration with propofol. Sedation level was monitored using bispectral index monitoring. Our results suggest that the multilevel complete collapse was statistically significantly associated with higher apnoea hypopnea index values. By including partial sites of obstruction greater than 50%, our results also suggest that multilevel collapse remains statistically and significantly associated with higher apnoea hypopnoea index values. Analyzing BMI distribution based on number of sites with complete and partial obstruction there was no significant difference. Finally, analyzing Epworth Sleepiness Score distribution based on number of sites with complete obstruction, there was a statistically significant difference between patients with 3-4 sites of obstruction compared to those with two sites or uni-level obstruction. In conclusion, our data suggest that DISE is safe, easy to perform, valid and reliable, as previously reported. Furthermore, we found a good correlation between DISE findings and clinical characteristics such as AHI and EPS. Consequently, adequate assessment by DISE of all sites of obstruction is very important, not only in patients with low-moderate AHI and EPS, but also in patients with a high AHI or/and high EPS, in particular to plan multilevel surgery that in these latter situations is more demanding since success may be harder to achieve.

KEY WORDS: Obstructive sleep apnoea syndrome • Drug-induced sleep endoscopy • AHI • BMI • EPS

RIASSUNTO

Attualmente, la sleep endoscopy indotta per via farmacologica (DISE) è ampiamente eseguita e la validità ed affidabilità di tale metodica sono state dimostrate in numerosi studi. La sua sicurezza e utilità sono promettenti, tuttavia, tale esame necessita di essere migliorato per raggiungere il livello di eccellenza tipico di un test gold standard utilizzato nella pratica clinica. Obiettivo del nostro studio è stato paragonare i risultati della valutazione clinica e diagnostica tradizionale con quelli della sleep endoscopy, mettendo a confronto i parametri clinici con i siti di ostruzione, ed in particolare prendendo in considerazione il numero di siti implicati, il livello di ostruzione e il pattern di chiusura. In questo studio abbiamo effettuato una valutazione prospettica longitudinale di 138 pazienti che sono stati sottoposti a sleep endoscopy con induzione farmacologica del sonno presso la nostra clinica. Ai pazienti è stato indotto il sonno mediante un basso dosaggio di propofol seguito da una somministrazione di boli progressivi. La profondità della sedazione è stata monitorata mediante il monitoraggio BIS. Sulla base dei risultati ottenuti è stato possibile stabilire che l'ostruzione completa multilivello si associa in modo statisticamente significativo ad un indice più elevato di apnea/ipopnea (AHI). Includendo nell'analisi anche i siti di ostruzione parziale con chiusura > del 50% abbiamo potuto dimostrare che l'associazione fra il collasso multilivello ed un valore di indice apnea/ipopnea più elevato rimane statisticamente significativa. Per quanto riguarda il BMI invece non sono state riscontrate correlazioni significative con il numero di siti di ostruzione completi o parziali. Infine, analizzando la scala della sonnolenza di Epworth e correlandola con il numero di siti con ostruzione completa abbiamo trovato una differenza statisticamente significativa tra i paziente con 3-4 siti di ostruzione rispetto ai pazienti con 2 o 1 livello di ostruzione. In conclusione, i nostri dati suggeriscono che la sleep endoscopy indotta per via farmacologica (DISE) costituisce una procedura sicura, di facile esecuzione, valida ed affidabile, come già descritto in altri studi. Inoltre abbiamo dimostrato una buona correlazione e coerenza tra i risultati della sleep endoscopy e gli indici di AHI e di Epworth. Concludendo riteniamo che un'adeguata valutazione dei siti di ostruzione mediante sleep endoscopy sia molto importante non solo nei pazienti con AHI ed indice di Epworth lieve/moderato, ma anche in quelli con AHI e/o indice di Epworth elevati, soprattutto nella pianificazione di una chirurgia multilivello che in questi casi è più impegnativa con un indice di successo più difficile da raggiungere.

PAROLE CHIAVE: *Sindrome delle apnee ostruttive durante il sonno • Endoscopia durante il sonno indotto farmacologicamente • AHI • BMI • EPS*

Introduction

Nowadays, drug-induced sleep endoscopy (DISE) is performed widely and its validity has been demonstrated by several studies; in fact, it provides clinical information not available by routine clinical inspection alone [1]. Even though sleep endoscopy during natural sleep is an ideal test, it is an impractical diagnostic tool because the study needs to be carries out during the night and the endoscope may disturb the sleeping patient. For these reasons, in 1991 Croft and Pringle [2] introduced drug-induced sleep nasendoscopy, which provides direct visualization of structural collapses of the upper airway under anaesthesia. The study during the awake state may offer erroneous information regarding upper airway obstruction. In fact, Campanini A et al. [1] recently demonstrated that awake and sedation ENT evaluation was identical in only the 25% of cases. In particular, discrepancies involved the oropharyngeal and laryngo-hypopharyngeal sites. Laryngeal obstruction was misunderstood in almost 33% of cases. These results are very important because diagnostically inaccurate information can lead to relevant negative implications in terms of treatment choices, particularly for surgical cases.

Identification of the site of obstruction and pattern of upper airway changes during sleep is a key point essential in guiding therapeutic approaches of obstructive sleep apnoea syndrome (OSAS). Several studies have demonstrated that DISE may help to specify therapy individually, leading to an increased surgical success rate [3 4]. For these reasons, DISE has been an essential breakthrough in evaluation of OSA patients. Nevertheless, it has been widely criticized due to the use of sedation that may cause false-positive results, as it assesses sleep in only a short interval that is not representative of a night's snoring, and that the patient's snoring quality and quantity of apnoea occurrences varies with sleeping position and sleep stages [5].

The reliability of DISE is good, and studies on its safety and utility are promising. Nevertheless, it needs to be improved to reach the level of excellence expected of gold standard tests used in clinical practice. In particular, additional research is required to determine the correlations between data obtained during DISE and results of standard clinical evaluation. Finally, some limitations remain unresolved: the lack of standardized protocols and validated grading scales; potential differences with natural sleep; effects of intravenous anaesthetic agents; test-retest reliability among different examiners [6 7].

Our study compares results of clinical and diagnostic evaluation with those of sleep endoscopy, evaluating the correlation between clinical indexes and sites of obstruction in terms of number of sites involved, entity of obstruction and pattern of closure. Furthermore, we analyze the validity of the sleep endoscopy to assess the best treatment for patients with OSAS, particularly those who are undergoing surgical treatment or receiving specific treatment such as oral devices.

Materials and methods

Subjects

From January 2011 to February 2013, we included 138 patients aged between 18 and 72 years (mean age 47.36 years) who successfully underwent sleep endoscopy at our institution (Department of Head and Neck Surgery, Institute of Otorhinolaryngology "A. Gemelli Hospital", Catholic University School of Medicine and Surgery, Rome). There were 108 males and 30 females. BMI ranged from 22.6 to 36.4 kg/m^2 (mean BMI 27.2 ± 3.04); mean neck circumference was 40.5 ± 2.6 cm with values ranging from 31 to 47 cm; mean waist circumference was 101±8.4 cm with range between 12 and 87 cm. Mean Epworth index was 9.8 ± 2.75. Mean apnoea-hypopnoea index (AHI) was 35 ± 9 events/hour. Mean ODI 9.8 ± 4.75 events/hour.

Study design

Single institution, longitudinal prospective evaluation of a consecutive group of patients that underwent DISE for management of OSAS. All patients were willing to participate and consented to their inclusion.

Baseline assessment

Each subject was evaluated with a baseline Epworth Sleepiness Scale (ESS) and Berlin Questionnaire (BQ). All patients received a full otolaryngologic examination to evaluate awake status of upper airway and in particular, size of uvula, soft palate and tonsils, tongue base, vallecula, size and shape of epiglottis and Mallampati Score. Following this preliminary evaluation, a full-night comprehensive PSG was scheduled.

Polysomnography

Each patient underwent a full-night ambulatory cardiorespiratory monitoring (A-PSG), performed to assess the sleep-related respiratory pattern. A-PSG was monitored continuously during the sleep-endoscopy procedure using a portable device. A-PSG recordings included airflow (nasal cannula trasducer), respiratory effort (chest and abdominal belts), oxygen saturation, snoring sound, heart rate and body position. An experienced sleep technician performed the application sensors for instructing the patients in their correct application. The frequency of obstructive events is reported as AHI. OSA severity was defined as *mild* for AHI ≥ 5 and < 15, *moderate* for AHI ≥ 15 and ≤ 30 and *severe* for AHI > 30.

PSG monitoring was also performed in continuous mode during the sleep endoscopy procedure. The PSG setup included 3 EEG (F3, C3, O1 referred to the contra-lateral mastoid), 2 EOG, surface EMG of submental and intercostal muscles, airflow (nasal cannula trasducer),

respiratory effort (chest and abdominal belts), oxygen saturation, snoring sound, heart rate and body position. A PSG technician attended the recording. Central, mixed and obstructive events were classified according to standardized criteria. Wake, drowsiness and sleep stages were scored on the basis of EEG, EOG and EMG traces, according to standardized criteria. This monitoring allowed performing sleep endoscopy during night, NREM sleep, and to visually identify obstructive apnoeas during the procedure [8-10].

Drug-induced sleep endoscopy

In a controlled, monitored setting (continuous PSG monitoring, as specified in the previous paragraph) with the help of an anaesthesiologist, all patients underwent DISE performed by a specialist ENT. Patients were induced to sleep with a low dose of propofol (0.01 mg/kg) followed by a titration of propofol (3 mg/kg/hr).

Sedation level was monitored using bispectral index (BIS) monitoring (Aspect Medical Systems, Newton, MA). When the patient was asleep and actively snoring with BIS between 50 and 70, a video-recorded fibreoptic nasopharyngoscope was used to assess the upper airway. In our procedures, the average BIS was 55.78 with a mean minimum BIS of 43.15 and a mean maximum BIS of 72.14 [5].

When the patient begins to snore and demonstrate airway collapse, the flexible endoscope is inserted through one of the nostrils and is placed on different levels of the upper airways to visualize the site of collapse in real time. Areas of obstruction (velum including soft palate and tonsils, tongue base, larynx and hypopharynx) were classified using a DISE scoring sheet reporting type of obstruction [complete (100%) or partial (grade I: 0-25%; grade II: 25-50%; grade III: 50-75%: grade IV: > 75%)] and dynamic pattern of closure (anterior–posterior, concentric, laterolateral). The DISE scoring sheet was completed in a second time by the principal investigator based on DISE assessment. To characterize the dynamic pattern of closure, DISE findings were reported using the VOTE classification system [11].

During the examination, we also performed a mandibular pull-up (MPU) manoeuvre. The manoeuvre consists in moving the jaw forward by 6-8 mm, and pulling-up the lower dental arch to evaluate the increase in the air space of the areas under examination while breathing improved or snoring disappeared [12].

In our institution, drug induced sleep endoscopy is generally contraindicated in patients with a high American Society of Anesthesiologists (ASA) score and propofol or midazolam allergies (albeit rare), owing to high risk. Relative contraindications are also severe OSA (an AHI > 70 events/hour) and severe obesity, as these patients are regarded as poor candidates for sleep surgery or an MRA.

Statistical analysis

Statistical analysis was performed using SPSS for Windows. Continuous variables were expressed as mean ± SD. Comparisons between groups were performed by Mann-Whitney U-test and t-test. The results were considered statistically significant for p values < 0.05.

Results

Taking into consideration grade of the sites of obstruction observed during DISE, it was possible to establish their prevalence. Considering a complete obstruction of 100%, we found that palatal obstruction was the most frequently observed site of obstruction (73%), followed by tongue base obstruction (43%), laryngeal obstruction (31%) and hypopharyngeal obstruction (23%). Data are shown in Table I in all patients at different AHI and BMI. Partial obstruction greater than 50% was present at a palatal site in 23%, at a base tongue site in 34%, at a laryngeal site in 37% and at a hypo-pharyngeal site in 26% of patients. Data are shown in Table II in all patients at AHI and BMI.

The prevalence of cases based on number of sites of complete obstruction and different AHI and BMI is shown in Table III. The partial sites with obstructions greater than 50% are shown in Table IV.

Table V details prevalence based on patterns of obstruction for each site following the VOTE classification system.

Correlating results of DISE with polysomnographic parameters, we found that the AHI was significantly higher in patients with multilevel obstruction compared to those with a unilevel one. In fact, our results suggest that the multilevel complete collapse was significantly associated with higher AHI values as shown in Figure 1a. Including partial sites of obstructions greater than 50%, our results suggest that multilevel collapse remains statistically and significantly associated with higher AHI values (Fig. 1b).

Considering BMI distribution basing on number of sites with complete obstruction, there was no significant difference (Fig. 2a). Considering partial (greater than 50%) sites of collapse, multilevel collapse was not significantly associated with higher BMI as shown in Figure 2b. Finally, analyzing Epworth Sleepiness Score distribution based on number of sites with complete obstruction, we found a significant difference between patients with 3-4 sites of obstruction compared to those with two sites or uni-level obstruction as shown in Figure 3. We did not observe any significant difference in terms of ESS considering sites of partial obstruction greater than 50%.

Comparing patients with or without a concentric complete oropharyngeal collapse, there was significantly higher AHI (40.42 versus 31.76 per hour) and higher BMI (26.3 versus 28.3) in the former group compared to the latter (Fig. 4).

Table I. Patient distribution considering site of complete (100%) obstruction and AHI and BMI.

	Complete retro palatal collapse	Complete retro lingual collapse	Complete oro-hypo-pharyngeal lateral wall collapse	Complete laryngeal collapse
All patients (n = 138)	102 (73.9%)	60 (43.47%)	32 (23.18%)	44 (31.88%)
AHI < 30 (n = 72)	42 (58.33%)	14 (19.44%)	4 (5.55%)	18 (25%)
AHI ≥ 30 (n = 66)	60 (90.90%)	46 (69.69%)	28 (42.42%)	26 (39.39%)
BMI < 30 (n = 108)	82 (75.92%)	42 (38.88%)	22 (20.37%)	36 (33.33%)
BMI ≥ 30 (n = 30)	20 (66.66%)	18 (60%)	10 (33.33%)	8 (26.66%)

Table II. Patient distribution considering sites of partial (greater than 50%) obstruction and AHI and BMI.

	Partial retro palatal collapse	Partial retro lingual collapse	Partial oro-hypo-pharyngeal lateral wall collapse	Partial laryngeal collapse
All patients (n = 138)	34 (24.63%)	48 (34.78%)	52 (37.68%)	36 (26.08%)
AHI < 30 (n = 72)	22 (30.55%)	32 (44.44%)	32 (44.44%)	18 (25%)
AHI > 30 (n = 66)	10 (15.15%)	14 (21.21%)	22 (32.33%)	18 (27.27%)
BMI < 30 (n = 108)	26 (24.07%)	44 (40.74%)	48 (44.44%)	28 (25.92%)
BMI > 30 (n = 30)	6 (20%)	4 (13.33%)	6 (20%)	8 (26.66%)

Table III. Patient distribution based on number of complete sites of obstruction and AHI and BMI.

	1 site	2 sites	3 sites	4 sites
All patients (n = 138)	54 (39.13%)	52 (37.68%)	16 (11.59%)	16 (11.59%)
AHI < 30 (n = 72)	38 (52.7%)	22 (30.5%)	4 (2.8%)	0
AHI ≥ 30 (n = 66)	14 (9.24%)	30 (45.45%)	12 (18.18%)	16 (24.24%)
BMI < 30 (n = 108)	50 (46.29%)	40 (37.03%)	8 (7.40%)	12 (11.11%)
BMI ≥ 30 (n = 30)	6 (20%)	10 (33.33%)	6 (20%)	4 (13.33%)

Table IV. Patient distribution based on number of partial (greater than 50%) sites of obstruction and AHI and BMI.

