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MicroRNA-21 expression in Vestibular Schwannoma: potential effect on growth and possible prognostic factor.

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Abstract

Background: Vestibular schwannomas are benign slow growing tumors arising from VIII cranial nerve. They are potential life threatening benign tumor because of intracranial located. The management could be surgical or conservative, but, left untreated, the tumor preserve the possibility to further growth and complication may arise. The natural history is however not predictable and prognostic factor to select patients manageable conservatively should be studied.
The molecular pathways that lead to tumorigenesis and growth are not completely defined and a role could be played by microRNA. Elevated levels of microRNA-21 may contribute to tumor growth by deregulating the tumor suppressor phosphatase (PTEN) and consequent activation of protein kinase B (AKT).
Aims: evaluation of microRNA-21 expression and measurement of PTEN levels in vestibular schwannoma specimens, compared with expression in normal nerve tissue, to assess a possible overexpression. A correlation of micorRNA-21 expression with tumor size and growth rate of the tumor, when available, was hypothesized to make a prognostic factor.
Methods: collection of vestibular schwannomas and great auricular nerve specimens was done sterilely during surgery and immediately stored at -80°C, until its use. Quantitative real-time PCR was used to assess levels of expression of micro-RNA 21 and mRNA for PTEN.

Levels of PTEN protein were assessed with immunohistochemical analysis. A retrospective correlation was done between data obtained and clinical notes of patients: tumor size and growth rate.

Results: 31 patients with vestibular schwannoma were studied. MicroRNA-21 was founded overexpressed in all cases when compared with normal nerve tissue. Levels of microRNA-21 were not statistically related with tumor size at time of surgery, but a positive correlation with growth rate was noted in 10 cases in which this data was available. PTEN mRNA was founded in all cases. The PTEN protein levels were low in 10 specimens of 13 in which the data was available, and an inverse correlation with levels of microRNA-21 was noted.

Conclusions: The microRNA-21 plays a role in tumor development and in growth regulation also in vestibular schwannoma. MicroRNA-21 may be a proper molecular target for therapies act to reduce the tumor growth and could represent a prognostic factor in selecting patients manageable with observation or early hearing preservation surgery.

Introduction

Vestibular schwannomas (VS) are benign slow growing tumors, arising from the VIII cranial nerve, generally involving the inferior vestibular nerve. This tumor could be part of a systemic disease called Neurofibromatosis type 2 (NF2), in which the tumors are bilateral and more aggressive. Vestibular schwannomas represent about 6% of all intracranial tumors and accounts for about 80% of all tumors diagnosed in the cerebello-pontine angle (CPA). The incidence reported is 10-20:1000000 per year[1]. The incidence apparently increased in the last 10 years, but it was due to the enlarged availability of MRI done for others reasons. However, the true incidence could be different and greater than the actually known, because of a lot of tumors remain silent and undiagnosed.

The typical presentation of the solitary VS includes: unilateral progressive sensorineural hearing loss (SNHL) in the high frequency range, unilateral tinnitus, and vertigo spells or imbalance[2]. However, abnormal clinical presentation may be present characterized by sudden sensorineural hearing loss, facial weakness, brainstem compression, and hydrocephalus. Sometime VS is completely asymptomatic and diagnosed casually. Generally, the retard of diagnosis since the development of the tumor is about 5 years.

Although slow, the growth rate is not estimable and the regulating factors are still unknown. It was estimated that the size of VS increases in diameter at an average of 1 to 2 mm per year. In 30% to 70% a growth is demonstrable over a variable period of time, but in some patients it could be observed a spontaneous tumor regression.

The variable percentage of growth reported may depend, at least in part, on the length of the observation period[3]. A rapid growth could be present in some tumors with cystic component due to accumulation of fluid into cystic space or to an improvise intratumoral hemorrhage[4].

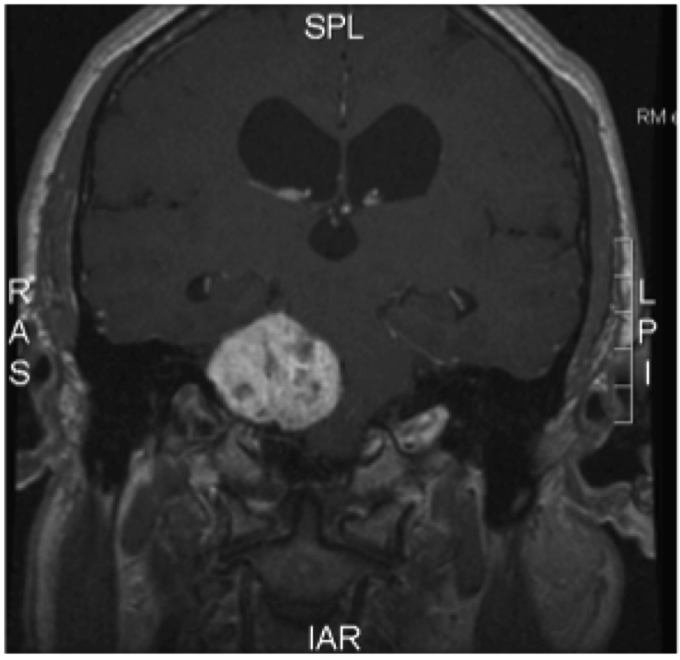


Fig. 1: MRI coronal scan T1-weighted after Gadolinium enhancement showing a giant vestibular schwannoma of the right cerebello-pontine angle.

The treatment of VS may be surgical, with radiotherapy or conservative by a wait and see program. Surgical management represents the classical and the widest adopted management of such tumors since first operations with modern approach that William House introduced[5]. The surgical excision includes total or subtotal (programmed) removal, depending on tumor size and location; the subtotal removal is generally selected in case of high risk of damage for the brainstem or facial nerve. The aim of the surgical treatment is

dual: remove a potential life-threatening disease, and preserve the hearing and facial nerve function as possible. In patients with unserviceable hearing the translabyrinthine approach is the standard technique adopted regardless the tumor size, because this approach give to the surgeon wide field for operation and low risks. The translabyrinthine approach, which damages completely the hearing, is mandatory also for tumor larger than 25 mm not considering the hearing status, because of the hearing preservation is not reasonably practicable in big sized tumor. The middle fossa approach is done generally in about one third of patients. This latter approach is used on patients with good hearing with intracanalicular tumors, or tumor with minimal extension into CPA, generally the size should be less than 20 mm. The retrosigmoid approach is done in patients with good hearing and medial tumors with prevalent extension toward CPA and minimal into IAC. The results of the surgery are quite homogeneous, with an average of hearing preservation in about 50% of patients treated with MCF or RS; correlated with the number of treated cases, every institute may have a better results in one of the two techniques. It is general idea that completely excised VSs do not recur and it is reasonable to consider less than complete removal despite the attendant increased risk of regrowth. The subtotal removal may be planned preoperatively under certain conditions. A planned incomplete resection may be undertaken when a more prolonged operation is judged unwise because of the patient's advanced age or performance status. Incomplete removal may be decided intraoperatively when dissection planes are poor and the surgeon think that total removal carries a high risk of damage of the facial nerve. In

selected cases subtotal removal increases the odds of hearing conservation, in particular in case of contralateral ear disease.

The aim of all therapies should be to prevent morbidity and mortality in the safest, non-invasive fashion that can yield effective results. For this reason, the management of VS has shifted in recent decades away from microsurgical resection toward more conservative strategies such as radiotherapy or observation. Vestibular schwannoma have all the characters of a disease manageable with the simple observation for a long period: slow growth, benign behavior, and few symptoms in early phases. Furthermore, a considerable number of tumors seem to be quiescent and do not become clinically significant within a patient's lifetime; such tumor may never warrant treatment. The conservative management consists of observation of the tumor by MRI scan, without any active treatment, delaying the treatment until the lesion exhibits a dangerous modification. Vestibular schwannomas are being diagnosed earlier and smaller because of improvement of imaging techniques and aggressive audiological screening in case of patients with tinnitus, dizziness, facial nerve weakness and unilateral hearing loss. Conservative management of VS have been reported since 1985[6]. From this beginning, successive reports affirmed that the majority of VS grew during the follow-up period. Others Authors reported patients who benefited from wait and see policy; 78% had growth rate of < 2 mm/year[7]. In a big observational study of the Danish Otoneurologic school emerged that VS exhibit growth only in the first 5 years after diagnosis[1]. It should be noted that, although serial observation may represent the conservative management, it is not without risks.

Deferring definitive treatment may lead to progression of hearing impairment or to evolution from an easily resectable lesion to one that carries increased surgical risks. The tumor size at initial presentation seems to be predictive of tumor growth. However the diagnosis of VS does not occur at a uniform stage in their natural history, then the tumor size at diagnosis may reflect a biological proclivity for growth, such that the detection of a large tumor at initial presentation may be indicative of past growth; to consider it as a marker for future growth potential is only a supposition. In 2003 the Tokyo Consensus Meeting on System for Reporting Results in Vestibular Schwannoma accepted the measuring system, described before, with the measurement of the largest extrameatal diameter of the tumor[8]. Actually is still the widest adopted system because of applicable in quite all institution with all type of MRI devices. The follow-up program is developed with a yearly MRI for 5 years, followed by MRI every other year for 4 years, and a new MRI after 5 years. After such period the observation is terminated if the tumor don't show new growth or some disabling symptoms occur.