	1 site	2 sites	3 sites	4 sites
All patients (n = 138)	6 (4.34%)	42 (30.43%)	30 (21.73%)	58 (42.02%)
AHI < 30 (n = 72)	4 (5.5%)	26 (36.11%)	12 (16.66%)	24 (33.33%)
AHI > 30 (n = 66)	2 (3.03%)	16 (24.24%)	18 (27.27%)	34 (51.51%)
BMI < 30 (n = 108)	6 (5.55%)	34 (31.48%)	18 (16.66%)	48 (44.44%)
BMI > 30 (n = 30)	0 (%)	6 (20%)	14 (46.66%)	10 (33.33%)

Table V. Distribution of patients based on patterns of obstruction for each site.

	Antero – posterior		Lateral		Concentric	
	Partial	*Complete*	*Partial*	*Complete*	*Partial*	*Complete*
Velum	18/138 (13.04%)	40/138 (28.98%)	6/138 (4.34%)	40/138 (28.98%)	28/138 (20.28%)	42/138 (30.43%)
Oropharynx	/	/	24/138 (17.39%)	14/138 (10.14%)	/	/
Tongue base	48/138 (34.78%)	60/138 (43.47%)	/	/	/	/
Epiglottis	20/138 (14.49%)	28/138 (20.28%)	16/138 (11.59%)	16/138 (11.59%)	/	/

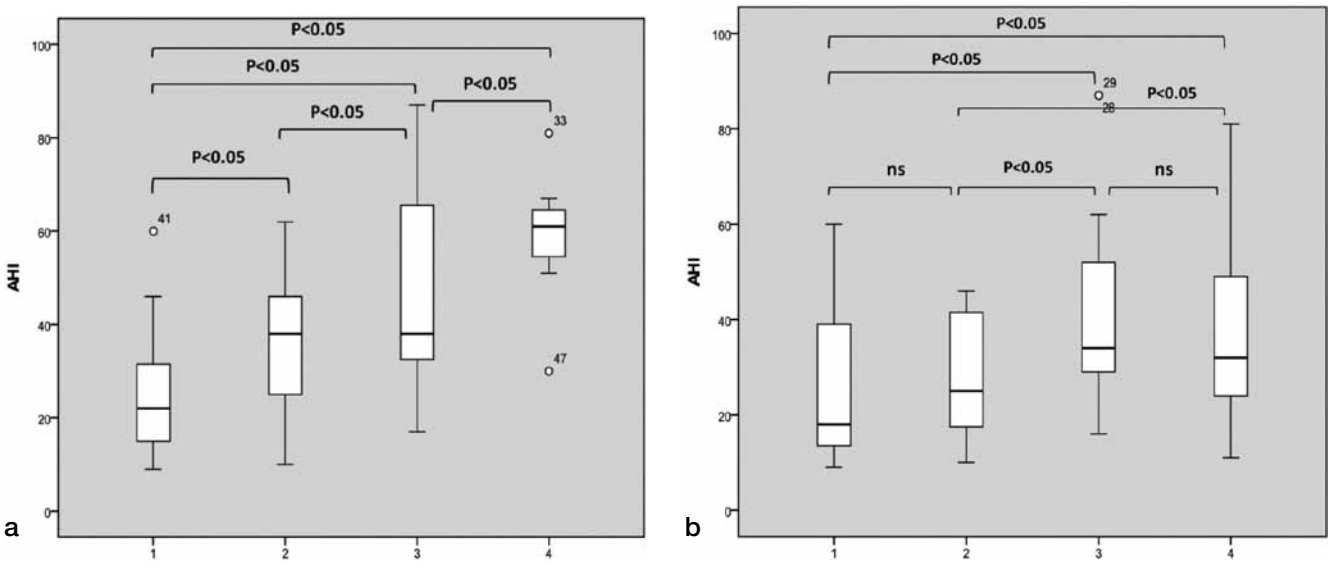

Fig. 1. AHI distribution based on the number of sites of complete collapse (a) and complete plus partial collapses greater than 50% (b). The box plots show the median and inter-quartile range and the error bars show the 5th and 95th percentiles.
a. 1: one complete site of obstruction of 100%; 2: two complete sites of obstruction of 100%; 3: three complete sites of obstruction of 100%; 4: four complete sites of obstruction of 100%).
b. 1: one site of obstruction of 100% or > 50%; 2: two sites of obstruction of 100% and/or > 50%; 3: three sites of obstruction of 100% and/or > 50%; 4: four sites of obstruction of 100% and/or > 50%).

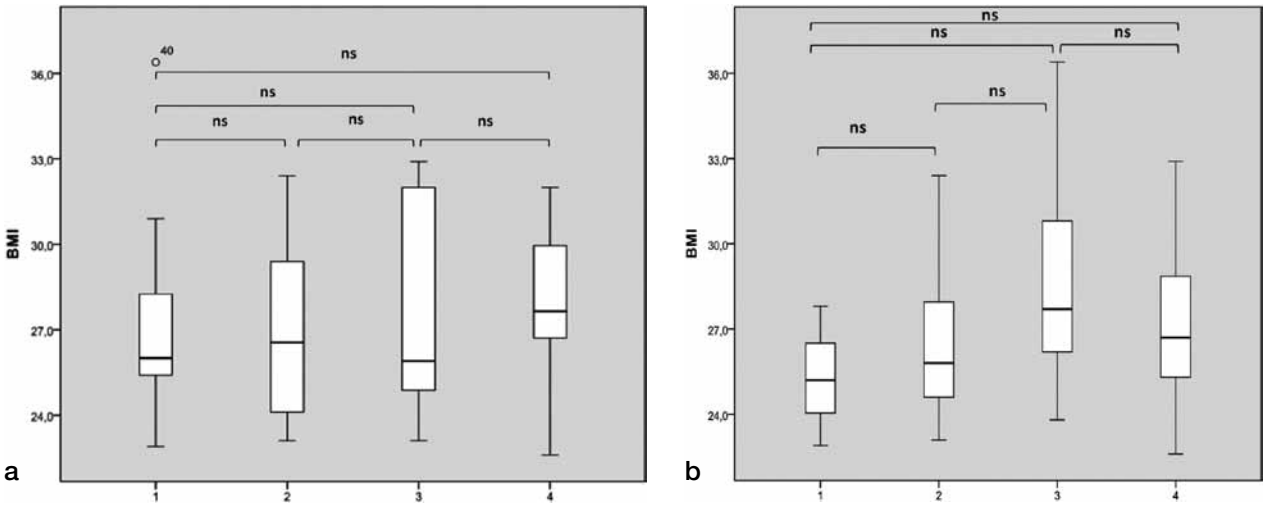

Fig. 2. BMI distribution based on the number of sites of complete collapse (a) and complete plus partial collapses greater than 50% (b). The box plots show the median and inter-quartile range and the error bars show the 5th and 95th percentiles.
a. 1: one complete site of obstruction of 100%; 2: two complete sites of obstruction of 100%; 3: three complete sites of obstruction of 100%; 4: four complete sites of obstruction of 100%).
b. 1: one site of obstruction at 100% or > 50%; 2: two sites of obstruction of 100% and/or > 50%; 3: three sites of obstruction of 100% and/or >5 0%; 4: four sites of obstruction of 100% and/or > 50%).

A difference was found in AHI in patients with or without an epiglottis-level obstruction, although this was not statistically significant (33.48 versus 38.22 per hour, P > 0.05; Fig. 5).

Table VI shows the data of the most appropriate treatment (oral device, surgery or CPAP) chosen for each patient based on the clinical information obtained during drug induced sleep endoscopy.

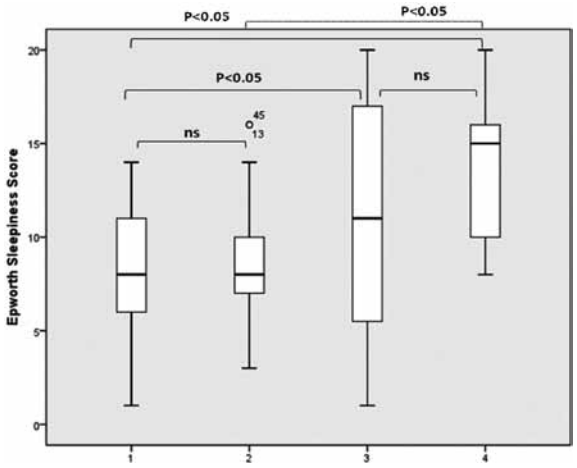

Fig. 3. Epworth Sleepiness Score distribution based on the number of sites of complete collapse. The box plots show the median and inter-quartile range and the error bars show the 5th and 95th percentiles.
1: one complete site of obstruction of 100%; 2: two complete sites of obstruction of 100%; 3: three complete sites of obstruction of 100%; 4: four complete sites of obstruction of 100%).

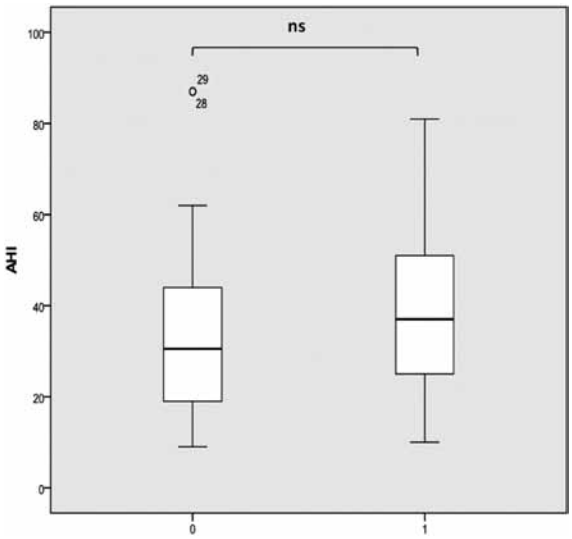

Fig. 5. AHI in patients with (1) or without (0) laryngeal site collapse.

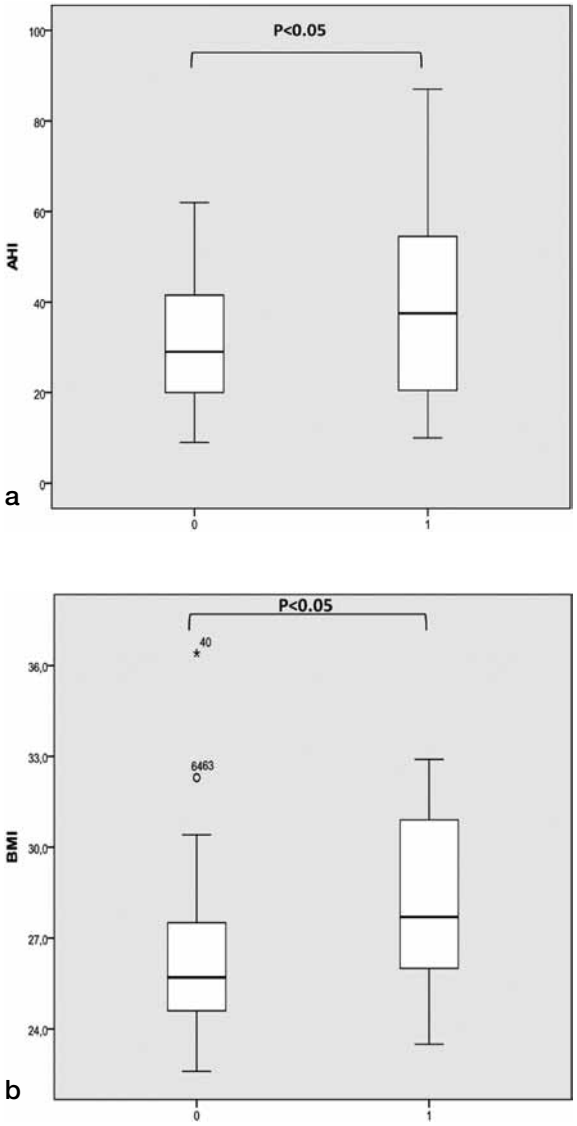

Fig. 4. AHI (a) and BMI (b) in patients with (1) or without (0) concentric complete oropharyngeal collapse.

Table VI. Distribution of patients based on treatment options chosen considering clinical information obtained during drug induced sleep endoscopy and subdivided based on AHI and BMI. In the last column, the number of cases referred to repeat polysomnography due to inconsistencies between DISE and AHI is reported.

	Oral device	Surgery	CPAP	Repeat PSNG
All patients (n = 138)	42 (30.43%)	28 (20.28%)	56 (40.57%)	4 (2.89%)
AHI < 30 (n = 72)	30 (41.66%)	18 (25%)	18 (25%)	3 (4.16%)
AHI ≥ 30 (n = 66)	14 (21.21%)	12 (11.32%)	38 (57.57%)	1 (1.51%)
BMI < 30 (n = 108)	34 (31.48%)	26 (24.07%)	44 (40.74%)	2 (1.85%)
BMI ≥ 30 (n = 30)	6 (20%)	4 (13.33%)	16 (53.33%)	2 (6.66%)

Discussion

Patients with OSAS experience excessive daytime sleepiness, impaired concentration, snoring, recurring nocturnal awakenings and non-restorative sleep with an increased risk of obesity and cardiovascular disease leading to substantial socio-economic implications [13]. Diagnostic evaluation is crucial to choose the best treatment options [14-16]. Baseline evaluation is very important, but it needs to be integrated with data obtained by polysomnography and sleep endoscopy in order to obtain, for each patient, all relevant information about the physiopathology of the sleep airway obstruction.

Currently, DISE is the most reliable standard method to determine the level, number and severity of sites of obstruction of the airway during the night in sleep apnoea patients and to specify the exact dynamic pattern of closure. In fact, even though overnight polysomnograph is the gold standard diagnostic study for sleep-disordered breathing, it fails to establish the precise site of collapse. Furthermore, the Müller manoeuvre has been questioned because it does not predict the success of surgery, location of upper airway obstruction or severity of the disease [1]. In fact, measurement of the collapsibility of the upper airway during the awake state is not a good indicator of collapsibility during sleep, due to differences in term of muscle tone, sensitivity of reflexes and respiratory physiology, between the conscious and the unconscious states. Finally, plain film cephalometry and CT scans only provide static information about the bony structure without evidence of soft tissue collapse. For this reason, new insight is expected from tests such as DISE that add a dynamic evaluation to classical static ones during induced sleep. Dynamic magnetic resonance imaging (MRI) is promising, and is increasingly used in the evaluation of the site of collapse in OSA. In this field, newer studies have also led to a computational model of the human upper airway by signal averaging of MRI. Based on this model, various surgical interventions have been simulated, offering new possibilities in the improvement of surgical and nonsurgical approaches to OSA patients. Future studies will suggest the clinical value of its application in the standard diagnostic work-up [17 18].

Our study compares the results of routine clinical and diagnostic evaluation with DISE results, evaluating the correlation between clinical indexes with number, dynamic pattern and severity of sites of obstruction. We scored four separate obstruction sites differentiating between partial and complete obstruction and defining the dynamic pattern of closure. We statistically correlated AHI, BMI and EPS not only with the number of sites of complete obstruction but also with partial ones, even though literature data are not consistent about this point. Salamanca et al. [19] recently published a large series of patients that underwent DISE without including partial sites of obstruction. Bachar et al. [20] recently proposed a novel grading system for quantifying upper-airway obstruction including partial sites.

In our series, the distribution of sites of obstruction coincides with the results published in the literature [21]. In fact, we observed that a retropalatal site is the most frequently involved in the obstruction followed by a retrolingual site. Multilevel obstruction is more common than a single-level one. In addition, the results of our study show that multilevel obstruction was significantly associated with higher AHI. We demonstrated that an higher number of sites of obstruction significantly correlates with higher AHI, not only considering complete obstruction but also including sites with partial obstruction greater than 50%. Taking into account the dynamic pattern of closure, there is a significantly higher AHI only when a concentric pattern of closure is present, and in particular at an oropharyngeal site. Finally, our data suggest that multilevel obstruction was significantly associated with higher EPS as a higher number of sites of obstruction significantly correlated with higher EPS scores. Thus, our study shows the appropriateness and reliability of the results obtained by DISE and their correlation with those obtained by polysomnography.