Certainly, the unpredictable behavior of the tumor is a concern in choosing a treatment plan that is generally consequent to: hearing status, tumor size, and performance status of patient. The identification of prognostic factor should help the otoneurologist in selecting a proper management. Whereas radiological features and presenting symptoms did not result good prognostic factor or predictor element of tumor development, molecular elements, as well as microRNA, could be useful to act as predictive factors of biological behavior of VS in time.

MicroRNA are small noncoding RNA molecules that regulate posttranscriptional gene expression, and are evolutionarily conserved. Mature microRNA binds to specific mRNA targets in region complementary to the microRNA and, by a mechanism that is not completely understood, resulting in translational repression or degradation of the mRNA[9]. It has been demonstrated that tumors exhibit aberrant microRNA expression profiles, this indicate that such molecules play an important role in cellular differentiation, development, metabolism, apoptosis, and cancer[10].

MicroRNA-21 (miR-21) has been founded overexpressed in many tumors including: breast, liver, and glioblastoma[11,12]. One of the target of miR-21was identified as mRNA encoding for phosphatase and tensin homolog (PTEN), a tumor suppressor[12]. The protein PTEN acts as tumor suppressor inhibiting phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway that promotes cell proliferation cell survival and tumor growth[13]. The PI3K/AKT pathway was founded activated in human VS development. The activation of antiapoptotic growth-promoting pathways such as the PI3K/AKT system may be a key mechanism whereby tumors gain a survival advantage[14]. Increased levels of miR-21 in VS have a determinant role in downregulating PTEN expression and, as consequence, hyperactivating AKT signal; input to VS development.

The deregulation of proliferation activity and cell apoptosis lead to tumor formation and growth, often associated with mutation of the *NF2* gene, which encodes the tumor suppressor protein called "merlin". This mutation is constitutionally present in NF2 patients, while is often acquired in sporadic VS. Whereas the merlin alteration

is well known in NF2, the development mechanism of the solitary VS was only recently studied.

The aim of the present investigation was to identify some possible molecular prognostic or predicting factor for VS growth, making also a correlation with presenting symptoms and post-operative follow-up. Discovering of some predictor factor of VS growth could avoid risky operations and aimless sacrifice of hearing and facial nerve.

Methods

The patients selected for surgical removal of VS were enrolled in this study started in 2008. All patients underwent to: head and neck examination, cranial nerve clinical evaluation, clinical vestibular tests, pure tone audiometry, MRI with gadolinium of the brain and IAC. MRI done in the previous years were recorded for the analysis of the growth rate, when available. The calculation of the tumor size was effectuated by measurement of the greater diameter of the extrameatal component of the VS on MRI. The surgical treatment was adopted for all patients evaluated in this series.

The collection of specimens was done during surgical removal of unilateral sporadic VS via translabyrinthine approach. The fresh tumor specimens, dissected with cold blades, were sterilely collected and immediately stored at -80°C until its use. As health tissue control we used specimens of great auricular nerve, which were collected in the same manner, during neck dissection for head and neck malignancy, but without signs metastatic neck disease.

Real-time RT-PCR was used to confirm data showing elevated expression of miR-21 in VS. Briefly, RT reactions containing total RNA, primers, 1 x RT buffer, RT, and RNAse inhibitor were incubated for 30 minutes each at 16°C and at 42°C. Primers were annealed to miRNA targets and extended by reverse transcription. Reactions containing miRNA specific forward primer, and reverse primers were loaded into a PCR plate in quadruplicate and incubated in a thermocycler for 10 minutes at 95°C and then 40 cycles of denaturing (15 s at 95°C), annealing, and extension (60 s at 60°C). Mean threshold cycles (C_T) were calculated by averaging the technical replicates for each experiment and then by averaging the mean replicate C_T across the 3 runs. Quadruplicates with an SD greater than 0.50 were eliminated, and these assays were repeated. The expression of miR-21 was normalized to U6B small nuclear RNA (ΔC_T) for each tissue. PTEN mRNA was evaluated with quantitative real-time PCR.
Furthermore, we performed immunohistochemical (IHC) assays for the detection of PTEN. Nuclear PTEN protein expression was evaluated according to rank scale of 0 to 2. Inflammatory and normal stromal cells were used as control markers of staining intensity. PTEN staining in tumor cells was graded as: 2, if the staining intensity was equal to or higher than that of control cells; 1, if their staining intensity was lower than that of control cells; and 0, if no staining was found in the tumor cells. Tumors with PTEN scores of 0 or 1 were considered to have PTEN loss. Cases with staining of 2 in more than 10% of the cells were considered positive for PTEN expression by IHC.

The follow-up of the patients was of 2 years, and consisted of a clinical evaluation and a MRI scan with fat suppression. The correlation was done between clinical notes recorded and data obtained from laboratory investigation. Statistical significance was determined using the Student's t test assuming unequal variance.

Results

31 patients affected by vestibular schwannoma were studied. The mean age of the series was 52 years (range 29-73). The sex distribution was: 18 males and 13 females. The symptoms recorded were: hearing loss in 28 patients, disequilibrium in 8 patients. Tinnitus was present in all series. Ten patients were in follow-up with periodical MRI scan but underwent surgery because of hearing deterioration and/or evidence of tumor growth. No disturbances of the equilibrium were present at time of the first evaluation. All patients were treated surgically by a translabyrintyne approach. The preoperative imaging showed the morphologic status of the tumors: cystic in 5 cases and solid in 26 cases. The mean tumor size of the series was 16,2 mm (range 0-40 mm; SD ± 10,1mm). The tumor growth rate was calculated in those patients in whom several MRI were done during a follow-up protocol and revealed an average rate of 2,9 mm per year.

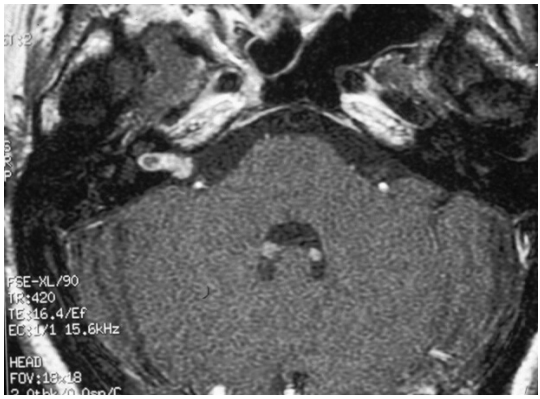


Fig. 2: MRI axial scan T1-weighted after Gadolinium enhancement showing a vestibular schwannoma involving the right internal auditory canal with a minimal extension into cerebello-pontine angle. The size measured was 3 mm.

MicroRNA-21 was founded overexpressed in all cases when compared with normal nerve tissue of 12 samples of normal great auricular nerve, respectively 7,56 ΔCt (SD ± 0,21) and 4,92 ΔCt (SD ± 0,54) in controls. The difference between cases and control was statistically significant with a t-score: 16.53 and a p-value < 0.001.

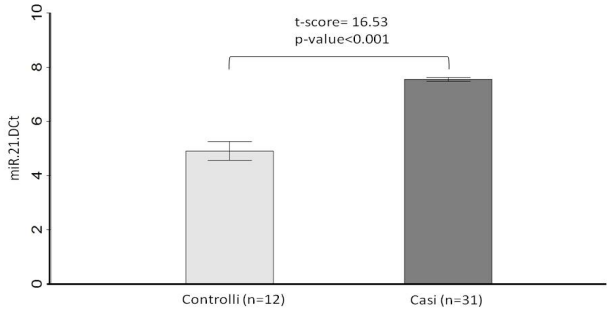


Fig. 1: miR-21 expression in Cases (specimens of VS) and Controls (specimens of great auricular nerve). The difference between the two groups is statistically significant, indicating a deregulation in miR-21 expression in tumoral nervous tissue. (p<0.001)

Levels of microRNA-21 were not statistically related with tumor size at time of surgery ($p > 0.07$), although was noted a linear correlation between the two data. This data is presumably due to presence of other factors and small size of the series. In fact, applying a correction for the age of patients the relation between miR-21 overexpression and final size becomes statistical significant ($p< 0.04$).

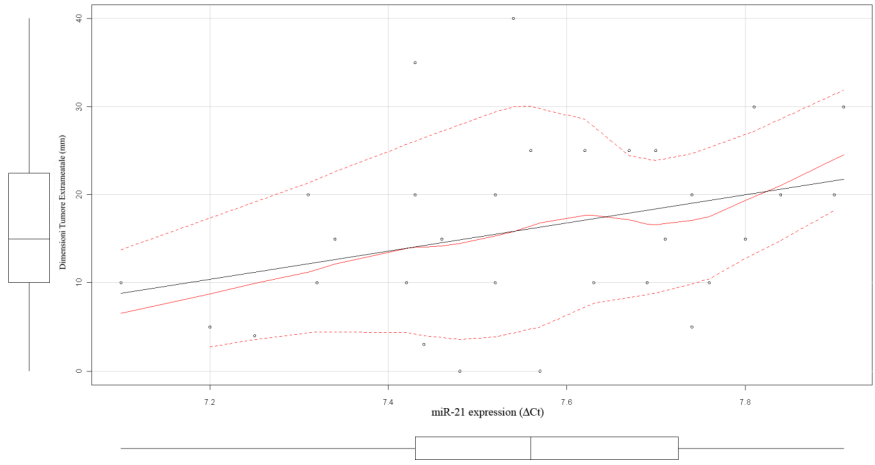


Fig. 2: Correlation between tumor size and miR-21 expression. The tumor size seems to be linearly correlated with miR-21 expression rate, but the data was not statistically significant (p>0.07).

A positive linear correlation between miR-21 expression and growth rate was noted in 10 cases in which this data was available. The small sample does not allow a statistical significance ($p > 0.07$).

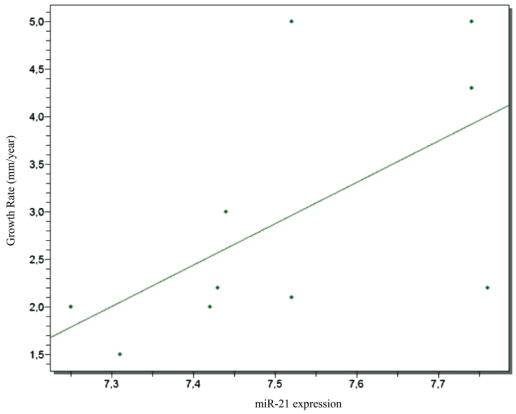


Fig. 3: Effect of miR-21 expression on the tumor growth rate. In 10 patients, in whom the growth was calculable, there was a positive linear correlation between miR-21 expression and growth rate expressed in mm per year.

The overexpression of miR-21 was more marked in cystic tumors rather than solid tumors.

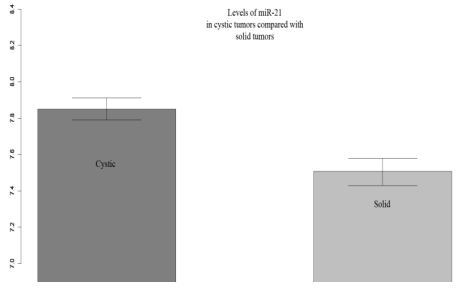


Fig. 4: The morphology of the tumor (i.e. cystic or solid) was correlated with miR-21 expression. Cystic tumors displayed a higher expression levels of miR-21 rather than solid type.

PTEN mRNA was founded in all cases. On IHC analysis of the specimens showed the PTEN protein expression: low in 14 specimens,

absent in 16 cases and normal in only 1 case. An inverse correlation with levels of microRNA-21 was noted.

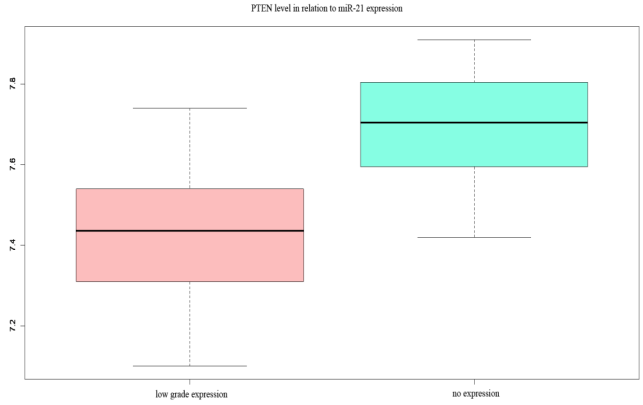


Fig. 5: miR-21 regulates levels of PTEN protein. The expression of PTEN was founded inversely correlated with the levels of miR-21.

After surgery no major complications were noted. All the patients have no evidence of residual or recurrent disease at last MRI control after 2 years. Any correlations of miR-21 with symptoms or surgical outcome were present.

Discussion

The discovery of microRNAs has broadened our understanding of the mechanism that control gene expression with the addition of an entirely novel level of regulatory control. These small noncoding transcripts of 18-25 nucleotides modulate protein expression by binding to complementary or partially complementary target mRNAs,

and thereby targeting the mRNA for degradation or translational inhibition[15].

The study of miRNA in VS originates by the observation of its behavior and effects in other tumors. Inhibition of miR-21 in hepatocellular carcinoma cell lines increased expression of tumor suppressor PTEN and decreased cellular proliferation, migration and invasion, whereas enhancing miR-21 expression caused opposite effects[12]. MicroRNA-21 has a role in several cancer-related processes. In breast cancer was showed that transfection of cells lines with anti-miR-21 resulted in increased apoptosis and inhibition of cell growth[16]. Also in VS cell cultures the proliferative rate an the cell survival was downregulated by a same procedure, indicating that miR-21 have a similar role[17]. In colorectal cancer has been demonstrated that the tumor suppressor PDCD4 (programmed cell death 4) is a target of miR-21 and its downregulation stimulated invasion, extravasation and metastasis[18].

In primary brain tumors high levels of miR-21 were founded, with maximum overexpression in glioblastomas[11]. MicroRNA-21 might block the expression of gene products that promote normal glia differentiation or that induce apoptosis, holding tumor cells in an inappropriately primitive and proliferative developmental state. Schwann cells are part of the glia tissue, hence may exhibit some deregulation of miR-21 expression in tumor cases as well. MicroRNA-21 overexpression in VS may become, consequently, a key point in the control of growth and development by PTEN regulation and its effects, as stated before, on AKT pathway. PTEN is the most highly mutated tumor-suppressor gene in the post-p53 era; it

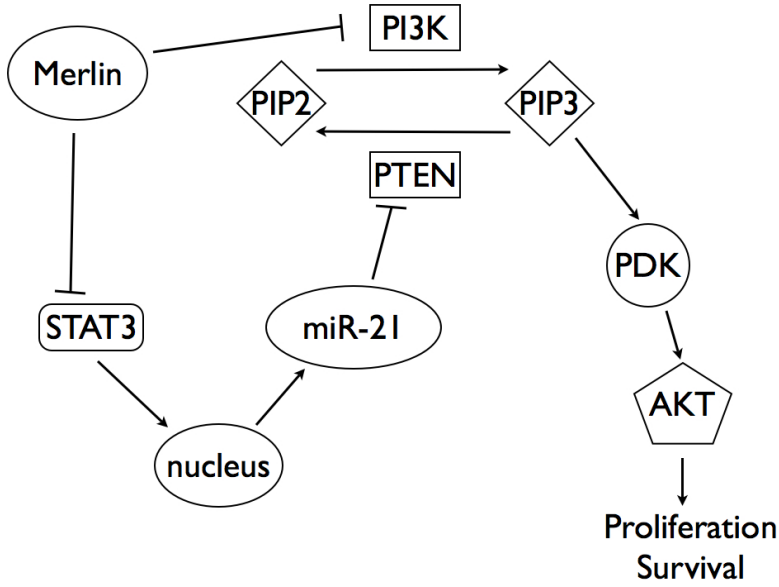
play a role not only in inducing cell cycle arrest and programming apoptosis, but also in other aspects of cell physiology, including cell adhesion, migration and differentiation. Perturbations in AKT signaling have been shown to induce malignant transformation in ovarian cancer, lymphomas, pancreatic cancer, hepatocellular carcinoma, gastric cancer, prostatic cancer, and thyroid cancer[19].

Decreased expression of PTEN would enhance proliferative signaling through the pathway of AKT regulation, by activating this kinase, and finally leading to proliferation, decreased apoptosis or both. The PI3K/AKT signaling pathway is a growth-promoting system in several human malignant tumors. AKT has been involved in cell survival and growth, in differentiation and apoptosis as well[20]. PI3K is a membrane-associated lipid kinase that catalyzes the conversion of phosphatidylinositol diphosphate (PIP2) to phosphatidylinositol diphosphate (PIP3). This event recruits AKT from the cytoplasm to the membrane to a direct action between PIP3 and AKT[20]. The activation of AKT is mediated by phosphoinositide-dependent protein kinase (PDK) by phosphorylation of an AKT site; a second phosphorylation is required for a maximal activation[21].

The principal negative regulator of AKT activation is PTEN, which role consists in the conversion of PIP3 in PIP2. PIP3 levels are very low in quiescent cells, but rapidly increase upon stimulation by growth factors, through activation of PI3K, as mentioned. Generally a loss of the PTEN function is secondary to a deletion on chromosome 10, but in low grade glioneural tumors PTEN mutation are rare, hence is the regulation of its activity that is deregulated. PTEN have opposite function of PI3K in regulating cell proliferation and survival by

regulation of PDK phosphorylation state. The activity of PTEN is also regulated by a phosphorylation that decreases its phosphatase activity. The series that we presented showed the importance of miR-21 role in VS growth with a linear correlation between expression and size at time of diagnosis. Furthermore, an interesting relationship emerged between miR-21 expression and growth rate that, although without statistical evidence, seems to be related with the level of miR-21, opening the perspective to perform an early hearing preservation surgery in those patients with high risk of tumor growth.

Probably other mRNA that may be targeted by miR-21 may either serve unrelated functions, or may serve to modulate the effect of PTEN. Based on target prediction algorithms, PTEN potentially could be targeted by miRNA other than miR-21, but PTEN needs to be verified experimentally as a good target for these miRNA, and a biologically relevant role shown.