We obtained different results when analyzing the results of DISE and BMI. Moreover, the available data about correlations between BMI and number of sites of obstruction is not homogenous. Abdullah et al. observed that a trend of a higher BMI was associated with four or more sites of obstruction compared to single-site obstruction [22]. In contrast, other authors [23] did not observe the same correlation. In our series, we found that a trend of higher BMI was associated with a higher number of sites of complete obstruction, and that this trend was consistent when including partial sites of obstruction, even though these differences did not reach statistical significance. Nonetheless, expert opinion and various reports [24-26] concur that concentric obstruction is related to higher BMI. In agreement with this, we found a significantly higher BMI in patients with a concentric pattern of closure, and in particular at an oropharyngeal-velum site compared to patients with other patterns of closure.

In our series, the depth of induced sleep was assessed using a BIS Monitor. In fact, the degree of upper airway narrowing can be intensified according to the depth of sedation. The monitoring of sedation during DISE is critical, especially in patients with mouth breathing [5]. BIS, originally developed to validate the depth of anaesthesia, has begun to be used in sleep research. Babar-Craig et al. reported on the efficacy of the bispectral index (BIS) monitoring system to validate the depth of sedation during DISE [27]. Sleigh et al. [11] found that light sleep was associated with BIS values of 75 to 90, and that slow-wave sleep was associated with BIS values of 20 to 70 [28]. Therefore, in agreement with literature data, we agree that while performing DISE the depth of sedation must be monitored,

and deeper sleep must be included in the test period. In our procedures, the average BIS was 55.78 with a range between a mean minimum BIS of 43.15 and a mean maximum BIS of 72.14.

The gold-standard treatment of OSAS is currently continuous positive airway pressure (CPAP), relegating other treatments – oral device and surgery – in case of failure of CPAP and only in moderate OSAS as the first option treatment. The introduction of DISE in helping to define the pathogenesis of the site of obstruction individually offers more targeted and tailored information that is changing the indications of initial treatment. Unfortunately, a significant number of patients do not tolerate CPAP (30- 50%) [4]. For this reason, many patients try to find surgical therapy as an alternative solution. Based on the available data in cases in which surgery is indicated after standard pre-operative evaluation, surgeons still consider sleep endoscopy as knowledge of the precise sites of obstruction is critical for successful sleep surgery; DISE, in fact, allows real-time identification of the levels of collapse and the severity and pattern of collapse at each level, offering an important predictive value of surgical success. Finally, sleep endoscopy shows potential for other applications and has been proposed for selecting candidates for other site specific interventions such as oral appliances and endoscopy-assisted CPAP titration [29]. In our series, as a final outcome of the diagnostic work up, surgery, oral device and CPAP were chosen based on DISE results. In particular, when surgery was indicated DISE appears to be fundamental in defining the type of intervention. In four cases, we preferred DISE over repeat polysomnography due to discrepancies between DISE results and AHI before suggesting the best treatment option. Several surgical approaches have been suggested for OSAS patients [30-33], although the surgeon should consider DISE results before planning the optimal surgical treatment.

In conclusion, our data suggest that DISE is safe, easy to perform, valid and reliable, as previously reported. Furthermore, we found a good correlation between DISE findings and clinical characteristics such as AHI and EPS, in agreement with literature data. In particular, we observed a significant association between higher AHI and higher number of sites of obstruction in terms not only of complete obstruction, but also of partial obstruction greater than 50%. In particular, for this latter point, larger study should better characterize the association with clinical indexes to understand its clinical significance. Based on our data, we suggest that adequate assessment by DISE of all sites of obstruction is very important, not only in patients with low-moderate AHI and EPS, but also in patients with high AHI or/and high EPS, which is important to plan multilevel surgery as it is more demanding and success may be harder to achieve. Moreover, it has recently been demonstrated [34] that the test-retest reliability of DISE is good and that DISE has a relevant influence on treatment recommendations, positively influencing success rates of OSA therapy by addressing airway obstruction in a targeted fashion, leading to surgical treatment that is tailored to a specific pattern of obstruction [3]. Future challenges for DISE remain standardizing the method of sedation, identification of a uniform DISE classification system and definition of a reproducible and titratable standard mandibular advancement manoeuvre. Future research should focus on these topics to increase the already well-recognized role of DISE.

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Audiology

Newborn hearing screening in the Campania region (Italy): early language and perceptual outcomes of infants with permanent hearing loss

Screening uditivo neonatale nella regione Campania (Italia): sviluppo delle prime competenze percettive e linguistiche nei bambini con deficit permanente dell'udito

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SUMMARY

Hearing loss in children causes a deficit in early perceptive and language skills. The objective of this study was to evaluate early receptive and expressive language outcomes in children with hearing loss, identified by hearing screening, compared to the time of diagnosis. We studied 18 severely hearing impaired children who were divided into two groups according to the time of diagnosis. Evaluation of communicative language ability was carried out at 18 month of age using the "MacArthur Child Development Inventory" questionnaire, while evaluation of acoustic-perceptual abilities was assessed with the Genovese-Arslan protocol every three months following diagnosis. The linguistic communicative and acoustic-perceptual outcomes of hearing impaired children diagnosed before 6 months of age followed those expected for normally hearing children, with a trend of temporal progression of skills that were faster than those of children diagnosed after 6 months of age.

KEY WORDS: Newborn hearing screening • Neurosensorial hearing loss • Linguistic communicative and acoustic-perceptual outcomes

RIASSUNTO

L'ipoacusia neurosensoriale nel bambino è una delle principali cause del mancato sviluppo delle prime competenze percettivo linguistiche. Lo scopo di questo studio è quello di valutare lo sviluppo linguistico recettivo ed espressivo nei bambini con disturbi permanenti dell'udito, identificati attraverso un percorso di screening uditivo, in base all'epoca di diagnosi. Abbiamo studiato 18 bambini con ipoacusia neurosensoriale grave che sono stati divisi in due gruppi in base all'epoca di diagnosi. La valutazione delle abilità comunicativo linguistiche è stata effettuata all'età di 18 mesi, attraverso la somministrazione del questionario "MacArthur Child Development Inventory"; mentre la valutazione delle competenze acustico percettive è stata condotta con somministrazione del protocollo Genovese-Arslan, ogni tre mesi a partire dalla diagnosi. Lo sviluppo delle abilità comunicativo-linguistiche ed acustico-percettive dei bambini ipoacusici diagnosticati entro i 6 mesi dalla nascita è sovrapponibile a quello dei bambini normoacusici di pari età, con un trend di progressione temporale, rispetto ad alcune di queste competenze, più rapido di quello dei bambini ipoacusici diagnosticati dopo i 6 mesi.

PAROLE CHIAVE: *Screening uditivo neonatale • Ipoacusia neurosensoriale • Abilità comunicativo linguistiche ed acustico-percettive*

Acta Otorhinolaryngol Ital 2013;33:414-417

Introduction

Congenital deafness is one of the most common disabilities in children with an incidence of about 1.2-1.5 per 1,000 births, becoming about 2 per 1,000 in school children. If we consider the population at highest risk, such as children hospitalized in neonatal intensive care units (NICU) or those with a family history of hearing loss, the incidence can be 10-20 times greater [1 2].

Over the past decade there has been a widespread consensus in favour of universal newborn hearing screening programmes for permanent hearing disorders [3 4] in order to identify the majority of children with binaural hearing loss in a very stage of life, no later than 3-4 months after birth, so that the rehabilitative process can be started immediately, and no later than 6 months, i.e. during the period of greatest brain plasticity (American Academy of Pediatrics, Joint Committee on Infant Hearing 2007) [5].

Studies in the literature [6] have shown that the sooner proper acoustic-perceptual feedback is restored, the lower the

gap between performances of a hearing impaired child and those of a child with normal hearing considering communicative and cognitive-linguistic-relational skills [7 8].
To enable a hearing impaired child to acquire appropriate verbal patterns of perception that are not different from those of normally hearing child, it is essential to restore a suitable threshold of hearing through the immediate application of a hearing aid [9 10].
This work is a prospective longitudinal study of acoustic and cognitive linguistic skills in a sample of profound hearing impaired children belonging to the Campania programme of neonatal audiological screening, in relation to early detection of hearing loss and early inclusion in rehabilitation therapy.

Materials and methods

Newborn hearing screening

In the Campania region, a programme of universal newborn hearing screening structured on three levels was started in 2006: the first level is represented by birth points, the neonatal intensive care unit (NICU) and the neonatal department of pathology, and the second by the ENT and audiology departments of hospitals in the Campania Region. The third level is the Regional Reference Center (RRC), located at the functional area of Audiology of the University Hospital "Federico II" in Naples.
In this structure, diagnosis of hearing impairment is confirmed, aetiologic diagnostic tests are performed [11], a hearing aid device is selected, rehabilitation treatment is initiated and a periodic monitoring of the development of auditory perception and language and communication skills is performed.
From June 2006 to September 2011, 262,267 babies were examined. Of these, 259 were identified as affected by bilateral sensorineural hearing loss, 36 as affected by mono-lateral sensorineural hearing loss and 7 as affected by conductive hearing loss.

Patient selection and clinical evaluation

A group of 18 unrelated subjects (age range: 6-29 months) attending the Audiology Unit, Department of Neuroscience, University of Naples "Federico II", diagnosed between March 2006 and December 2007, was enrolled in this study. Medical history and pedigree information were obtained from parents to verify that hearing loss did not result from such acquired environmental factors as infection, trauma, acoustic trauma or ototoxic drugs, to evaluate the type of transmission of hearing loss and to exclude a syndromic form of hearing impairment. To evaluate hearing loss, all selected patients, according to international standards [12], underwent TEAOE, ABR, tympanometry and acoustic reflex, which are without risk, fast, easy to perform, highly sensitive and specific. For ABR recordings, a replicable waveform at 30 dB nHL within the expected latencies was considered 'normal'. The 18 subjects enrolled were all affected by bilateral sensorineural hearing loss (SNHL) with a replicable waveform at 70-80dB nHL.
The sample was divided into two groups according to the time of diagnostic confirmation of hearing loss:

- group 1: 12 patients with a diagnosis before or within 6 months of age;
- group 2: 6 patients with a diagnosis between months 7-11 of age.

The sample had the following characteristics:

- all patients are carriers of conventional hearing aids, continuously used since diagnosis of hearing loss;
- lack of disease associated with deafness (without disabilities);
- cultural level of families: average (parents possess a high school diploma);
- rehabilitation: All patients had regular counseling sessions with audio-speech therapists, within the Audiology service and based on the principles of the audio-verbal methodology, from diagnosis to inclusion in a rehabilitation program on a local circuit.

Follow-up (3, 6, 9, 12, 18 months from the application of the hearing aid device) was performed to monitor perceptual abilities. All patients, at 18 months of chronological age, were evaluated to compare the development of the first communicative and linguistic skills using of the *MacArthur questionnaire – "Gestures and Words"*, both receptive and impressive.
The family was actively involved (parent training) in stimulation training.
The evaluation of communicative language ability was carried out through administration of the "MacArthur Child Development Inventory" questionnaire –*"Gestures and Words"*, and the results were compared with normative values of the test [9].
This questionnaire evaluates the development of receptive and expressive vocabulary in children from 9 to 18 months of age by computing the number of words understood and produced. It is administered by parents.
The evaluation of acoustic-perceptual abilities was carried out using the Genovese-Arslan protocol at 3, 6, 12 and 18 months after fitting of a hearing aid [13].
This test classifies the perceptual skills of children in 6 categories (Moog & Geers categories):

- category 0: no detection of words;
- category 1: no perception of verbal patterns;
- category 2: perception of verbal patterns;
- category 3: first perception of words;
- category 4: identification of words by recognition of vowels;
- category 5: identification of words by recognition of consonants;
- category 6: identification of words in open sets.

Table I. Time of progress in perceptual skills in group I.

	Time after application of hearing aid device			
Perception's categories	3 months (n = 12)	6 months (n = 11)	12 months (n = 5)	18 months (n = 6)
1	11 (92%)	1 (9%)		
2	1 (8%)	10 (91%)		
3			5 (100%)	2 (33%)
4				3 (50%)
5				1 (17%)
6				

Table II. Time of progress in perceptual skills in group II.

	Time after application of hearing aid device			
Perception's categories	3 months (n = 6)	6 months (n = 6)	12 months (n = 5)	18 months (n = 3)
1	2 (34%)			
2	4 (66%)	3 (50%)		
3		3 (50%)	4 (80%)	2 (67%)
4				
5			1 (20%)	1 (33%)

Results

Evaluation of acoustic perceptual abilities

At 3 months after hearing aid first fit, 92% of children fell into the first category of perception; at 6 months, 91% of children fell into the second category of perception; at 12 months, 100% of children fell in a third category of perception and at 18 months, 50% of patients fell in the fourth category of perception.

Thus, in group I, a linear and constant growth profile of the investigated skills was seen (Table I). In the group of patients with hearing aid first fit between 7 and 11 months (9 ± 2): at 3 months, 60% of children fell in the second perceptual category; at 6 months, 50% of children are split over the second one and the remaining 50% in the third category of perception; at 12 months, 80% of children fell in the third category of perception; and finally, at 18 months, only 67% were in the third category and 33% fell in the fifth category of perception.

In this second group, it therefore is evident that there is a linear growth profile as above, but with slower progression (Table II). Patients in the second group, at three months, fell in higher categories of perception because

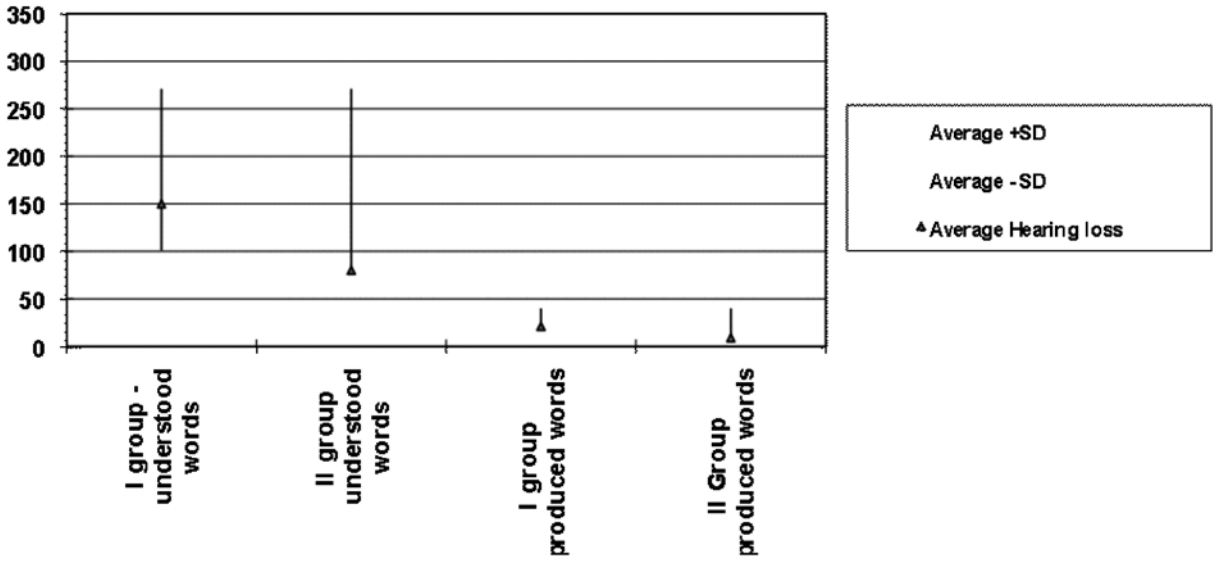

Fig. 1. Number of words understood and produced in Groups I and II at 18 months compared to normative data.

of longer exposure time to language than the first group (greater chronological age).

Evaluation of development in language abilities

Through the administration of the MacArthur questionnaire, in the two groups of hearing impaired patients, it can observed that the average number of words understood by patients in the first group (with a diagnosis before 6 months) is 150 ± 90 words, which is at the 50th percentile compared with normative values of the test (Fig. 1).With regard to expressive language, the average number of words produced is 21 ± 11; which is between the 25th and the 50th percentile.

The average number of words understood by patients in group II (with a diagnosis between 7 and 11 months) is 80 ± 40 words, which is between the 25th and the 50th percentile compared with normative values of the test. With regard to expressive language, the average number of words produced was 9 ± 6; which is at the 10th percentile compared with normative values.

Discussion and conclusions

The purpose of this study was to confirm the hypothesis that the time of diagnosis and consequently hearing aid first fit have a significant impact on the language skills in children with severe bilateral neurosensorial hearing loss. In particular, our data demonstrate that the perceptual abilities of hearing impaired children diagnosed before 6 months of age follow values that are similar to those expected for normally hearing children of an equivalent chronological age, with a trend of temporal progression faster than the group diagnosed later.

Moreover, restoring acoustic feedback has an important impact on language development, and in particular on vocabulary skills. In fact, children in Group I at 18 months of chronological age had a normal receptive and expressive vocabulary development (> 25th percentile), while the second group had poorer performance.

These results confirm the importance, in a neonatal hearing screening programme, of early diagnosis, followed by the immediate rehabilitation with hearing aids through speech therapy and family [14].

The data in this study, however, should be considered preliminary to a larger one that will analyze the development of linguistic, perceptual and curricular skills, related to hearing impaired, in children identified through the Neonatal Auditory Screening Program of the Campania region.

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VESTIBOLOGY

Vertical eye movements during horizontal head impulse test: a new clinical sign of superior vestibular neuritis

Movimenti oculari verticali durante test impulsivo cefalico sul piano orizzontale: un nuovo segno clinico di neurite vestibolare superiore

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SUMMARY

In some patients suffering from acute unilateral peripheral vestibular deficit, the head impulse test performed towards the affected side reveals the typical catch-up saccade in the horizontal plane, and an oblique, mostly vertical, upward catch-up saccade after the rotation of the head towards the healthy side. Three cases are reported herein, which have been studied using slow motion video analysis of the eye movements captured by a high-speed webcam (90 fps). The clinical evidence is discussed and a pathophysiological explanation is proposed, consisting in a selective hypofunction of the superior semicircular canal during superior vestibular neuritis.

KEY WORDS: Superior vestibular neuritis • Vertical catch-up saccade • High-speed video head impulse test • Selective superior semicircular canal paresis

RIASSUNTO

In alcuni pazienti affetti da deficit vestibolare periferico acuto, il Test Impulsivo Cefalico (HIT) eseguito verso il lato malato evidenzia un tipico saccadico di rifissazione sul piano orizzontale, mentre, quando eseguito verso il lato sano, provoca un saccadico obliquo, in maggior misura verticale, verso l'alto. Sono stati studiati tre pazienti in cui il movimento oculare è stato registrato con webcam ad alta frequenza di campionamento (90 fps) ed analizzato al rallentatore. Sono esposte e discusse le evidenze cliniche e ne viene proposta una interpretazione fisiopatologica consistente nella ipofunzione selettiva del canale semicircolare superiore in corso di neurite vestibolare superiore.

PAROLE CHIAVE: *Neurite vestibolare superiore • Saccadico di rifissazione verticale • Test impulsivo cefalico video-assistito • Ipofunzione selettiva del canale semicircolare superiore*

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Introduction

The head impulse test (HIT) is of fundamental importance in the examination of the dizzy patient because it directly explores the function of the lateral semicircular canal (LSC), allowing accurate diagnosis of peripheral vestibular deficit where the analysis of the nystagmus (ny) is often non-specific [1].

In order to increase the sensitivity of HIT when it generates unclear results, since February 2012, a high-speed webcam has been used in our facility to obtain a more accurate evaluation of eye movements during routine vestibular exam. This novel protocol led to unexpected results.

In almost 10 months of activity, the high-speed video-assisted head impulse test (HSVA-HIT) has been performed on 65 patients presenting with vertigo of various origins; 30 patients had unilateral peripheral vestibular deficit, identified by HIT evidence of a horizontal catch-up saccade after torsion of the head towards the affected labyrinth. Among these, 6 patients showed an unexpected downward eye movement during the torsion of the head towards the healthy side, followed by an oblique upward catch-up saccade. Three of the six patients showing such behaviour were further studied and underwent routine instrumental audio-vestibular tests and brain MRI.

Materials and methods

All patients were examined within a week since the beginning of their vertigo, and a second check-up was scheduled one month later. Further visits were then programmed for instrumental tests or rehabilitative sessions as needed.

To begin with, each patient was examined for clinical evidence of otologic disease and was administered a pure

tone audiometry test (with Amplaid 319 in a soundproof cabin). After that, patients underwent a careful clinical bedside vestibular exam consisting in the search, under Frenzel's glasses, for spontaneous ny, positional and positioning ny (Dix-Hallpike), gaze and rebound ny, mastoid vibration ny (100 Hz), head shaking ny and hyperventilation ny. Finally, patients were given the Romberg Test, the Untemberger Test and the HIT.

HSVA-HIT: the patient, sitting in front of the webcam (Philips SPC 900NC PC camera at 90 fps) at a distance of 50 cm, is asked to look at the camera (which has a white led just upon the lens), while the clinician at his back moves his head in the yaw plane with brief abrupt unpredictable torsions of about 30°. The camera is placed at the same height of the patient's eyes, on an adjustable tripod, well aligned horizontally. The video of the exam is recorded at 90 fps with a resolution of 352 × 288 pixels, and then viewed in slow motion (0.33×) to precisely assess eye movements during and after the head impulse. HSVA-HIT was performed in both the yaw and the vertical planes [pitch, left anterior-right posterior (LARP) and right anterior-left posterior (RALP)] [2].

Caloric vestibular stimulation was performed according to Fitzgerald and Hallpike's standards with computerized ENG evaluation of the caloric ny.

Cervical vestibular evoked myogenic potentials (C-VEMPs), induced by air-conducted sound stimuli (130 dB Spl 500 Hz logon transmitted bilaterally by headphones), were recorded at the level of the sternocleidomastoid muscles, with the patient lying in the supine position while keeping his/her head actively uplifted [3].

Ocular VEMPs (O-VEMPs) were recorded from the inferior oblique muscles, with the patient lying supine, while staring at a visual target 20° above his/her horizon, using the same air-conducted sound stimulus mentioned above for C-VEMPs. Both ENG and VEMPs were performed using an Amplaid MK12 instrument [4].

Results

Case 1

Male, 62-years-old, smoking more than 20 cigarettes a day, suffering from hypertension (treated with ramipril 10 mg QD). The patient presented for a vestibular examination, complaining of acute vertigo and nausea with acute onset 5 days prior, without hearing symptoms, headache or loss of consciousness. He had never suffered from such symptoms before and had a family history of vascular disease.

Bedside vestibular examination showed a horizontal ny with fast phase beating towards the left (of the patient) and mild torsional clockwise component (as seen from the clinician's point of view); this ny stopped under fixation of a visual target and did not change its direction in any of the head positions tested (sitting, supine and side lining), reducing its amplitude when lying on the left side. The patient had a difficult gait (not ataxic) and a clear rightward step deviation at Untemberger's test. Neurological exam and CT scan were negative. Pure tone audiometry was normal for the age (mild presbycusis). Brain MRI, performed two months after onset of vertigo, revealed many areas of leukoencephalopathy of microvascular origin.

HIT was positive when the head was turned to the right with a clear catch-up saccade in the horizontal plane, but an unexpected oblique upward catch-up saccade was observed when the head was turned to the left. HSVA-HIT was performed and the above-mentioned oblique upward saccade was confirmed (Figs. 1A-F).

HSVA-HIT in the pitch plane was also recorded revealing a clear upward catch-up saccade after nose-down tilt of the head, and a normal eye movement during nose-up tilt of the head with no catch-up saccade. HSVA-HIT in the RALP and LARP planes revealed a catch-up saccade only in RALP plane after nose-down tilt of the head, whereas all other movements had a normal gain of the vestibulo-ocular reflex (VOR) with no catch-up saccades.

Vestibular neuritis (VN) of the right side was diagnosed, possibly due to microvascular disease; the patient was instructed about home vestibular rehabilitation exercises and received steroid therapy (prednisone 25 mg QD for 7 days, then progressive reduction over 2 weeks) together with gastric protection (lansoprazole 15 mg QD for 2 weeks), and ASA (75 mg QD).

One month later the patient was examined, and his previous vertigo had disappeared except for some residual difficulties while walking in wide-open space and in darkness. However, he had been complaining of postural vertigo for 4 days. The clinical vestibular exam evidenced a typical paroxysmal positional vertigo (PPV) due to lithiasis of the right inferior semicircular canal (ISC) that led to a diagnosis of Lindsay-Hemenway Syndrome [5].

HSVA-HIT in the yaw plane was performed again, and confirmed the same findings revealed during the first visit. No evidence of spontaneous ny in the sitting position and normal results obtained with Untemberger's test (rightward deviation within 30°) indicated good compensation of the vestibular deficit.

For two months, sessions of vestibular rehabilitation (using Semont's Liberatory and a personal canalith repositioning manoeuvre) were held, but although subjectively improved, PPV was still present 8 weeks later. The absence of a liberatory ny after rehabilitative manoeuvres led to the diagnosis of persistent cupulolithiasis of the ISC; PPV finally disappeared one month later without further treatment [6 7].

A caloric vestibular test was performed two months after vertigo onset, revealing a right canal paresis (CP 55%) with mild directional preponderance (DP 28%) of the ny towards the left.

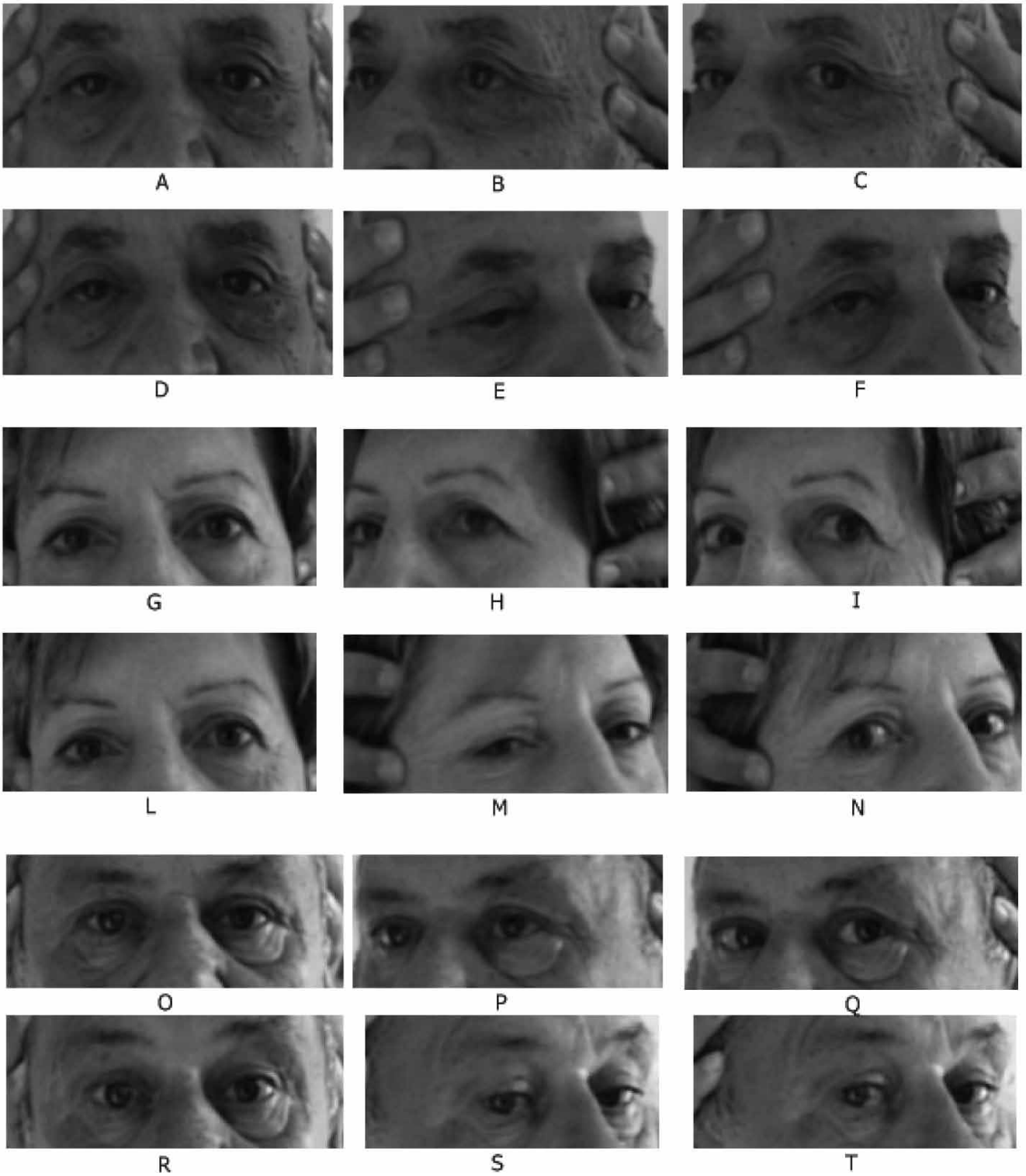

Fig. 1. Sequence of photos captured during HIT in patients suffering from right superior vestibular neuritis. Case 1: A-F, case 2: G-N, case 3: O-T (see text). For each patient, the first line of photos shows the head before the impulse to the right (A, G, O), after this impulse, just before the catch-up saccade (B, H, P) and after the saccade (C, I, Q). The second line of photos shows, for each patient, the head before the impulse to the left (D, L, R), after this impulse, just before the catch-up saccade (E, M, S) and after the saccade (F, N, T).

C-VEMPs were normal in both sides, while O-VEMPs were absent under the left eye. Four months after vertigo onset, the HIT in the yaw plane revealed the same pattern of ocular response seen before; HSVA was not repeated due to the large amplitude of the catch-up saccade that was clearly visible, as in previous visits.

At the end of follow-up (4 months), all these findings confirmed the diagnosis of right superior vestibular neuri-

tis (SVN) with persistent deficit of LSC and superior SC (SSC) function, in good central compensation, and persistent deficit of utricular macula function, with preservation of saccular macula and ISC function [8].

Case 2

Female, 62-years-old, who had never suffered from vertigo before. The patient arrived to the hospital emergency room complaining of acute vertigo and vomiting; these symptoms had started 2 days earlier. Neither headache nor auditory symptoms were reported at the time of vestibular assessment. Neurological examination was negative, pure tone audiometry was normal. Brain MRI, performed a week later, evidenced subcortical and deep tissue point signal alterations of ischaemic microvascular origin and dilation of perivascular spaces in the brainstem.

In addition, vestibular examination revealed acute peripheral vestibular deficit of the right side with the following signs: spontaneous ny with horizontal fast phase to the left side and torsional component beating clockwise. This ny was the same in all positions of the head and was inhibited by fixation of a visual target, whereas hyperventilation and 100 Hz mastoid vibrations did not change it. Clear rightward step deviation in the Untemberger's test was seen.