The microRNA-21 gene presents an upstream enhancer region containing two binding site for STAT3 (signal transducer and activator of transcription 3). It was also demonstrated that the activation of STAT3 induces expression of miR-21[22]. STAT3 is a regulator of gene expression in response to many growth factors and cytokines. The neuropoietic cytokines ciliary neurotrophic factor (CNTF) bind to specific ligand-binding receptor subunits and share with others ligand the signal transduction subunit gp130, activating the transcription pathway[23]. STAT3 is activated also by the neuropoietic cytokines IL-6 playing an important role in nerve repair and regeneration[23]. STAT3 may induce miR-21 expression also in multiple myeloma cells[22].

Merlin, the protein product for the NF2 gene, is structurally similar to the ezrin/radixin/moesin cytoskeletal proteins, but has unique tumor-suppressive properties[24]. Overexpression of merlin suppresses growth of rat schwannoma cells, whereas merlin inactivation leads to loss of contact inhibition and increased cell proliferation[25]. The merlin regulate also the PI3K activation through its interaction with an enhancer, consequently and indirectly acts as a suppressor of the AKT pathway activation[26]. The merlin was founded mutated in sporadic VS with loss its biological function in 53-70% of examined cases[27], and also our previous unpublished data confirm these information. As showed by Scoles et al., merlin protein play a role in suppressing STAT3 activation through interaction with hepatocyte growth factor-regulated tyrosine kinase substrate (HRS) in human schwannoma cell line[28]. The mutation occurring in NF2 patients interferes with binding of HRS with merlin abolishing the

ability of merlin to inhibit STAT3 activation. This open the possibility that overexpression of miR-21 in VS may be a consequence of a deregulated activation of STAT3 by an autocrine or paracrine mechanism involving neuropoietic cytokines[17].

The activation of STAT signaling is regulated also by epidermal growth factor receptor (EGFR) pathway, which contribute to cell proliferation in tumoral cell of NF2 patients and in primary VS cultures[29]. This mechanism is not clear, but the use of a EGFR inhibitor in NF2 subjects showed some benefit in term of arrest of growth[30], although not statistically proved, the targeted therapy hold some promise.

MicroRNA-21 acts as an antiapoptotic factor in glioblastoma cells. An aberrant increased expression of miR-21 may down-regulate the translation or stability of mRNA coding for apoptosis-related genes, this was showed by an inhibition of miR-21 expression that leaded to caspase activation and associated apoptotic cell death[11]. The precise target is still now unknown.

The cystic phenotype of VS was indicated as more aggressive form of tumor, because of the accumulation of fluid into cyst may determine a rapid expansion of the mass, compressing rapidly the surrounding structures[31].

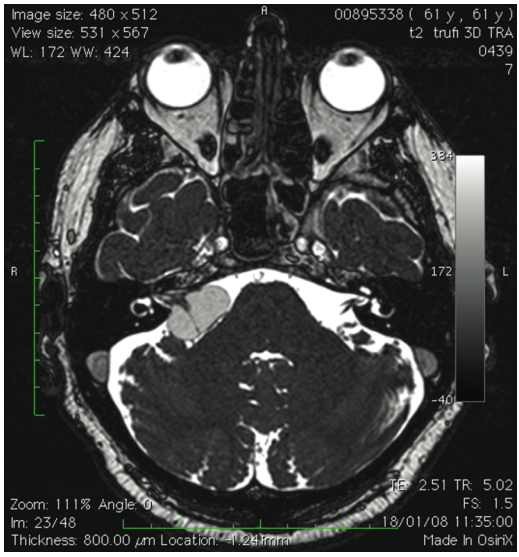


Fig. : MRI axial scan T2-weighted showing a cystic vestibular schwannoma. The cystic component is the prevalent portion displayed with an intermediate gray due to difference in proteins content compared to cerebrospinal fluid.

MicroRNA-21 increases matrix metalloproteinase-2 (MM2) expression in cardiac fibroblasts by the PTEN pathway, and MM2 has been associated with cyst formation in VS[32]. Our results indicate that the cystic type of VS exhibits a higher expression of miR-21 compared with solid type and it is presumable that the cyst formation has a close relationship with the overexpression of miR-21.

Recently, it was discovered that extracellular miRNAs circulate in the blood of both healthy and diseased patients, although ribonuclease is present in both plasma and serum[33]. Most of the circulating miRNAs are included in lipid or lipoprotein complexes, such as apoptotic bodies, microvesicles, or exosomes, and are, therefore, highly stable. The existence of circulating miRNAs in the blood of cancer patients has raised the possibility that miRNAs may

serve as a novel diagnostic marker. However, the secretory mechanism and biological function, as well as the meaning of the existence of extracellular miRNAs, remain largely unclear. These findings may resolve the problem of difficulty access to VS specimen to analyze preoperatively the miR-21 levels and, consequently, establish a prognosis.

Conclusions

It is clear that miR-21 plays a significant role in the regulation of multiple pathways controlling cell proliferation in many cancers, and this attribute makes it a very attractive target for the development of new therapies. Future experiments aimed at manipulating miR-21 expression in schwannoma models will allow us to test the relative importance of miR-21 on VS growth in vivo. The close relationship between growth and miR-21 expression lead to considerate such molecular factor as a prognostic indicator, after further verifications, to select patients manageable with observation or with an early hearing preservation surgery.

Furthermore, the application of proteomics strategies in these cells should help identify new molecular targets of miR-21 as has been demonstrated in the breast cancer cell line[34,35]. The application of these methods and findings in other biologic systems may shed new light on the molecular pathways controlling tumor growth and help identify novel therapeutic targets for the treatment of VS.

Should miR-21 be confirmed to be integral to the growth and regulation of VS, it is possible to clinically manipulate this biologic

phenomenon. Using molecules that can bind and interfere with these microRNAs, would be one strategy to downregulate this pathway. Early clinical trials using this approach have been used in patients with macular degeneration and respiratory syncytial virus infections[36]. A miR-21 specific RNA interference knockdown could be achieved systemically by administering a viral gene expression vector; however, the side effects on a patient may be undesirable because of off target effects. A more focused delivery via an endoscopic direct injection or delivery during an intentionally incomplete resection of the VS could be an alternative method.

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Curriculum Vitae

PhD Course

Francesco Dispenza MD

Academic Career:

1. Graduated in Medicine and Surgery in 2003 with summa cum laude at University of Palermo.
2. Specialized in Otorhinolaryngology in 2007 with summa cum laude at University of Palermo.

Fellowship:

1. Neurotology and Skull Base Surgery in 2008 at Gruppo Otologico Piacenza, Piacenza Italy, Director: Prof. M. Sanna.
2. Endoscopic Sinonasal Surgery in 2009 at S. Giuseppe Hospital, Milano Italy, Director: Prof. A. Dragonetti.

Professional Career:

1. Consultant of Otorhinolaryngology at U.O. Otorinolaringologia, University of Palermo
2. 374 surgical operations done in the last three years at University of Palermo and during the Fellowship.
3. Lecturer of Otorhinolaryngology at General Practitioner Course in 2009-2010
4. Contract Professor of Otorhinolaryngology at Logopedic Graduating School in University of Palermo 2010-2011

Professional Societies Memberships:

1. SIO (società italiana di otorinolaringologia)
2. EAONO (European academy of otology and neurotology)
3. AUORL (associazione universitari otorinolaringoiatria)
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Scientific Activities:

1. Editorial board membership of Otorinolaringologia Journal Ed. Minerva Medica, Italy; ISSN: 0026-4938
2. Reviewer of Scientific Journal: Quality of Life Research, Elsevier; Laryngoscope, Wiley; Bratislava Medical Journal Slovak Academic Press.
3. Guest Editor of Special Issue of Otorinolaringologia, Minerva Medica. Issue number 3, 2010.
4. Course: Trattamento delle lesioni del nervo facciale. Milano, 25-26 gennaio 2008.
5. International Hands on Course on Auditory Implants. Piacenza, 17-18 aprile 2008.
6. Course: Microchirurgia dell'orecchio medio e dissezione dell'osso temporale. Piacenza, 05-09 maggio 2008.
7. 95° Congresso Nazionale della S.I.O. e Ch. cf. Torino, 21-24 maggio 2008.
8. Cours de Dissection de Rhinologie. Montpellier, France 23-25 giugno 2008.
9. Course: Chirurgia del Collo e Microchirurgia Laser. Vittorio Veneto (TV), 23-27 marzo 2009.

10. 96° Congresso Nazionale della S.I.O. e Ch. cf. Rimini, 13-16 maggio 2009

11. 8th Copenhagen-Nottingham Head, Neck and Nose Dissection Course. Copenhagen, Denmark 18-20 giugno 2009.

12. Course: I Tumori del Cavo Orale. Percorsi diagnostici e terapeutici. Palermo, 23-24 ottobre 2009.

13. Cochlear Implants Surgery Course. Piacenza, 16 dicembre 2009

14. 97° Congresso Nazionale della S.I.O. e Ch. cf. Riccione, 19-22 maggio 2010

15. 9th Copenhagen-Nottingham Ear, Nose and Throat Dissection Course. Copenhagen, Denmark 17-22 giugno 2010.

16. Course: Videochirurgia Endoscopica dei Seni Paranasali. Agrigento, 8 ottobre 2010.

17. Course: Tracheoesophageal Puncture and Prosthetic Voice Rehabilitation. Catania, 5 novembre 2010.

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Original Paper

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Decision Making for Solitary Vestibular Schwannoma and Contralateral Meniere's Disease

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Key Words
Meniere's disease · Intratympanic gentamicin · Vestibular schwannoma

Abstract
The existence of dual inner ear pathology such as unilateral Meniere's disease (MD) with a contralateral vestibular schwannoma (VS) is very rare, but provides the otologist with a significant management dilemma. In this study, we present 5 cases of unilateral disabling MD with a contralateral VS in the better hearing ear. Conservative management of the VS is mandated unless there are impending complications, with management directed toward controlling the vertigo attributed to MD. If and when the VS requires intervention, or the hearing in that ear deteriorates to unserviceable levels, cochlear implant of the ear affected by MD prior to addressing the VS provides optimal management.

Introduction

Meniere's disease (MD) is an inner ear disorder characterized by recurrent episodes of vertigo, fluctuating hearing loss, tinnitus and aural fullness. This usually leads to a permanent, moderate to severe hearing deficit in the affected ear. Bilateral involvement, whilst not common, occurs in 10–50% cases based upon the audiological criteria that are used and length of the period over which patients are followed up [Stahle, 1976; Shojaku et al., 1995; Wareing and O'Connor, 1997; Zwolan et al., 1993; Morgan et al., 1999].

The incidence of vestibular schwannoma (VS) is 1 per 100,000 per year. The commonest presenting symptom is that of hearing loss, and almost inevitably there will be a further decline as a result of the treatment process [Ramsden et al., 2005].

The presence of a VS in the better hearing ear is uncommon (0.3% in our series) and there has been much debate surrounding the optimal management of this situation. The association of concomitant, contralateral MD is exceptionally rare, and represents a significant therapeutic challenge in order to optimize the patient's quality of life. Three cases of VS and contralateral MD have pre-

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Table 1. Follow-up of acoustic neurinoma in patients with contralateral MD

Patient	Age years	Sex	Right ear		Left ear		Side	Tumor size cm	Follow-up years	Growth cm
			PTA, dB	SDS, %	PTA, dB	SDS, %				
1	72	F	70	0	35	100	L	2	7	0
2	59	F	55[1]	80	90	0	R	1	8	0.2
3	58	M	50	80	110	0	R	0.5	3	0
4	58	F	90	20	20	100	L	0.3	4	0
5	63	M	70	10	45	70	L	1.2	5	0.4

[1] PTA worsened by 10 dB at last control and SDS was 70% due to growth of tumor.

Table 2. Outcome of treatment of MD in patients with contralateral acoustic neurinoma reported in accordance with the American Academy of Otolaryngology-Head and Neck Surgery evaluation scale

Patient	Age years	Sex	Right ear		Left ear		MD side	Treatment	Follow-up years	Outcome of treatment
			PTA, dB	SDS, %	PTA, dB	SDS, %				
1	72	F	70	0	35	100	R	IG	1	A
2	59	F	55	80	90	0	L	medical	2	A
3	58	M	50	80	110	0	L	medical	12	A
4	58	F	90	20	20	100	R	IG	1	A
5	63	M	70	10	75	20	R	medical	1	A

viously been reported [McDaniel and Silverstein, 1987; Thedinger et al., 1993], and 5 cases of VS with contralateral disabling MD are reported here.

Materials, Methods and Results

1458 VS were diagnosed at our quaternary referral centre between January 1987 and December 2005. Of these, 136 patients were initially elected to be treated conservatively, with 6 monthly MRI scans to monitor for growth. Generally, the adoption of a conservative approach is made in small tumors (under 20 mm CPA/extrameatal component), with good hearing and no vestibular symptoms. In addition, elderly patients, those with a poor performance status, and those with a tumor in the only hearing ear are strongly considered for a conservative approach. Of the 136 patients initially treated conservatively, 5 patients suffered from contralateral disabling MD. At our institution, the management of MD is based first on medical therapy. In the case of failure, a 1-day protocol of intratympanic gentamicin (IG) is used, delivering a total dose of 81 mg [De Stefano et al., 2007], allowing for complete control of vertigo in 76% of cases. Recalcitrant cases are then considered for surgical management.

Five cases of VS and contralateral MD are presented, and displayed in tables 1 and 2.

Case 1

A 72-year-old woman has been followed for 6 years at our institute with a left 2-cm (IAC/CPA) VS. One year following diagnosis, she developed a progressive right-sided hearing loss, aural fullness and recurrent episodes of vertigo (6/month), consistent with right-sided MD. Audiometry revealed a left pure tone average (PTA) of 35 dB with a speech discrimination score (SDS) of 100%, with a right PTA of 70 dB and 0% SDS. Episodic vertigo returned after 4 years of medical therapy requiring IG. She remains vertigo-free 1 year following this therapy and repeat MRI confirms no tumor growth.

Case 2

A 59-year-old woman has been followed for 6 years with a right 1-cm (IAC/CPA) VS. Two years ago, she developed left hearing loss and tinnitus with episodic vertigo (5/month). Audiometry revealed a right PTA of 55 dB with 80% SDS, and left PTA of 90 dB and 0% SDS. A repeat MRI scan showed absence of growth of her VS and a normal contralateral side. Medical therapy was instituted, providing 2 years of symptom control. Further MRI scan has revealed modest (2-mm) tumor growth and mild decline in hearing thresholds in the right ear to 60 dB and 70%. At this stage, further conservative management is warranted with the consideration of left-sided cochlear implant (CI) if there is progressive loss of hearing in the right ear.

Case 3

A 58-year-old man initially presented with a 1-year history of right-sided hearing loss. He had been previously diagnosed with left-sided MD some 12 years ago, controlled with medical therapy. Audiometry revealed a mild low frequency and moderate–severe high frequency loss in the right ear with an SDS of 80%, and profound loss and 0% SDS in the left ear. MRI revealed the presence of a 5-mm VS in the right ear (CPA/IAC).

Conservative management was advised, and repeat MRI over the last 3 years has confirmed no tumor growth, with stable hearing in the right ear.

Case 4

A 58-year-old woman was referred to our institution with a prior diagnosis of right-sided MD, and a 4-year history of a left 3-mm intracanalicular VS with fundus of IAC involvement. The symptoms attributed to her MD had recently become recalcitrant to medical therapy with episodic vertigo (2/week), tinnitus and further hearing loss of her right ear. Audiometry revealed a PTA of 90 dB and an SDS of 20% in the right ear, with normal hearing in the left ear (PTA 20 dB and 100% SDS). Her symptoms have been well controlled following intratympanic gentamicin with complete cessation of vertigo, and repeat MRI has confirmed no tumor growth over the past year.

Case 5

A 63-year-old man presented with a 1-year history of right-sided hearing loss, tinnitus and episodic vertigo (4/month) on the background of a conservatively managed left-sided 12-mm VS over the past 5 years. Audiometry revealed a left PTA of 45 dB with an SDS of 70%, with a right PTA of 70 dB and an SDS of 10%. Medical therapy was instituted with the presumptive diagnosis of MD. The patient was well controlled symptomatically, but a repeat MRI revealed tumor growth of 4 mm, with stable hearing bilaterally. We advised continued conservative management of the VS with insertion of a CI into the right ear. Unfortunately, the patient elected to undergo tumor resection and insertion of an auditory brainstem implant at another center, via a retrosigmoid approach. At a further review at our institution, the patient was severely disabled with the hearing in his implanted ear not serviceable, and his right PTA remaining at 75 dB, but he was free of vertigo.

Discussion

The coincidental occurrence of MD and contralateral VS represents an unusual clinical situation and consequently presents the otologist with difficult management decisions. The primary goal of treatment is to ensure that there are no significant risks imposed by the VS, and then to conserve hearing and optimize the patient's quality of life. In accordance with 2 prior reports, we have found that it is the episodic vertigo that is the patient's primary concern [McDaniel and Silverstein, 1987; Thedinger et al., 1993]. Therefore, control or cessation of the vertigo, with maintenance of residual hearing is of primary importance.

The initial step in the management of MD is to institute a stratified regime of medical therapy, including low salt diet, diuretics, corticosteroids and vasoactive medications. This has been shown to control symptoms in 50–70% of patients [Gates, 1999]. This was possible in 3 of the patients in our study. Refractory disease necessitates consideration of further treatment including IG, endolymphatic sac surgery, labyrinthectomy and vestibular nerve section. Certainly in the setting of MD in the worse hearing ear gentamicin is the best first step [Lange, 1977], minimizing risks and complications of other procedures. The 2 remaining patients in our series have received complete control with this therapy (class A of the American Academy of Otolaryngology-Head and Neck Surgery evaluation scale) [Committee on Hearing and Equilibrium, 1995]. While deterioration of hearing in the presence of a VS is more likely in those showing growth [Suga and Lindsay, 1976; Kobayashi et al., 1996], there remains a significant risk of loss in those remaining static [Warrick et al., 1999]. However, despite this the best chance to preserve hearing in the short- to medium-term is to avoid surgery [Lin et al., 2005]. As in all cases presented, the ear containing the tumor was the better hearing ear, so maintaining conservative management as long as this remains safe, is the best option. Surgery of CPA/IAC tumors in the only hearing ear is indicated only when nonintervention may lead to high risk of deafness [Driscoll et al., 2000; Naguib et al., 1994]. Close follow-up is required with regular MRI scanning, and if impending complications are likely or hearing becomes unserviceable, intervention is mandatory. In this case, CI of the contralateral ear affected by MD prior to surgical removal of the VS is recommended, with good evidence that CI in end-stage MD is efficacious [Lustig et al., 2003; Talbot et al., 1994].