HIT was positive when the head was turned to the right with a clear catch-up saccade in the horizontal plane, but an unexpected oblique upward catch-up saccade was observed when the head was turned to the left. HSVA-HIT was performed and the above-mentioned oblique upward saccade was confirmed (Figs. 1G-N).

VN of the right side was diagnosed and steroid therapy was started (prednisone 25 mg BID for 2 days, then progressive reduction over 2 weeks) together with gastric protection (lansoprazole 15 mg QD) and an oral heparinoid (sulodexide 250 ULS 1 cpr BID for 2 months).

At a control visit 10 days later, the patient felt much better. She reported that acute vertigo had disappeared in a week and, at that time, she was suffering only from mild unsteadiness. The bedside vestibular examination revealed a small spontaneous horizontal ny beating to the right in all the positions of the head, which was inhibited by fixation and augmented after head shaking test. HIT was bilaterally negative both in horizontal and vertical planes, and Untemberger's test was within the norm. Recovery syndrome after VN of the right labyrinth was diagnosed.

Twenty days later the patient was checked again: she did not complain about vestibular symptoms and bedside vestibular examination was negative. At that time, C-VEMPs were registered on both sternocleidomastoid muscles with the same amplitude; O-VEMPs were recorded only under the right eye. This led to the assessment of persistent right utricular deficit, with preserved bilateral saccular function.

The final diagnosis was right SVN that recovered with "restitutio ad integrum" of the canal function and persistent subclinical damage of the utricular macula.

Case 3

Male, 62-years-old, truck driver, smoking more than 20 cigarettes a day. The patient came for urgent vestibular examination, complaining of acute vertigo that started 7 days before, together with vomiting and epigastric pain; neither auditory symptoms nor headache were present. He did not report any significant pathology in his history and had never suffered from vestibular diseases. Neurological exam and CT were negative, pure tone audiometry was normal for his age (mild bilateral deafness for high frequencies due to chronic acoustic trauma and presbycusis). Brain MRI performed a few weeks later showed marked dilatation of the lateral ventricles and the cortical sulci, and many areas of leukoencephalopathy of microangiopathic origin.

Vestibular clinical examination evidenced right acute peripheral vestibular deficit with the following signs: spontaneous ny beating to the left with a torsional component beating clockwise, present in all the positions of the head and inhibited by fixation. Clear rightward step deviation during Untemberger's test was evidenced.

HIT was positive when the head was turned to the right with a clear catch-up saccade in the horizontal plane, but an unexpected oblique upward catch-up saccade was observed when the head was turned to the left. HSVA-HIT was performed and the oblique upward saccade above mentioned was confirmed (Figs. 1O-T).

VN of the right side was diagnosed and the patient was instructed about home vestibular rehabilitation exercises; he received 2 weeks of steroid therapy (prednisone 25 mg QD at the beginning) together with gastric protection (lansoprazole 15 mg QD) and ASA (75 mg QD).

One month later the patient was controlled, his vertigo had disappeared, spontaneous ny was not evident and step deviation was within the normal range; HIT was still positive with the same pattern of ocular response reported before. He had a persistent peripheral right vestibular deficit with good central compensation.

A few weeks later the patient suffered from mild positional vertigo, but he recovered without any treatment and did not undergo vestibular examination.

Four months after the beginning of his vertigo, he underwent a scheduled control visit: he was free of any vertigo symptoms and did not complain of unsteadiness; neither spontaneous ny nor step deviations were evident, but HIT was still showing the same ocular response seen before. HSVA-HIT was again performed in the yaw plane confirming the oblique upward saccade above mentioned while in the pitch plane a very little catch-up saccade only after nose-down movement was inconstantly seen. HIT in RALP and LARP plane was normal, with only minor anomalies in the RALP plane.

Caloric stimulation evidenced a severe hyporeflexia of the right labyrinth (CP 90%) without latent ny (DP 5% to the left). O-VEMPs were recorded bilaterally, as well as C-VEMPs that presented reduced amplitude in the right sternocleidomastoid muscle, indicating the integrity of the utricular macular function bilaterally and slight damage of the right saccular macula.

Discussion

All patients herein had acute labyrinthine damage, of various origins, which impaired the function of the SCs and maculae to different degrees. All patients had a clear deficit of the LSC that was shown by HIT in the horizontal plane towards the affected side and measured by caloric test in cases 1 and 3.

In case 1, a clear deficit of VOR in the vertical plane was observed at HIT during nose-down tilt of the head (pitch and RALP), confirming unilateral SSC impairment; in case 2, vertical HIT was within the norm and in case 3 it produced unclear results.

In patients 1 and 2, the damage also involved the utricular macula, while in case 3 this was preserved whereas a slight damage of the saccular macula was seen (this patient was examined with caloric test and VEMPs only 4 months after the onset of the vertigo).

In all these patients, slow motion analysis of eye movement during HIT on the yaw plane towards the healthy side revealed an active downward movement of the eyes that was more evident in the eye ipsilateral to the affected ear.

The analysis of the eye positions was carried out on still frame images captured at the beginning and end of the head movement, and at the beginning and end of the following catch-up saccade.

This type of analysis only detects the direction of the eye movement in the horizontal and vertical planes (not torsional), does not allow quantifying it and presents some difficulties for the eye located furthest from the webcam (due to the perspective effects). Despite these limitations, the movements seen are so clear that the reported ocular sign is evident with negligible bias. Figure 2 shows the analysis performed on case 2. Similar results were obtained in the other cases.

According to recent literature, a movement of the head in the yaw plane activate mostly the LSC, up to 94% of the angular acceleration, although both the vertical SCs are activated in a smaller percentage: up to 26% of the angular acceleration on the ISC and up to 18% on the SSC [9].

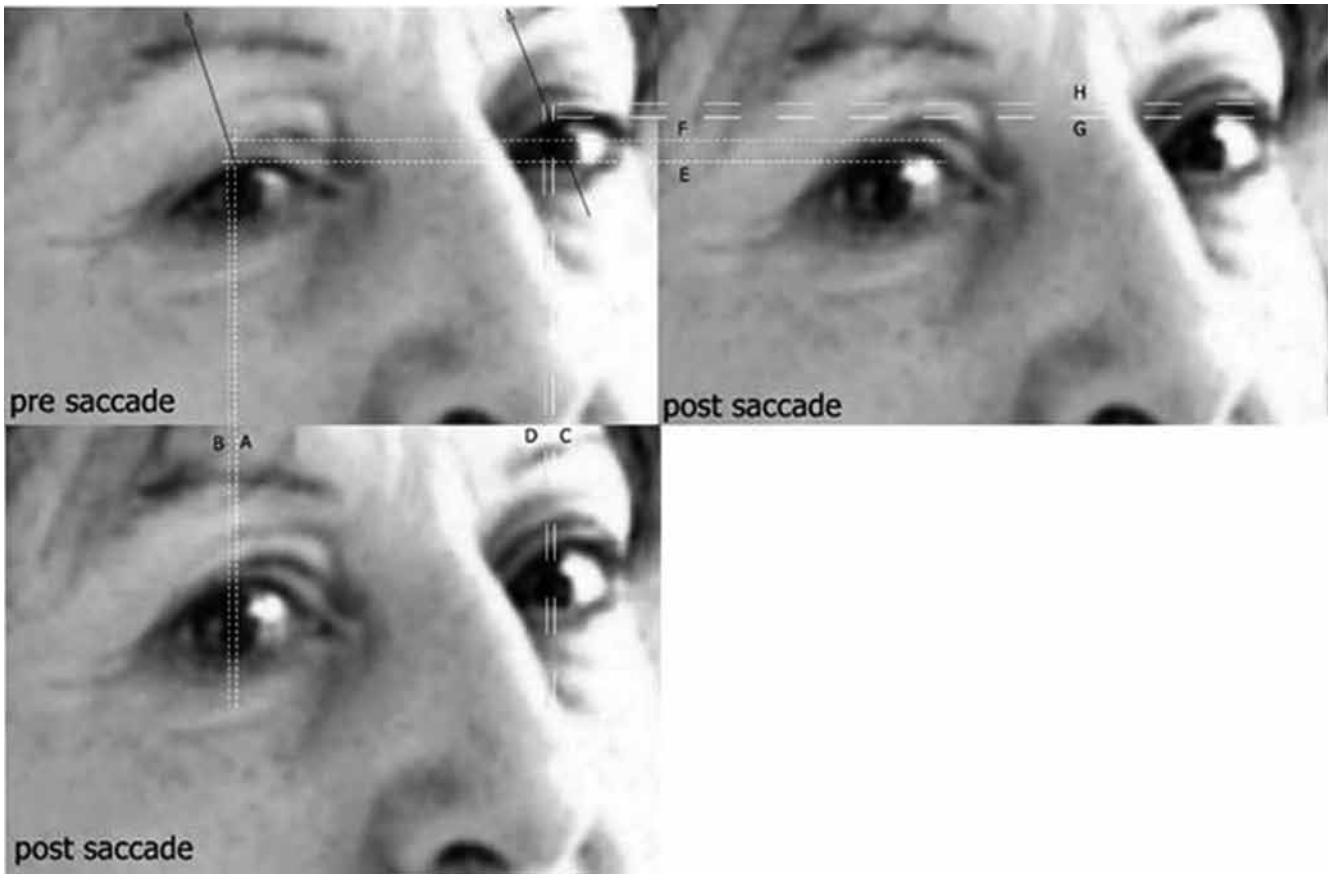

Fig. 2. Photo analysis of the oblique catch-up saccade after impulse test towards the healthy side. Dotted lines are for the right eye, and dashed lines are for the left eye. A and C lines show the position of the pupils before the saccade and B and D their position after the saccade. E and G lines indicate the level of the eyelids before the saccade and F and H their position after the saccade. Arrows show the direction of the saccade: it is mainly vertical with a slight horizontal component and the amplitude is greater at the right eye (ipsilateral to the lesion).

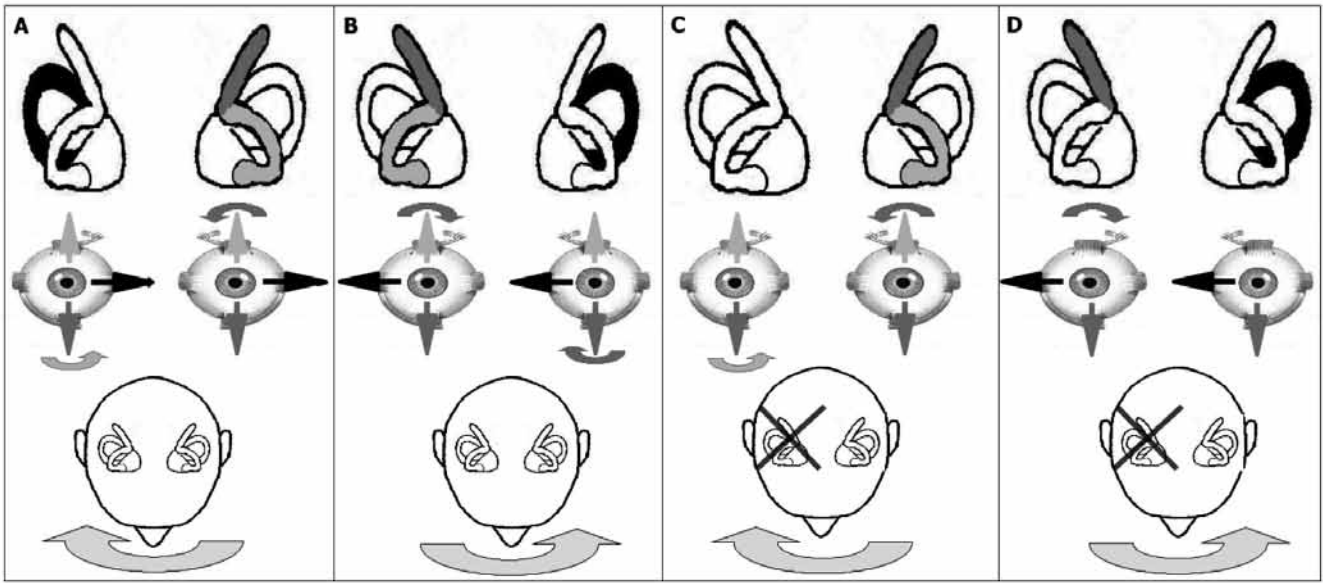

Fig. 3. Activation of semicircular canals and eye movements during HIT in normal conditions (A and B) and in superior vestibular neuritis (C and D). In normal conditions, activation of both vertical semicircular canals stabilizes the eyes in the vertical plane, only the action of LSC moves the eyes: no catch-up saccades are necessary to stare at the target. During superior vestibular neuritis, only the ISC of the affected side is still functioning. During torsion of the head towards the affected side, contralateral vertical semicircular canals stabilize the eyes in the vertical plan, but they do not move horizontally, so a horizontal catch-up saccade is necessary to bring back the sight on the visual target. During torsion towards the healthy side, eyes move almost normally in the horizontal plane (a slight deficit of VOR is due to the absence of inhibitory action of LSC of the affected side), but due to the isolated action of ISC, eyes move improperly downward, so that an oblique (mostly vertical) catch-up saccade is triggered.

According to Ewald's second law, both vertical canals are excited by ampullofugal endolymphatic flows. This is the reason why they are both activated by movements towards the opposite ear, whereas the LSC is activated by movement towards the ipsilateral ear.

Concerning vertical eye movements only, in the normal labyrinth stimulation of both SSC and ISC of the same side leads to bilateral activation of antagonist ocular muscles with no resulting eye movement in the vertical plane. (Figs. 3A, B)

In labyrinths with lesions of the SSC and preserved function of the ISC (as in SVN), impulse head torsion towards the healthy side leads to a downward eye movement that responds to the inputs coming from the ISC that is no longer counteracted by the antagonist action of the damaged SSC. (Figs. 3C, D)

According to the muscular projections of the single SC through the VOR, the eye movement recorded in the patients analysed is consistent with this hypothesis [10 11].

The clinical sign observed revealed a much greater involvement of both vertical SCs during impulsive head rotation in the yaw plane than previously indicated in the literature [12-14].

Conclusions

Patients suffering from SVN present vertical downward eye movements during HIT performed in the yaw plane towards the healthy side, followed by an oblique (mostly vertical) upward catch-up saccade. HIT in the horizontal plane acts at the same time on all three SCs, although with different directions and magnitude. The reported clinical sign is consistent with lack of excitation of the SSC of the affected labyrinth, while the ISC still works properly.

HIT in the vertical planes never reached substantial significance in routine bedside vestibular examination: in the pitch plane, it has a very low sensitivity due to the contemporary activation of vertical SCs of both sides (SSCs for nose-down pitch, ISCs for nose-up pitch). In RALP and LARP planes, its quite difficult to perform a satisfactory test because the amplitude of the head movement is restricted and the catch-up saccade is very small; this leads to uncertain results even with the support of high-speed video recording; computer analysis of both head acceleration and eye movement is essential to properly assess this function.

The sign reported here gives clear indications of SSC impairment, when ISC is still functioning, even in those patients having unclear responses to HIT performed in the vertical planes, and even using high-speed video recording. This is because the eye movement occurs in a plane that is orthogonal to the head movement, and it is an active downward shift that makes it clearly visible without any instrument.

This clinical sign is typically not reported because its significance is unknown, unexpected and usually ascribed to the patient's distraction; high-speed video recording is able to augment the sensitivity and helps to study doubtful cases. The positivity of this sign is a direct expression of the SSC dysfunction and remains evident even after sat-

isfactory central compensation of vestibular impairment. Since the HSVA-HIT has been initially performed only in patients with doubtful horizontal saccade, many cases with vertical catch-up saccade on the affected side were missed at that time. Systematic application of this technique has been introduced only in the last 4 months (all the studied cases belong to this period); this brings about the hypothesis that the prevalence of such a clinical sign is much higher than what is presented in this study (6/30). Further studies on the physiology of the vertical SC involvement during head impulses in the yaw plane are necessary to fully understand this new evidence.