Other treatment options for VS include total or subtotal surgical removal and stereotactic radiosurgery. While advances in surgical and diagnostic techniques have significantly reduced morbidity associated with VS, surgical treatment continues to carry some risk, even in the hands of the most experienced surgeon [Naguib et al., 1994]. Certainly, there are those who may argue that early removal whilst the hearing is good and the tumor small should be entertained. Published hearing preservation rates vary widely ranging from 10 to 73%, and the size of the tumor and the level of preoperative hearing are the most important predictive factors regarding preservation rates [Khrais and Sanna, 2006; Meyer et al., 2006; Rohit et al., 2006; Arts et al., 2006]. Landmark publications on hearing preservation surgery include Brackmann et al. [2000], who reported maintenance of serviceable hearing in 58.8%, and Meyer et al. [2006] who recently reported hearing preservation rates of 76% for small (under 1 cm) tumors, but rates of 39% for those in the 1- to 1.5-cm range. The patient should also be counseled regarding the possibility of a failure of conservative treatment. Accord-

ing to reports in the literature, failure ranges from 11 to 32%, with a meta-analysis by Smouha et al. reporting a figure of 20.0% [Smouha et al., 2005; Raut et al., 2004; Flint et al., 2005; Tschudi et al., 2000]. While delayed growth always remains a possibility, growth rates in the 1st year appear to be predictive of further growth, and the chance of significant growth after 5 years is remote [Stangerup et al., 2006]. Furthermore, Rosenberg [2000] reported that only 5% of patients over 65 years old with VS treated conservatively required definitive management.

Sterotactic radiosurgery alone or after partial removal is an alternative treatment modality reported to provide adequate tumor control [Regis et al., 2002; Kondziolka et al., 2003; Unger et al., 2002], but we do not think that this is a viable treatment option. We feel, however, that the rate of hearing preservation, even in the range of 50–70%, is not acceptable in those patients with a tumor in the only hearing ear.

Our experience has shown that in those rare patients affected by MD and a contralateral VS, the correct management involves control of the symptoms attributed to MD, with close observation of the VS. Of course, it is very important to confirm that the vertigo is the result of MD not due to the tumor itself. If and when the VS requires intervention, and/or the hearing in that ear deteriorates to unserviceable levels, CI of the ear affected by MD provides optimal management.

Conclusion

MD and contralateral VS is a very uncommon clinical presentation that provides the otologist with difficult management decisions. The patient must be properly counseled regarding the natural history of VS and the possibility of future interventional management, and the expected outcomes, especially in regard to their hearing.

While no absolute algorithm exists, and treatment must be individualized, our goal is to first control the disabling vertigo of MD, and manage the VS conservatively. CI of the contralateral ear is indicated prior to surgical removal of the VS if this becomes necessary.

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Management of Chronic Otitis by Middle Ear Obliteration With Blind Sac Closure of the External Auditory Canal

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Objective: Description of a technique of middle ear obliteration (MEO) with blind sac closure of the external auditory canal with discussion of the indications for its use in cases of recalcitrant chronic otitis and in far advanced disease.
Patients: All patients underwent otologic examination and audiologic and radiologic assessments in a quaternary center.
Results: Fifty-three cases of MEO were analyzed. For 9 patients, primary surgery was performed. One case of residual disease was identified. The minimum follow-up was 2 years.
Conclusion: The decision to perform a MEO is one that is made only rarely. However, this is a technique that should be part of every otologist's armamentarium. Whereas the indications for its use are more straightforward in an ear with unserviceable hearing, a MEO is occasionally required in an ear with good cochlear reserve due the severity of disease. All of our patients managed by MEO have had an improvement in their quality of life and a high rate of successful eradication of disease. **Key Words:** Cholesteatoma—Chronic otitis—Mastoid obliteration—Meningoencephalic herniation—Middle ear obliteration—Middle ear revision surgery.

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Middle ear obliteration (MEO) using abdominal fat with blind sac closure of the external auditory canal (EAC) and obstruction of the eustachian tube is a surgical option for difficult cases of chronic ear disease. It is a technique that aims to give the patient, often plagued with chronic discharge, multiple previous surgical interventions, and unserviceable hearing a safe dry ear.

Although most chronic ear disease is managed successfully using an individualized approach, it is the meticulous eradication of disease and the creation of a stable cavity able to prevent recurrence that is the cornerstone of success. The restoration of hearing function is a secondary, albeit important, goal. There are cases, however, where even the most experienced otologist is unable to prevent ongoing suppuration despite multiple revision surgeries and assiduous office-based management.

The presence of large areas of exposed dura, and/or meningoencephalic herniation, coexisting with active disease places the patient at significant risk of serious complications (1). Whether iatrogenic or the result of the disease process, most cases can be managed using a combined transmastoid and extradural middle cranial fossa approach (2,3). There are those instances, however, where this is impracticable or inadequate, and a MEO provides the safer option.

Readily available magnetic resonance imaging (MRI) with the use of fat suppression and diffusion sequences makes surveillance of these cases more straightforward, removing the need for second-look surgery but still requiring long-term follow-up (4,5).

In this study, we analyzed the indications and results of our series of 53 patients undergoing MEO for the management of chronic suppurative otitis media with or without meningoencephalic herniation at the Gruppo Otologico between 1983 and 2005.

MATERIALS AND METHODS

A retrospective chart review of 53 patients with an MEO treated at Gruppo Otologico (quaternary center) between 1983 and 2005 was conducted. We included in the present study only patients with a minimum of 2 years of follow-up. Thirty-four patients were men, and 19 were women. Average age was 57 years (range, 7–84 yrs). The right side was involved in 28 cases, and the left side in 25. All patients underwent

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clinical otologic examination, preoperative, and postoperative audiologic assessment, including pure-tone average (PTA; average of 0.5-1-2-4 kHz) and SDS (speech discrimination score) and a computed tomographic scan of temporal bone. These cases represented a very small proportion (1.06%) of more than 5,000 cases of chronic suppurative ear disease treated by the senior author (M.S.).

INTERVENTION

Meticulous technique is required to perform a blind sac closure. Care not to tear the skin flap of the EAC is important, and the use of a second layer of soft tissue to reinforce the closure is preferable. In the setting of previous surgery, however, especially with the presence of a large meatoplasty, this can be challenging.

Complete exenteration of the disease, mastoid air cells, and mucosa with removal of all skin, tympanic membrane, malleus, and incus is performed. Canal plasty and lowering of the floor of the canal is essential to ensure complete removal of squamous epithelium.

The presence of cholesteatoma matrix adherent to dura can be difficult to manage. The dura itself is often friable, and attempts to achieve complete removal can lead to a dural defect and cerebrospinal fluid (CSF) leak. Bipolar devitalization of residual matrix should be performed as opposed to dural resection (6).

In the presence of meningoencephalic herniation, the prolapsed tissue is reduced using the bipolar diathermy, and a muscle plug or cartilage is placed to reinforce the defect (7).

Once eradication of disease has been completed, the opening of the eustachian tube is abraded and packed with bone wax and soft tissue. The cavity is then obliterated with an abdominal fat graft and immersed in rifampicin. Fibrin glue is also used in the presence of a CSF leak.

Because of the closure of the EAC, radiologic follow-up is mandated. Although CT will give information regarding further bone destruction, an MRI scan using fat suppression and diffusion sequences allows accurate identification of residual disease. We advocate an initial scan 1 year postoperatively, followed by a further scan at 3, 5, and 10 years (4,5,8).

RESULTS

Primary MEO

Middle ear obliteration as the primary surgery was performed in 9 of 53 cases. Cholesteatoma with meningoencephalic herniation was found in 5 cases. In 4 cases, PTA showed a conductive hearing loss (air conduction PTA, 50 dB; bone conduction PTA, 18 dB), all of whom had significant meningoencephalic herniation with cholesteatoma. The remaining 5 cases had a preoperative profound sensorineural hearing loss (SNHL), 4 of which had extensive cholesteatoma, the other with persisting otorrhea after a temporal bone fracture associated with a facial nerve injury.

Sensorineural hearing function was preserved in 3 patients with preoperative conductive hearing loss (interestingly, the air conduction worsened in only 1 case). In 1 patient with mesotympanic cholesteatoma, meningoencephalic herniation, and a CSF leak, a complete SNHL occurred unexpectedly 1 year after MEO.

Secondary MEO

Of the 44 patients undergoing revision surgery; 18 patients had already undergone more than 2 procedures, whereas in the remaining 26 patients, MEO was the second operation. Thirty-five cases revealed recurrent cholesteatoma. Twenty-five patients were found to have meningoencephalic herniation (16 cases with CSF leak), and in 6 cases, significantly exposed dura with the intraoperative discovery of a CSF leak were identified (Table 1).