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Case Series

Transoral robotic surgery for retromolar trigone tumours

La chirurgia robotica transorale (TORS) nei tumori del trigono retromolare

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SUMMARY

The retromolar trigone is a challenging transoral surgical site due to the difficulty of visualization. Our aim is to report a new technique of transoral robotic resection of retromolar trigone tumours. We present three patients with retromolar trigone tumours with pathological diagnosis of squamous cell carcinoma who underwent successful transoral robotic resection. Robotic retromolar trigone resection and concurrent supraomohyoid neck dissections were performed in all patients without any complication. In conclusion, transoral robotic surgery is a safe and feasible technique for resection of malignant retromolar trigone tumours with minimal complications and favourable outcomes.

KEY WORDS: Retromolar trigone • TORS • Transoral robotic surgery • Oral cavity

RIASSUNTO

Le difficoltà riscontrate nella corretta esposizione del campo operatorio rendono impegnativo l'approccio transorale al trigono retromolare. Con il presente lavoro é nostra intenzione descrivere un approccio innovativo alla resezione dei tumori interessanti il trigono retromolare, mediante chirurgia robotica transorale. Presenteremo tre casi nei quali pazienti con diagnosi di tumore del trigono retromolare ad istologia squamocellulare, sono stati sottoposti con successo ad una resezione della lesione con metodica robotica transorale. In tutti i pazienti sono stati effettuati simultaneamente, e senza registrare alcuna complicanza, sia la resezione del trigono retromolare mediante chirurgia robotica, che lo svuotamento latero cervicale sovraomoioideo. In conclusione la chirurgia robotica transorale, applicata alla resezione dei tumori maligni del trigono retromolare, é una tecnica sicura, che offre un outcome favorevole con complicanze minime.

PAROLE CHIAVE: *Trigono retromolare • TORS • Chirurgia robotica transorale • Cavo orale*

Acta Otorhinolaryngol Ital 2013;33:425-427

Introduction

The retromolar trigone (RMT) is the portion of the oral cavity mucosa overlying the ascending ramus of the mandible at the junction of two dental arcades behind the last molar. This region can be a challenging transoral surgical site due to the difficulty of visualization. Cancers originating in the RMT, although rare, are usually squamous cell carcinoma (SCC). On occasion minor salivary gland tumours can also originate from RMT [1-3]. The presence of bone invasion leads to poor prognosis. Sequential therapy starting with surgery is the recommended treatment [4 5]. Transoral robotic surgery (TORS) has been reported to be safe and feasible in transoral resection of laryngopharyngeal tumours [6-8]. However, there has been no report related to transoral robotic RMT resection (TORRR). This report presents a new technique of TORS for RMT cancer resection.

Case series

Description of clinical cases

Case 1: a 63-year-old Caucasian male presented to a dental clinic with a persistent RMT lesion after dental extraction three months ago. He denied any symptoms other than mild left posterior oral pain. Otolaryngologic exam showed a 2.5 cm ulcerative, erythematous and granular lesion at the left retromolar trigone. Biopsy revealed SCC. He was a heavy smoker and alcohol consumer. The patient was evaluated with CT of the neck to exclude possible mandibular invasion.

Final pathologic staging after TORRR demonstrated a T1N1 RMT carcinoma with perineural and lymphovascular invasion with negative surgical resection margins. He has completed adjuvant radiotherapy and is disease free at 15 months clinical follow-up.

Case 2: a 57-year-old Caucasian male presented to his dentist with a right-sided oral cavity mass. Food occasion-

ally got stuck in this region, but he denied pain, bleeding, or a neck mass. Subsequent biopsy of the 2 cm granular lesion of the right RMT involving the anterior tonsillar pillar showed SCC (Fig. 1). He was also a heavy smoker and drinker. There was no radiological evidence of mandibular invasion in CT of the neck.

Final pathologic staging confirmed a T1N0 carcinoma with negative surgical margins. He did not need any adjuvant treatment and is disease free at 16 months follow-up.

Case 3: an 80-year-old male with history of larynx cancer and previous radiation treatment presented with right sided globus sensation and intermittent pain for 6 weeks. He denied dysphagia, odynophagia or a neck mass. He was a heavy smoker and previous drinker. Physical examination showed a 3 cm ulcerative mobile lesion at the right RMT. Biopsy of the lesion showed SCC. Radiological evaluation with neck CT excluded any mandibular invasion.

The patient underwent transoral robotic surgery and concurrent bilateral neck dissection. Final pathological staging confirmed T2N2b carcinoma with lymphovascular and perineural invasion. Surgical margins were negative. The patient was disease free at 1 month follow-up. All three RMT carcinoma cases were HPV negative.

Surgical technique and results

Similar surgical steps were followed for all TORRR procedures. Robotic retromolar trigone resection and concurrent selective neck dissections (Levels I-IV) were performed. Standard TORS room setting was used in the surgery. After the transoral intubation a Crowe-Davis mouth gag was placed to expose RMT region (Fig. 2). A straight (0°) robotic camera provided optimal exposure without necessitating the 30° camera. 5 mm monopolar cautery and Maryland dissectors were used for resection (Figs. 3, 4). Mucosa and submucosa were incised deep to mandibular periosteum. The resection plane was reached and resection extended up to anterior tonsillar pillar medial to the mandibular bone. Superficial layer of tongue base muscles and the lingual nerve formed the deep margin of excision. A non-robotic marginal mandibulectomy was needed to get a safe margin for the second case only. Exposed mandibular bone after tumour removal was reconstructed and covered with local mucosal advancement flaps.

The average robotic setup time was 20 min, TORRR time was 7 min, with estimated blood loss of 20 ml for these robotic RMT resections.

Discussion

Exposure and resection of RMT carcinoma is a challenge especially when it involves the posterior floor of the mouth, base of tongue, or pharynx. Traditional surgical approaches to the RMT region are transoral surgery with or without laser for early stage and open transfacial/transcervical approaches for advanced stage disease. Minimally-invasive procedures with minimal collateral tissue damage are preferred to decrease surgical morbidity, postoperative complications and improve quality of life together with a shorter hospital stay [1-3].

Robotic assisted surgeries have been popularized more in other surgical fields like gynaecology, urology and cardiac surgery before it was used in the head and neck area in the last four to five years [4]. Compared to conventional surgical techniques, a robotic transoral approach offers potential advantages. The primary advantage of this approach is decreased surgical morbidity for patients [5]. Robotic optics gives magnified three-dimensional visualization with the option of angled camera. Tissue dissection with TORS avoids external incision while respecting the uninvolved tissues that would otherwise be involved in open surgical approaches.

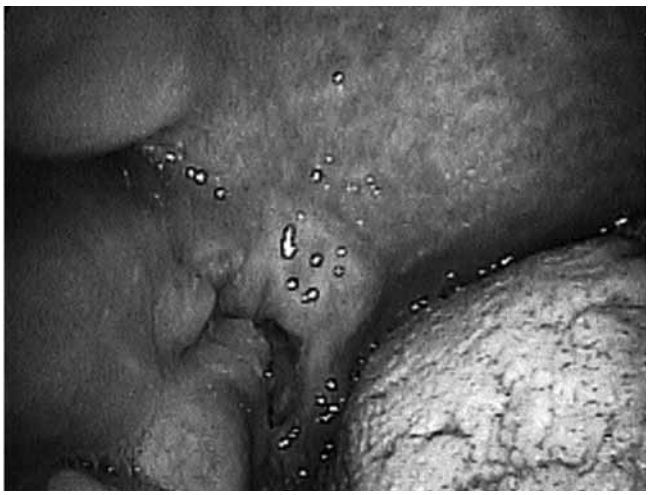

Fig. 1. Clinical picture showing a right RMT carcinoma.

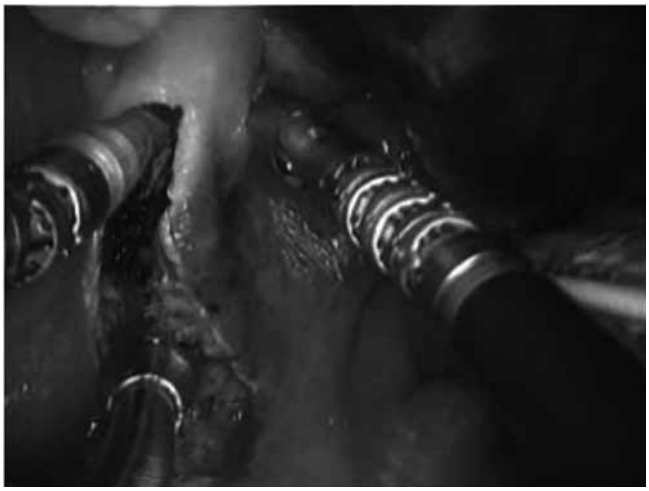

Fig. 2. Transoral robotic resection of the left RMT carcinoma; just after the start of the incision.

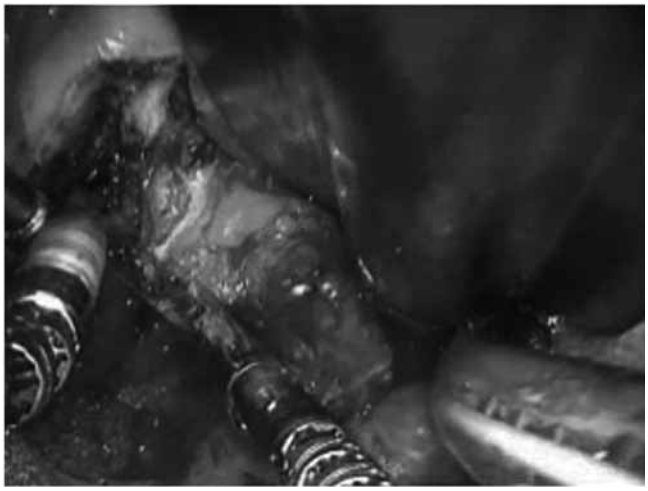

Fig. 3. Transoral robotic resection of the left RMT carcinoma; in progress.

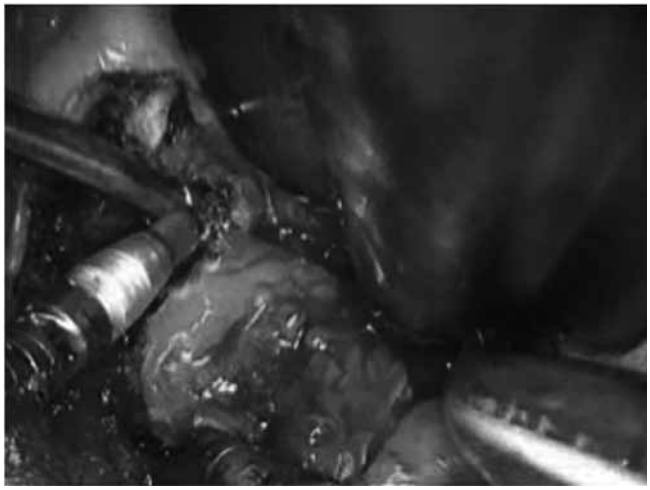

Fig. 4. Transoral robotic resection of the left RMT carcinoma; excision is complete, and the specimen is free.

TORS is shown to be feasible and safe procedure with minimal complications and blood loss [6-8]. Advantages of TORS over transoral laser surgery include wide, angled and more comprehensive visualization of the surgical field and significantly shorter operative time. Robotic RMT resections take only 7 min to complete. The only disadvantage of the current robotic tools is the need of a bone resecting robotic arm in the event of bone invasion.

Conclusions

TORRR is a feasible, safe and effective procedure with minimal complications and favourable outcomes for the resection of benign and malignant tumours of the RMT. This procedure may be useful in patients where optimal visualization of the RMT lesion is not possible with the naked eye or a straight microscopic view.

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Case report

Keratoacanthoma: an unusual nasal mass

Cheratoacantoma: un'insolita neoformazione nasale

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SUMMARY

We report a case of keratoacanthoma in a non-sun-exposed nasal vestibule of an 84-year-old man. He presented with a progressively growing left nasal mass that had been present for 8 months. Examination showed a non-tender protruding mass arising from medial vestibular wall of the left nostril. Histopathology indicated it was a keratoacanthoma. In an elderly patient with a history of a progressively growing mass in the nose, a differential diagnosis of malignancy should be ruled out, and histological conformation is essential. To our knowledge, only a very small number of cases of nasal vestibular keratoacanthoma have been reported.

KEY WORDS: Keratoacanthoma • Nasal vestibule

RIASSUNTO

Descriviamo un caso di cheratoacantoma riscontrato a livello del vestibolo nasale in un uomo di 84 anni di età senza storia di esposizione solare. Il paziente presentava una neoformazione nel vestibolo nasale di sinistra comparsa da 8 mesi e progressivamente aumentata di volume. All'esame obiettivo si presentava come una massa esofitica non dolorante a base d'impianto a livello della parete mediale del vestibolo della narice di sinistra. L'esame istologico definitivo poneva diagnosi di cheratoacantoma. In un paziente anziano con storia di neoformazione nasale progressivamente aumentata di volume è necessario escludere la malignità della lesione. Per tale motivo l'esame istologico della lesione è indispensabile. Sulla base della nostra esperienza, sono stati descritti pochi casi di cheratoacantoma del vestibolo nasale.

PAROLE CHIAVE: *Cheratoacantoma • Vestibolo nasale*

Acta Otorhinolaryngol Ital 2013;33:428-430

Introduction

Keratoacanthoma (KA) is a common benign epithelial tumour that originates from the pilosebaceous glands [1]. In most cases, it is characterized by rapid evolution, followed by spontaneous resolution over 4 to 6 months [1]. KA usually presents as a solitary flesh-coloured nodule with a central keratin plug on the sun-exposed skin of elderly individuals. The aetiology of this tumour is not completely understood; however, exposure to excessive sunlight is associated with its occurrence. Herein, we report a case of keratoacanthoma that occurred in a non-sun-exposed nasal vestibule of an 84-year-old man. The diagnosis of KA was established after excisional biopsy. To our knowledge, only a very small number of cases of nasal vestibular KA have been reported.

Case report

An 84-year-old Malays male presented to our Ear, Nose and Throat-Head and Neck clinic for a left nasal mass that had been present for 8 months. It was painless and progressively increasing in size. He had no other associated symptoms and reported no history of trauma to the nose or prolonged exposure to sunlight. On examination there was a firm, non-tender pedunculated mass arising from the medial vestibular wall of the left nasal vestibule (Fig. 1). Rigid nasoendoscopy revealed no other abnormalities. The patient had no palpable cervical lymphadenopathy. The remainder of his physical examination was unremarkable.

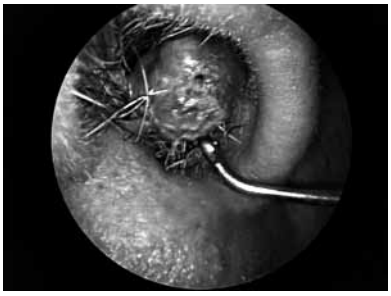

Fig. 1. Pre-operative view by nasoendoscopy.

The tumour was excised completely under local anaesthesia with minimal bleeding and the incision was closed using vicryl 5.0 sutures. Post-operative recovery was uneventful. The biopsy consisted of a mass of pale, greyish tissue with an irregular surface measuring 1 cm in diameter. Histologically, it showed solid proliferation of squamous epithelium comprising large mature squamous cells forming a central crater filled with parakeratotic keratin (Fig. 2). Keratin cysts were present within the squamous epithelium, which showed mild atypia. At the base and margins there were irregular epidermal proliferations with a partly solid and partly netlike appearance. The adjacent dermis showed a lymphohistiocytic infiltrate. A diagnosis of KA was made. No recurrence of disease was noted during a follow-up period of 10 months.