Nineteen patients had a dead ear at preoperative audiologic assessment. The average air conduction PTA of the remaining 25 patients was 79 dB (range, 50–110 dB), whereas mean bony conduction PTA was 42 dB (range, 20–70 dB). After MEO, both conductive and sensorineural hearing function were preserved in 20 patients. In 1 case with a primary LSC (lateral semicircular canal) fistula, the bony threshold worsened by 10 dB. Worsening of bony conduction and improvement of air conduction were obtained in 1 case. Two patients suffered a complete SNHL, 1 of whom had a deep fistula into the LSC.

During follow-up, 1 case of residual cholesteatoma was identified 2 years postoperatively on routine MRI scanning. This was easily removed, with evidence of only minimal infiltration of the surrounding fat (Fig. 1).

One patient developed a postaural fistula 2 months after surgery recalcitrant to conservative management. Reinforcement using a mucoperiosteal flap was successful in resolving this problem.

DISCUSSION

From the first description of MEO by Rambo in 1957, there have been sporadic reports regarding its use (9–13). Most recently, Kos et al. (9) published their series of 46 patients undergoing tympanomastoid obliteration for

TABLE 1. *Intraoperative finding*

	Primary surgery (9 patients)	Revision surgery (44 patients)	Whole series (53 patients)
Stenosis of external auditory canal	0	8	8
Cholesteatoma	8	35	43
Facial nerve exposed	3	15	18
Dura exposed	6	30	36
Meningoencephalic herniation	5	25	30
CSF leak	1	16	17
Labyrinthine fistula	2	12	14

CSF indicates cerebrospinal fluid.

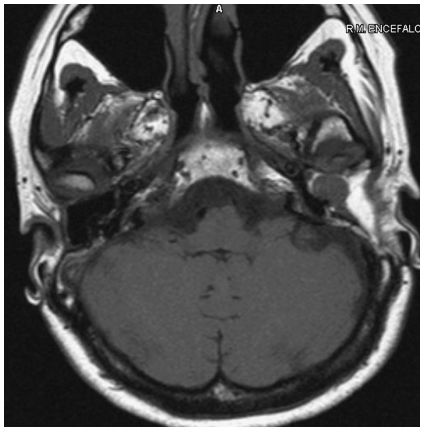

FIG. 1. T1-Weighted axial scan showing residual cholesteatoma. Note the fat creating an ideal interface to detect residual disease.

chronic ear disease. Of 32 cases with cholesteatoma, they reported 4 recurrences, 1 of which required the reversal of the obliteration due to multiple recurrences. Seven cases of postoperative abscess formation or discharge were also noted, with no continuing problems after secondary intervention. Our reduced rate of infective complications can be explained by the routine use of antibiotics with antipseudomonal action. The other interesting aspect of this article was that, despite long-term success, 1 of 4 patients was not satisfied. This emphasizes the importance of patient selection and detailed preoperative counseling.

A high proportion of our series had evidence of meningoencephalic herniation (30 of 53). Meningoencephalic herniation of the temporal bone is most commonly associated with chronic suppurative ear disease, with a high proportion of cases having undergone previous surgery (1,2,14–16). In this series, 25 of 30 cases had had previous surgery at alternate centers. Although there is no doubt that iatrogenic injury plays a role in the cause, active disease also plays a significant part. This can often be a difficult diagnosis to make preoperatively, and a high index of suspicion should be maintained in all revision mastoid surgery. Magnetic resonance imaging scanning is a helpful adjunct in this setting to delineate cholesteatoma, granulation tissue, and meningoencephalic tissue.

The treatment of meningoencephalic herniation is dependent on the status of middle and inner ear, the extent of herniation, and the presence or absence of active disease. When conditions are favorable, a middle cranial fossa approach is used, allowing preservation of middle ear function (1,2,14,16), which is the situation in a high proportion of cases. However, in ears with poor reserve, in cavities unable to sustain a middle cranial fossa repair, and those with extensive herniation, MEO is the safest and most definitive treatment modality. This is especially so when there is a combination of active disease and an active CSF leak. The significant degree of herniation in 4 of our primary cases with good cochlear reserve was the essential reason to perform a MEO.

The decision on whether to obliterate after EAC closure and what material to use is an important point. We advise the use of abdominal fat, as supported by Kos et al. (9) and Mehta and Harris (13), for a number of reasons. First, in cases of meningoencephalic herniation and CSF leak, obliteration minimizes the risk of persisting leak and meningitis. The presence of obliterative material also reinforces the closure of the external canal and minimizes the cosmetic defect. Others have reported the use of muscle, pericranial, and or periosteal flaps to obliterate their cavities, but in revision cases, there is often insufficient local tissue to adequately obliterate the cavity without significant tissue mobilization and attendant morbidity. Despite some expressed concerns in the literature regarding infection of the fat graft, this did not present a problem in this series. Indeed, the fat itself has been reported to have inherent immunoreactive properties that may suppress infection (17).

Importantly, the use of fat provides a ready contrast medium to help detect residual cholesteatoma. The use of fat suppression and diffusion sequences on MRI provides us with a very accurate method to detect early recurrence. The routine use of postoperative radiologic surveillance obviates the need for reexploration unless suspicions are raised by these investigations.

The decision to perform an MEO is one that is made only rarely. Of the more than 5,000 cases of chronic suppurative ear disease we have performed, only 53 had MEO. However, this is a technique that should be part of every otologist's armamentarium no matter how skilled or experienced. Whereas the indications for its use are more straightforward in an ear with unserviceable hearing, an MEO is occasionally required in an ear with good cochlear reserve due the severity of disease.

Follow-up scanning is essential in all cases, and this must be reinforced to the patient before the procedure.

In almost all cases, the patient greatly appreciates the creation of a safe, dry ear, with minimal associated morbidity and no lifestyle restrictions, at the cost of a maximal conductive hearing loss in an ear that is already significantly impaired.

It also provides definitive management of CSF leaks through the temporal bone and in the management of meningoencephalic herniation.

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Thyroid cartilage involvement in patient affected by IgA multiple myeloma: Case report

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Abstract

Neoplasms originating from plasma cell are rare in the head and neck region. A correct clinical evaluation is very important in order to formulate a differential diagnosis as well as to distinguish local from metastatic disease. We report a case of larynx involvement by an IgA multiple myeloma in a 69-year-old female diagnosed in October 2004 and treated with chemotherapy; the 1 year control do not show progression of disease and the laryngeal lesion is unchanged. We highlight the radiological findings and clinical features to suspect plasma cell tumors in cases with a similar presentation.

Keywords: Multiple myeloma; Thyroid cartilage; Plasma cell tumor of larynx

1. Introduction

Neoplasms originating from plasma cell are rare in the head and neck region. They arise as a monoclonal proliferation of plasma cells during their various stage of differentiation (classified as a peripheral B-cell neoplasm in a revised European-American classification [1]). The clinical classification divides these neoplasm into three types: multiple myeloma (MM), solitary plasmacytoma of bone (SPB) and extramedullary plasmacytoma (EMP).

A correct clinical evaluation is very important in order to make the correct diagnosis as well as to distinguish this kind of tumor and the extent of disease, to institute the correct treatment and to estimate survival time. A plasma cell tumor classified as a solitary plasmacytoma of bone if evidenced in bone; in soft tissue as a extramedullary plasmacytoma, while the systemic form of the disease is called multiple myeloma.

These three clinical entities are considered as representing distinct manifestations of a continuum of disease. About 20–30% of EMP may progress to a MM [2].

We report the clinical and radiological features of a patient affected by IgA MM with laryngeal involvement, treated by chemotherapy; we outline the importance of differential diagnosis considering also this rare entity.

2. Case report

A 69-year-old woman affected by high-plasma level of IgA was diagnosed with a monoclonal gammopathy of undetermined significance (MGUS). She experienced progressive hoarseness and slight dysphagia. The patient did not complain of dyspnea nor did she have risk factors for laryngeal cancer (smoking and alcohol). She had no previous intubation, trauma or surgical procedures. She was a type II diabetic with hypertension, both efficiently controlled by medical therapy.

Indirect laryngoscopic examination revealed sub-mucosal swelling of the right ventricular fold (false cord), ventricle and true vocal cord, reduction of right side motility, normal mucosa (Fig. 1). A mass in the right thyroid ala was found during neck examination; after a CT scan without contrast enhancement of the neck, a structural alteration within thyroid cartilage in right ala with cortical thinning and right supraglottic and concentric cricoid ring thickness was evidenced (Fig. 2).

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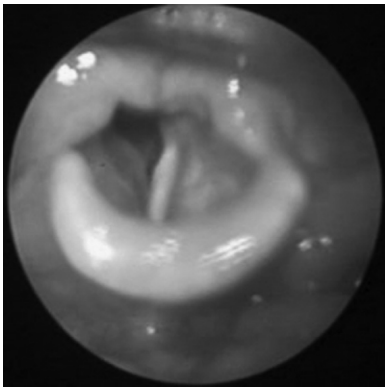

Fig. 1. Indirect laryngoscopic examination show a sub-mucosal swelling of right false cord, ventricle and true vocal cord and normal mucosal surface.

Biopsy of the mucosa and sub-mucosal layer was performed under direct microlaryngoscopy. Histopathology demonstrated a diffuse massive infiltration of plasma cells.