Discussion

KA is a common epithelial neoplasm that originates from pilosebaceous follicles and consists of keratinizing squamous cells that produce a flesh-coloured nodule with a central keratin plug. It is characterized by rapid evolution and spontaneous resolution with residual scarring in weeks to months [2]. Though KA was initially considered a benign growth, evidence indicates that it may progress to low grade squamous cell carcinoma. Therefore, it is now regarded as an immunologically well-controlled, low grade squamous cell carcinoma [3].

KA has been reported in all age groups, with a peak incidence in the 7th decade of life or beyond. It is rare in persons younger than 20 years of age. KA is uncommon in dark-skinned patients. Most cases occur on sun-exposed skin and rarely on the mucous membrane of the oral cavity. The face, neck, and dorsum of the upper extremities are common sites.

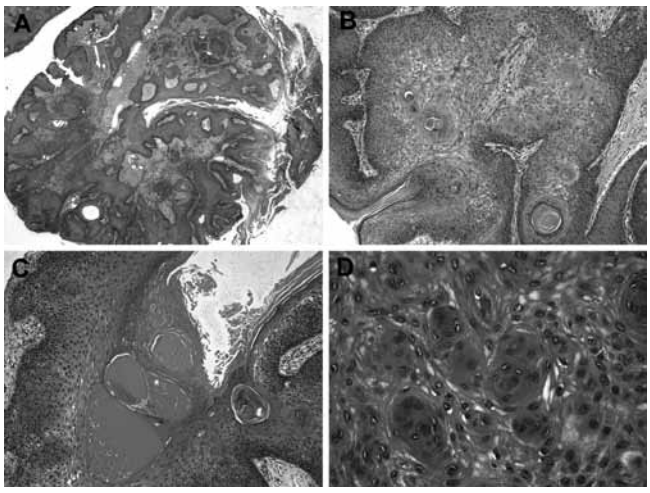

Fig. 2. Micrograph of the keratoacanthoma: (A) Low-power view of the lesion showing solid proliferations of squamous epithelium with intervening fibrovascular stroma. (B) Keratin cysts are present within the squamous epithelium. (C) Formation of a central crater filled with parakeratotic keratin. (D) High-power view of the squamous proliferation where cells show mild atypia.

Sun exposure has a key role in pathophysiology of KA [1], so the nasal vestibule is not a common location for the mass and our patient's medical history was negative for prolonged sun exposure. In persons with a genetic predisposition, sunlight may activate an oncogene or inactivate a suppressor gene. Other risk factors include tar exposure, immunosuppression, burns, oncogenic chemicals and psoriatic lesions previously treated with psoralen and ultraviolet A therapy, as well as other dermatoses [1 4]. In recent years, an increasing number of reports have described KA arising at sites of trauma [5]. A study by Miot et al. in 2006 suggested a strong association between cigarette smoking and KA [6]. Their regression is likely to be mediated by activated CD4+ cells and lymphocytes [2].

Rare variants of KA are seen in both solitary and multiple forms of the disease. The solitary forms include subungual, mucosal and giant KA, in addition to KA cemtrifugum marginatum. The multiple types include multiple self-healing KA of Ferguson Smith and multiple eruptive KA of Grzybowski.

Diagnosis is based on clinical history and physical examination, and is confirmed by skin biopsy and histological examination. Differential diagnosis includes squamous cell carcinoma and basal cell carcinoma; therefore, for a definitive pathological diagnosis, the biopsy must be fully representative of the lesion [7]. The margins of the KA have the most characteristic feature, which is elevation of the normal adjacent mucous membrane toward the core of the ulcer with a sudden change in the normal epithelium at the hyperplastic, acanthotic border [7]. With an incisional biopsy, the central part of the lesion is often sampled, and diagnosis may not be possible because the margin of the specimen, which is important in the differential diagnosis, is not included [7].

Various factors need to be considered in choosing the type of treatment. These include the site, size and number of lesions, recurrence, age and general condition of the patient, competence of the clinician with various therapeutic techniques, aesthetic considerations compatible with complete removal of the growth and patient compliance [8]. Although KA usually regresses spontaneously, surgical excision is the primary treatment nowadays. A full- thickness vertical excision with narrow margins is recommended [9]. Medical treatment is reserved for exceptional cases where surgical intervention is either not feasible or desirable. Medical intervention may be used for multiple lesions or lesions not amenable to surgery because of size and location. Systemic retinoids, intralesional methotrexate, 5-flourouracil, bleomycin and steroids have been used with success [10 11] Radiotherapy may be useful for tumour recurrences [12] in selected patients who are not good surgical candidates as surgery would result in cosmetic deformity. In the present case, we were able to excise the tumour completely.

Conclusion

KA, a benign epithelial tumour, rarely occurs in the nasal vestibule. Correct diagnosis is usually made by histological examination. In an elderly patient with a history of a progressively growing mass in the nose such as the present, malignancy should be ruled out.

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CASE REPORT

Giant osteoma of the ethmoid sinus with orbital extension: craniofacial approach and orbital reconstruction

Osteoma gigante del seno etmoidale con estensione orbitaria: approccio craniofacciale e ricostruzione dell'orbita

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SUMMARY

Osteomas are the most common fibro-osseous lesions in the paranasal sinus. They are benign tumours characterized by slow growth and are often asymptomatic. Treatment is indicated in sphenoid osteomas that threaten the optic canal or orbital apex and in symptomatic cases. The choice of surgical management depends on the location, size and experience of the surgeon. An open approach allows tumour removal with direct visual control and remains the best option in large tumours, but the continued progression in endoscopic approaches is responsible for new indications in closed techniques. Immediate reconstruction allows aesthetic and functional restoration of neighbouring structures, which should one of the goals in the treatment of this benign entity. We report a case of a giant ethmoid osteoma with orbital invasion treated by a combined open craniofacial approach with reconstruction of the anterior cranial base and orbital walls. The literature is reviewed and aetiopathogenic theories, diagnostic procedures and surgical approaches are discussed.

KEY WORDS: Orbital osteoma • Giant osteoma • Ethmoidal osteoma • Orbital reconstruction

RIASSUNTO

Gli osteomi sono le più comuni lesioni osteo-fibrose dei seni paranasali. Si tratta di neoplasie benigne, frequentemente asintomatiche, caratterizzate da un lento accrescimento. Il trattamento è indicato negli osteomi sfenoidali che minacciano il canale ottico o l'apice orbitario, e nei casi sintomatici. La scelta dell'approccio chirurgico dipende dalla localizzazione e dalla grandezza della lesione, nonché dall'esperienza dell'operatore. La tecnica aperta consente la rimozione del tumore con controllo visivo diretto e rimane l'opzione di prima scelta nelle neoplasie estese, ma i continui progressi in ambito endoscopico hanno portato ad un aumento dei casi in cui è indicata la tecnica chiusa. La ricostruzione immediata permette un ripristino estetico e funzionale delle strutture adiacenti, che rappresenta l'obbiettivo primario del trattamento di tali lesioni. In questo lavoro abbiamo descritto un caso di osteoma etmoidale gigante con invasione dell'orbita trattato mediante approccio combinato craniofacciale aperto e ricostruzione del pavimento della fossa cranica anteriore e delle pareti orbitarie. Vengono inoltre discusse le teorie eziopatogenetiche, le procedure diagnostiche e gli approcci chirurgici descritti in letteratura.

PAROLE CHIAVE: *Osteoma orbitario • Osteoma gigante • Osteoma etmoidale • Ricostruzione orbitaria*

Acta Otorhinolaryngol Ital 2013;33:431-434

Introduction

Osteomas are relatively rare, benign bone neoplasms that usually develop in craniofacial and jaw bones [1]. They are slow-growing tumours, often asymptomatic for many years, and diagnosed incidentally on radiographs. They are the most frequent neoplams of the paranasal sinuses, most often originating from the ethmoid and frontal bones. Ethmoid osteomas are detected earlier because of the limited anatomical space. Orbital or skull base involvement is very unusual, causing ophthalmologic and neurological symptoms, and is one of the indications for early intervention.

Surgery is the treatment of choice for symptomatic ethmoid osteomas. Due to the rapid progress of endoscopic sinus surgery, even small osteomas can be easily removed without the need for an external approach. However, large cases with intraorbital or skull base expansion are still treated with an external approach.

We report a case of an anterior skull base osteoma of ethmoid cells with frontal and orbital extension producing exophthalmos. The aetiology, manifestations and management of this rare entity are discussed.

Case report

A 62-year-old woman was referred to the Maxillofacial Department of La Paz University Hospital, Madrid, Spain, with a 1-year history of gradual painless proptosis of her right eye. The patient reported loss of visual field and visual acuity in her right eye as well as a reduction in her capacity to smell.

An ophthalmologic examination showed proptosis of the right eye. Extra-ocular movements were not restricted, with no alteration of the anterior segment or fundus. Visual acuity was impaired due to cataracts in both eyes. Anterior rhinoscopy showed deviation of the lateral nasal wall. Computed tomography (CT) revealed a 4 × 4.5 cm right ethmoid polylobulated lesion, with a dense compact cortical margin and a matrix with medullary-like attenuation (Fig. 1). The lesion extended from the right frontal sinus floor to the right sphenoid sinus, and grew superiorly and posteriorly into the right orbit, pushing down the extraocular musculature, optic nerve and eyeball in an inferior and anterior direction. Magnetic resonance imaging (MRI) demonstrated a homogeneous extraconal mass with iso-low signal intensity on T1-weighted imaging. An endoscopic transnasal biopsy was performed and histopathological findings confirmed the diagnosis of benign osteoma.

Surgical intervention was performed under general anaesthesia. After a coronal flap and subciliary approach, the frontal bone, upper rims of the orbit and nasal root were exposed. A right frontal craniotomy and a right fronto-orbital bar extending to the lateral orbital wall were performed, and the tumour was removed.

The defect was reconstructed immediately. Temporal fascia was used in dural reconstruction. Two autogenous bone grafts obtained from calvarial bone were used to reconstruct the medial and orbital floor, with the additional use of a titanium mesh. A galeal-pericranial flap was used to cover the floor of the anterior cranial fossa. The fronto-orbital bar was replaced using 15 mm titanium miniplates. Epidural and subgaleal drains were placed (Fig. 2). The patient made excellent recovery in the immediate and late postoperative periods. The final histopathologic report confirmed a diagnosis of osteoma with osteoblastic and osteoclastic activity. Proptosis resolved, ocular movements remained intact and no visual defects were detected. A postoperative CT scan showed no residual tumour. At one year after intervention, a frontal osseous irregularity was corrected using a bone filler (Norian®, Norian Corporation, Cupertino, CA) (Fig. 3). There has been no recurrence after 5 years of follow-up. Two years postoperatively the patient underwent surgical correction of cataracts, with improvement of visual acuity.

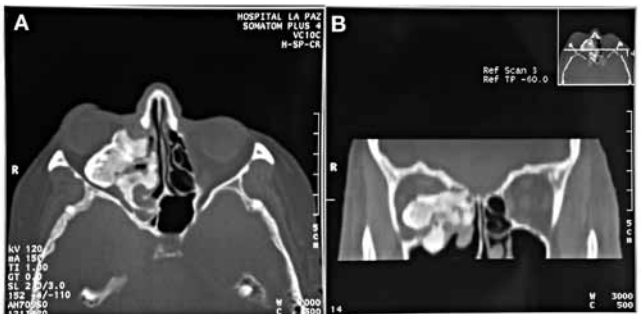

Fig. 1. Preoperative CT. A, axial view: 4 × 4.5 cm right ethmoid polylobulated lesion. B, coronal view: the lesion extended from the right frontal sinus floor to the right sphenoid sinus, and grew superiorly and posteriorly into the right orbit.

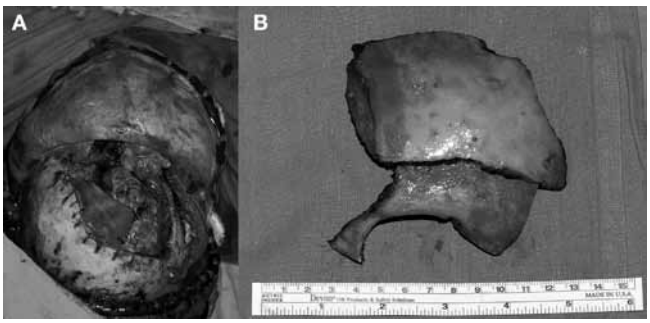

Fig. 2. A, Intraoperative view of the combined cranioorbital approach. B, Portion of cranioorbitotomy.

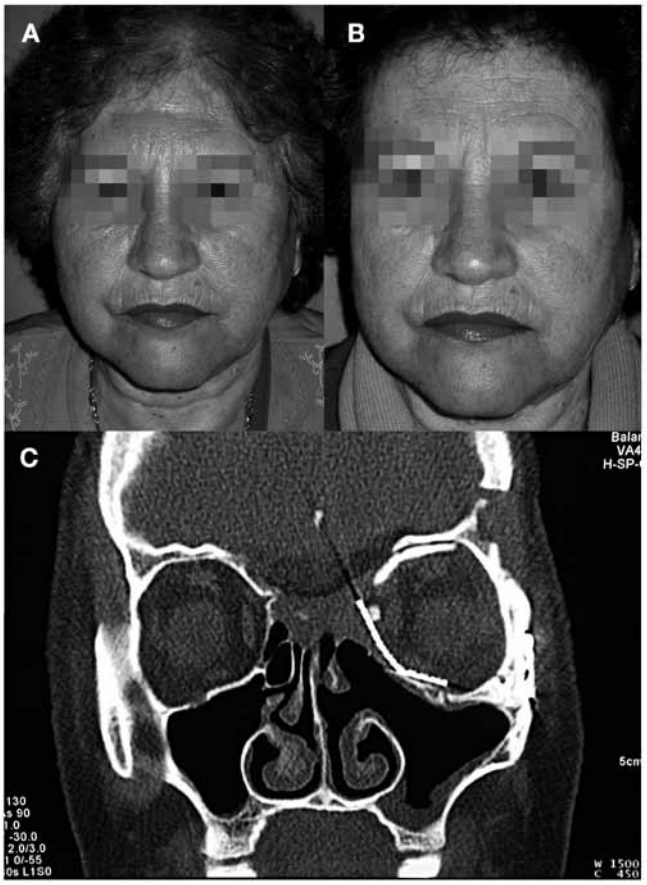

Fig. 3. A, Postoperative view showing the frontal contour defect. B, The frontal contour defect was corrected in a second intervention using a bone filler. C, One-year postoperative CT showed no residual tumour.

Discussion

Osteomas are the most common benign tumours of the paranasal sinuses [2], usually found in the frontal sinus (71.8%) and less often in the ethmoid sinus (16.9%), maxillary sinus (6.3%) or sphenoid sinus (4.9%) [3].

Osteomas are slow-growing neoplasms that are generally diagnosed incidentally in 1% of plain sinus radiographs and in 3% of CT of the sinuses [3 4]. They affect 0.43-1% of the population [5], with a male preponderance. Only 5% of cases become symptomatic or require surgery [3]. Although giant sinus osteomas have been reported, they are rare with the average size being below 2 cm [1].

Different theories exist concerning the factors responsible for their formation (Table I). A combination of traumatic, inflammatory and embryologic hypotheses is the most widely accepted at present [3 4 6].

Osteomas are usually asymptomatic. When they become symptomatic, it is often related to the location of the tumour. The most common symptom is headache [6 7]. When osteomas grow into the anterior cranial fossa, they can produce meningitis, cerebrospinal fluid leakage, pneumatocele [8] or brain abscess [9 10].

Secondary orbital invasion is relatively uncommon, representing 0.9 to 5.1% of all orbital tumours [3], and occurs more frequently in ethmoid, fronto-ethmoid and frontal locations. Tumour growth into the orbit may cause eyeball displacement with gradual proptosis and diplopia, and eventually restriction of extraocular movements. Rare complications include amaurosis [11], orbital emphysema or cerebrospinal fluid rhinorrhoea.

Histologically, osteomas can be divided into ivory, mature or mixed types [1]. Almost all osteomas contain different proportions of the three types, suggesting that they grow outwards from the centre, with increasing maturation at the periphery of the tumour. This may explain why partial resection leaving residual peripheral tissue does not often lead to recurrence [5].

The radiological appearance is a homogeneously calcified, lobulated, sharply defined tumour that fills the internal contour of the sinus of origin [5]. MRI is superior to CT scan in showing optic nerve or optic canal invasion. Radionuclide bone scan may help to differentiate an actively growing lesion from a stable one.

Osteoblastoma and osteoid osteoma are usually the major differential diagnostic considerations [12]. Other benign fibro-osseous and cartilaginous lesions include fibrous dysplasia, ossifying fibroma, or chondroma [1 5]. A biopsy of the lesion is required if the clinical and radiological presentation is unusual.

Management depends on symptoms as well as the size and location of the tumour. Observation and periodic radiological controls are recommended in most asymptomatic cases, except for those located in the sphenoid sinus that threaten the optic canal or orbital apex [3-5].

Table I. Pathogenetic theories of paranasal sinus osteoma.

Traumatic theory of Gerber	Injuries suffered during puberty may cause the growth of osteomas from bone sequestra
Inflammatory theory	Sinusitis may stimulate osteoblastic proliferation or it can be a secondary symptom arising from obstruction of sinus drainage
Embryologic theory	Osteoma arises from the remains of persistent embryologic cells located at the junction of the ethmoid and frontal sinuses

In our case, the mass extended beyond the orbit causing ocular displacement. Visual acuity was most likely affected by two factors, namely cataracts and tumour compression. It was decided to defer cataract intervention given the risk of dehiscence of the corneal incisions due to the compression.

Surgical treatment can be carried out by either endoscopic or open surgery. The choice must consider several factors such as tumour location, extension, dimension and the experience of the surgeon. Rapid progress in endoscopic surgery has enabled more effective endoscopic approaches in small and medium sized tumours [2 4 13]. The advantages of an endoscopic approach are limitation of blood loss and reduced postoperative morbidity, with a shorter hospitalization time [2 14]. The most important disadvantages are the difficult management of intraoperatory complications, such as bleeding, inadequate control of the margins of the lesion and the surgical experience needed.

Open approaches allow radical tumour removal under direct visual control. Transfacial approaches are limited to selected cases depending on the extension of the tumour [7 15]. An intracranial open approach is the technique of choice for large lesions such as the one described here, where the tumour extended to the orbit or the anterior skull base. However, there are disadvantages, such as a longer hospital stay and the risk of damage to the frontal branch of the facial nerve. Depending on the location, a combined cranioendoscopic approach is recommended to perform complete excision with optimal brain control [2 14 16].

Orbital invasion usually necessitates early surgical treatment. In larger cases, orbitocranial approaches combined with other transfacial approaches may be necessary [17]. A frontal craniotomy combined with a burr hole fronto-orbitotomy and a subciliary approach was used in our case, providing excellent control of the disease in the skull base, posterior orbital region and orbital walls.

The resulting defect should be repaired immediately. Small dura defects can be addressed with local flaps, such as pericranial or galeal-pericranial flaps [18], which were used in the present case. For orbital reconstruction, calvarial grafts are preferred in adults as resorption is more

predictable and it is possible to obtain a large amount of bone from the same operative area [19].

Postoperative morbidity depends on the surgical approach. Injury to the periorbita, optic nerve or cribriform plate is possible. Tumour recurrence due to incomplete resection is very unusual. Once the area is stable, yearly controls for at least three years are recommended to identify recurrent or persistent tumour [20].

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Calendar of events – Italian and International Congresses and Courses

Acta Otorhinolaryngol Ital 2013;33:435-437

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JANUARY-DECEMBER 2014

CORSO DI CHIRURGIA OTOLOGICA, OTONEUROLOGICA E IMPLANTOLOGIA UDITIVA – Dissezione dell'osso temporale e del basicranio • ***January 7-9, 2014 • Paris – France***

Direttore del Corso: Olivier Sterkers. Info: Daniele Bernardeschi, Reparto di Otorinolaringoiatria e Chirurgia Cervico-facciale, Ospedale Pitié-Salpétrière e Università Paris Diderot - Paris VII, France. E-mail: daniele.bernardeschi@psl.aphp.fr

II CORSO "SCUOLA DI DISSEZIONE ANATOMICA CERVICO-FACCIALE"
January 20-24, 2014 • Florence – Italy

II sessione
• Blefaroplastica e otoplastica – P. Persichetti, R. Polselli, A. Rusciani, Y. Saban
• Chirurgia endoscopica seni paranasali (avanzato) – P. Bossolesi, E. Emanuelli, F.G. Pagella
• Rinoplastica – L. D'Ascanio, G. La Fauci, R. Polselli, A. Scattolin
• Anatomia chirurgica della laringe – M. Lucioni, G. Rizzotto, G. Succo, L. D'Ascanio
Direttore del Corso: Alberto Scattolin. Segreteria Organizzativa: Nord Est Congressi – E-mail: mail@nordestcongressi.it – Website: www.nordestcongressi.it

THREE-DIMENSION TRANSNASAL ENDOSCOPIC TREATMENT OF SKULL BASE DISEASES
January 23-24, 2014 • Brescia – Italy

Organizing Secretariat: Katia Gissi, Servizi C.E.C. Srl, Via G. Verdi 18, 24121 Bergamo, Italy. Tel. +39 035 249899 – Fax +39 035 237852 – E-mail: k.gissi@servizicec.it – Website: www.servizicec.it

4th ANNUAL NORTH AMERICAN RHINOLOGY & ALLERGY CONFERENCE (NARAC)
January 23-26, 2014 • Puerto Rico

E-mail: info@NARAConference.org – Website: www.NARAConference.org

I CORSO – RINGIOVANIMENTO NON CHIRURGICO DEL VISO
January 30 - February 1, 2014 • Florence – Italy

Faculty: D. Draganic, A. Rusciani, R. Polselli, Y. Saban. Segreteria Organizzativa: Nord Est Congressi. E-mail: mail@nordestcongressi.it – Website: www.nordestcongressi.it

TEMPORAL BONE DISSECTION COURSES 2014
February 19-22, June 10-13, December 9-12, 2014 • Brazil

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3° CORSO TEORICO PRATICO DI LARINGOLOGIA PEDIATRICA • ***February 3-4, 2014 • Modena – Italy***

Segreteria Organizzativa: Meet and Work s.r.l., p.zza del Sole e della Pace 5, 35031 Abano Terme (PD), Italy. Tel. +39 049 8601818 – Fax +39 049 8602389 – E-mail: meet@meetandwork.com

CORSO TEORICO-PRATICO DI LIFTING CERVICO-FACCIALE E MEDICINA ESTETICA DEL VISO
February 7-8, 2014 • Rome – Italy

Direttore del Corso: Domenico Riitano, Domimedica Roma, Ospedale Israelitico Roma. Segreteria Scientifica: Pierluca Venturino, Aurelio Cardaci, Domimedica Roma, via Antonio Chinotto 1, Tel. +39 06 3233956 – E-mail: eventi@domimedica.it. Website: www.domimedica.it. Segreteria Organizzativa: Meeter Congressi srl, via Salvatore Trinchese 22, 00188 Roma Tel. +39 06 33680034 – Fax +39 06 33680033 – E-mail: eventi@meeter.it – Website: www.meeter.it

ATLANTIC OTOLARYNGOLOGY HEAD AND NECK SURGERY UPDATE
February 15-17, 2014 • San Juan, Puerto Rico

Website: www.HopkinsCME.edu

EXTREME LIVE SURGERY ARENA • *February 20-21, 2014 • Varese – Italy*

Direttori: Paolo Castelnuovo e Pietro Palma, Website: www.extremelivesurgery.com – Info: MZ Congressi. Tel. +39 02 66802323 / 02 36753900 – Fax +39 02 6686699 / 02 49542900 – E-mail: exlsa@cq-travel.com

RHINOPLASTY INTERNATIONAL COURSE • *March 11-12, 2014 • Milan – Italy*

Course Director: Mario Bussi. Organizing Secretariat: San Raffaele Congress Centre, via Olgettina 58, 20132 Milan, Italy. Tel. +39 02 2643 6227 – Fax +39 02 2643 3754 – E-mail: isella.linda@hsr.it Website: www.entcourses.it

11th RHINOCAMP WINTER • *March 12-16, 2014 • Saint Moriz – Switzerland*

Website: www.rhinocampwinter.org

4th INTERNATIONAL RHINOPLASTY COURSE IN LEUVEN 'EXCELLENCE IN RHINOPLASTY'
March 19-21 2014 • Leuven – Belgium

Website: www.excellenceinrhinoplasty.be

CORSO DI ANATOMIA E CHIRURGIA CERVICO-FACCIALE • *March 19-21, 2014 • Nîmes – France*

Information: Pierfrancesco Pelliccia, E-mail: pierfrancesco.pelliccia@hotmail.it

CORSO TEORICO-PRATICO DI RINOPLASTICA OPEN E MEDICINA ESTETICA DEL 3° MEDIO E DEL 3° SUPERIORE • *March 21-22, 2014 • Rome – Italy*

Direttore del Corso: Domenico Riitano, Domimedica Roma, Ospedale Israelitico Roma. Segreteria Scientifica: Pierluca Venturino, Aurelio Cardaci, Domimedica Roma, via Antonio Chinotto 1, Tel. +39 06 3233956 – E-mail: eventi@domimedica.it – Website: www.domimedica.it. Segreteria Organizzativa: Meeter Congressi srl, via Salvatore Trinchese 22, 00188 Roma. Tel. +39 06 33680034 – Fax +39 06 33680033 – E-mail: eventi@meeter.it Website: www.meeter.it

AMERICAN ACADEMY OF AUDIOLOGY AAA ANNUAL CONVENTION
March 26-29, 2014 • Orlando, Fla – USA

Website: www.audiologynow.org

11th INTERNATIONAL COURSE IN ADVANCED SINUS SURGERY TECHNIQUES
March 27-28, 2014 • Amsterdam – The Netherlands

Course secretariat: AMC, ENT Dept., P.O. Box 22660, Location D2-312, 1100 DD Amsterdam, The Netherlands. Tel. 00 31 20 5668586 – Fax 00 31 20 56 69 573 – E-mail: M.B.vanhuiden@amc.uva.nl – Website: www.sinuscourse.nl

ASOHNS ASM 2014 MODERN APPROACHES TO ENT
March 29-April 1, 2014 • Brisbane Queensland – Australia

Website: www.asohns.consec.com.au

10th CONGRESS OF THE EUROPEAN LARYNGOLOGICAL SOCIETY – 2nd JOINT MEETING OF ABEA & ALA
April 9-12, 2014 • Antalya – Turkey

Website: www.els2014.org

18th INTERNATIONAL VOICE WORKSHOP 2014 • *April 11-12, 2014 • Paris – France*

Information to: Jean Abitbol, 1, Rue Largillière – 705016 Paris. E-mail: voice.abitol@gmail.com

SINO-NASAL & SKULL BASE DISSECTION COURSE • *April 12-13, 2014 • Milan – Italy*

Organizing Secretariat: San Raffaele Congress Centre, via Olgettina 58, 20132 Milan, Italy. Tel. +39 02 2643 6227 – Fax +39 02 2643 3754 – E-mail: isella.linda@hsr.it – Website: www.entcourses.it

4th MIDDLE EAST CONGRESS ON RHINOLOGY AND FACIAL PLASTIC SURGERY (MERC2014)
April 12-14, 2014 • Tehran – Iran

Website: www.merc2014.com

18th WCBIP/WCBE
18th WORLD CONGRESS FOR BRONCHOLOGY AND INTERVENTIONAL PULMONOLOGY
18th WORLD CONGRESS FOR BRONCHOESOPHAGOLOGY
April 13-17, 2014 • Kyoto – Japan

Website: www2.convention.co.jp/wcbipwcbe2014/

THE FOURTH MIDDLE EAST CONGRESS ON RHINOLOGY & FACIAL PLASTIC SURGERY
April 23-25, 2014 • Tehran – Iran

Website: www.merc2014.com

3rd INTERNATIONAL SYMPOSIUM ON OTOSCLEROSIS AND STAPES SURGERY
April 24-26, 2014 • Siófok – Hungary

President of the Congress: I. Sziklai – Secretary of the Congress: T. Karosi. Website: www.otosclerosis2014.com

2nd ANNOUNCEMENT OTOLOGY JUBILEE: 150 YEARS OF THE ARCHIV FUR OHORENHEILKUNDE
Past-Present-Future in Otology & Neurology • *May 7-10, 2014 • Halle/Saale – Germany*

Website: www.otology-jubilee.com

3rd IRANIAN CONGRESS ON COCHLEAR IMPLANT & RELATED SCIENCE
May 10-12, 2014 • Tehran – Iran

IRANCI 2014 Secretariat: Tel. - Fax 098-21-8860-0006 – E-mail: info@irancochlear.com – Website: www.iran-cochlear.com

101° CONGRESSO NAZIONALE SIO – Società italiana di Otorinolaringoiatria e Cervicofacciale
May 28-31, 2014 • Catania – Italy

President: A. Serra. Website: www.sio2014.org – www.eac.it

4th HANDS ON DISSECTION ADVANCED COURSE: "FROM REMOVAL TO RECONSTRUCTION IN HEAD AND NECK CANCERS" • *June 17-20, 2014 • Paris – France*

Directors: Marco Benazzo, Department of Otolaryngology HN Surgery, University of Pavia, Italy; Fausto Giuseppe Chiesa, Department of Otolaryngology HN Surgery, IEO Milan, Italy. Organizing Secretariat: Bquadro Congressi srl, via S. Giovanni in Borgo 4, 27100 Pavia. Tel. +39 0382 302859 – Fax +39 0382 27697 – E-mail: bolla@bquadro-congressi.it.

24th CONGRESS OF EUROPEAN RHINOLOGIC SOCIETY (ERS) and 32nd INTERNATIONAL SYMPOSIUM OF INFECTION AND ALLERGY OF THE NOSE. THE NOSE AS INTERFACE
June 22-26, 2014 • Amsterdam – The Netherlands

President: W.J. Fokkens. Website: www.ers-isian2014.com – E-mail: ers-isian2014@kenes.com

5th WORLD CONGRESS OF THE INTERNATIONAL FEDERATION OF HEAD AND NECK ONCOLOGIC SOCIETIES (IFHNOS) – ANNUAL MEETING OF THE AMERICAN HEAD AND NECK SOCIETY (AHNS)
July 26-30, 2014 • New York – USA

Congress Chairman: Jatin Shah. Program Chairman: Bevan Yueh. Websites: www.ifhnos2014.org, www.ahns2014.org

BEST EVIDENCE ENT 2014 • *August 2-5, 2014 • Wisconsin – USA*

Course directors: John S. Rhee, David R. Friedland, Charles J. Harkins. Department of Otolaryngology 9200 West Wisconsin Avenue Milwaukee, WI 53226

40° CONGRESSO CONVENTUS SOCIETAS ORL LATINA • *September 1-5, 2014 • Baia de Luanda – Angola*

Info: Departamento de ORL da Facultdade de Medicina da Universidade Agostino Neto Hospital Josina Machel-Maria Pia Av. 1° Congresso do MPLA. Tel. 00244-923784901/914381304 – E-mail: mfilipe@snet.co.ao, drmatuba@gmail.com

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