Haematological consultation was sought in order to further assess the nature of the disease. Serum and urine electrophoresis was performed which confirmed the previous findings of a high-plasma level of monoclonal IgA; bone marrow biopsy revealed plasma cell infiltration of 20%. Routine laboratory tests showed anaemia (haemoglobin 8.9 g/dl; RBC 2,980,000/mmc; WBC 3200/mmc; plasmatic albumin 3.5 g/dl, beta-2-microglobulin 5.6 g/dl). All these findings affirmed the diagnosis of MM stage IIIa. The patient underwent chemotherapy with VAD protocol (vincristine, doxorubicin and dexamethasone) for a total of 4 cycles; 1-year clinical and radiological follow-up did not show progression of disease with the laryngeal involvement unchanged.

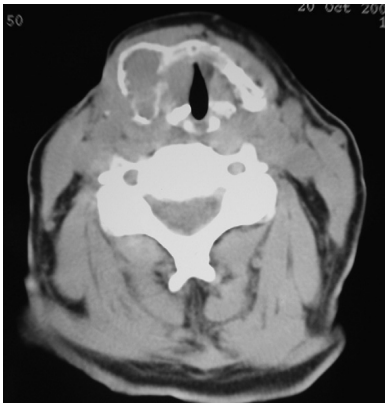

Fig. 2. CT scan of larynx without contrast enhancement showing a structural alteration within thyroid cartilage in right ala with cortical thinness.

3. Discussion

Laryngeal involvement in patients affected by MM is rare and few cases are reported in literature [3–9].

Two pathogenetics mechanisms are postulated by several authors to explain the involvement of laryngeal cartilage: (1) cartilage may be involved by an adjacent plasmacytoma; (2) cartilage, particularly in older people, may undergo to osseous metaplasia with formation of central marrow space, therefore a plasmacytoma may directly originate from this bone marrow [10]. Thyroid cartilage expansion and destruction evidenced in the CT scans suggests as in our case a myelomatous involvement of extraskeletal bone marrow formed by osseous metaplasia [8].

Consideration of this process is mandatory considering that laryngeal involvement in EMP is between 5% and 18% [11–13] with different treatment and with a better prognosis than MM. As a matter of fact EMP may evolve to MM many months or years later after diagnosis [14,15]. When a plasma cell tumor involving the larynx is diagnosed the next step is to exclude systemic disease. The patient must undergo detection of monoclonal gammopathy in serum or urine, a bone marrow aspiration biopsy and complete radiological examination in order to demonstrate osteolytic bone lesions.

Diagnosis of MM is based on: histological evidence of plasmacytoma or plasmacytosis in bone marrow; clinical signs of disease such as bone pain, anaemia and renal failure; detection of the monoclonal gammopathy in serum or urine and demonstration of osteolytic bone lesion. EMP and SBP are diagnosed if plasmacytoma is present in soft tissue or bone with no dissemination of disease.

Involvement of the thyroid cartilage is very rare [8,9]. CT examination can demonstrate a typical pattern: thinning and expansion of the lamina of the thyroid ala (as in our case), thus confirming its origin within the thyroid structure caused by osseous metaplasia of the cartilage [8]. Treatment of different form of plasma cells tumors is related to their extension: EMP and SBP can be treated by external radiation therapy with 40–50 Gy for a 4-week period including cervical lymph nodes in order to prevent lymph node recurrences [16]. Surgical removal is a second line treatment particularly in case of salvage therapy after radiation failure.

The treatment of symptomatic patients affected by MM, even with larynx involvement, involves chemotherapy or bone marrow transplantation. Surgery is mainly diagnostic in the majority of cases and tracheotomy is performed in case of airway obstruction.

Usually plasma cell neoplasms appear in the elderly while MM variant about 10 years later than the others two. After diagnosis MM have a mean survival of about 2–3 years, while EMP and SPB have a better prognosis.

4. Conclusion

Plasma cell neoplasms are unusual in the head and neck region and are histologically indistinguishable because they represent a continuum disease, as illustrated by progression of EMP and SPB to MM. The diagnosis is made on the basis of clinical, radiological and pathological findings, and the distinction between EMP, SPB and MM is critical for treatment and survival. In the case of typical CT scan larynx pattern a plasma cell tumor must be suspected for correct management.

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CASE REPORT

Post-traumatic lipoma of the parotid gland: case report

Lipoma post-traumatico della parotide: caso clinico

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SUMMARY

The incidence of lipoma among parotid tumours ranges from 0.6% to 4.4%, with most series reporting an incidence of 1%. The most common origin of these tumours, in the parotid gland, is from the superficial lobe and, only rarely, from the deep lobe. Lipomas, upon clinical history, are found to be most frequently related to an episode of trauma. Computed Tomography scan and Magnetic Resonance Imaging can lead to a pre-operative diagnosis of lipoma. The case is described of lipoma of the superficial lobe of the parotid gland.

KEY WORDS: Parotid • Lipoma • Facial palsy • Diagnosis • Surgical treatment

RIASSUNTO

I lipomi della parotide rappresentano lo 0,6%-4,4% dei tumori della ghiandola. Diversi studi riportano un'incidenza dell'1%. Più comunemente questi tumori originano nel lobo superficiale della parotide e solo raramente da quello profondo. I lipomi sono frequentemente correlati ad un pregresso episodio traumatico della regione coinvolta. La tomografia computerizzata e la risonanza magnetica possono condurre ad una diagnosi di lipoma pre-operatoria. Riportiamo un caso di lipoma del lobo superficiale della parotide.

PAROLE CHIAVE: *Parotide • Lipoma • Paralisi facciale • Diagnosi • Terapia chirurgica*

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Introduction

Lipoma is a common benign tumour of mesenchymal origin, arising in every location where fat is normally present, 13% of which occurring in the head and neck region. Rarely, lipomas can arise in the oral cavity, pharynx, larynx and parotid gland [1]. The incidence of lipoma among parotid tumours ranges from 0.6% to 4.4%, with most series reporting an incidence of 1% [2]. A case of post-traumatic lipoma of the parotid gland is described.

Case report

A 30-year-old female had experienced a painless, slow growing, mass on the right side of the face, 5 years previously, after a trauma due to a bite on that area. Examination revealed a soft, mobile, non tender, regular mass in the right parotid extending toward the neck. There was no detectable cervical lymph nodes. Progressive paresis of the mandibular branch of the facial nerve had become evident over the last 3 months. The computed tomography (CT) scan revealed a well demarcated low density mass 5 x 5 cm, in the superficial lobe of the right parotid gland (Fig. 1). The magnetic resonance imaging (MRI) scan showed a high signal intensity on T1-weighted images (Fig. 2) and intermediate intensity on T2-weighted images. The lesion extended to both superficial and deep lobes of the gland leaving a small portion in the deep lobe. These results were consistent with a lipomatous lesion. Surgical removal of the tumour with facial nerve preservation was performed. Post-operative facial nerve function was normal with resolution of mandibular branch paresis. Histopathology confirmed the diagnosis of lipoma.

Discussion and conclusion

Adipose tissue is normally present in the parotid gland, but the incidence of lipomas here is very low. Different causes of lipomas are mentioned in the literature: heredity, obesity, diabetes, radiation, endocrine disorders, insulin injection, corticosteroid therapy and trauma. As in our case, trauma and lipoma are found to be most frequently correlated on clinical history [3]. Trauma to soft tissue has been hypothesized to result in haematoma, with subsequent lymphatic effusion, fat necrosis and lipoma formation located in the subcutaneous plane [4]. The local effects related to the trauma, in our case, were not well defined since a long period of time had elapsed from presentation of the patient, but a local haematoma was present in the clinical history. The facial nerve is not usually involved, but one case with complete palsy

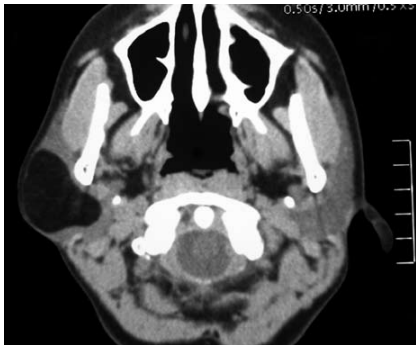

Fig. 1. CT scan shows a well demarcated low density mass in superficial lobe of right parotid gland with residual portion of deep lobe.

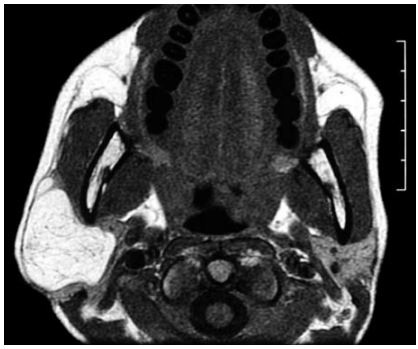

Fig. 2. MRI scan shows high signal intensity on T1-weighted image. Black rim around mass clearly defines borders from subcutaneous tissue.

has been reported in the literature [5]. The highest reported incidence of lipoma in the parotid gland is 4.4% [2], with males most frequently affected (62.5%) [6]. Sonography can be used as the initial study and shows a hyper-echoic elliptical or rounded mass, sometimes iso-echoic or even hypo-echoic [6]. CT shows a homogeneous mass with few septations and less than water density [1]. MRI presents the typical signal intensity patterns already described. A black rim is present around the mass clearly defining the borders from the subcutaneous tissue. In the literature, correct categorization of benign *vs*. malignant parotid gland tumour has been reported to be 87% after CT/MRI examination [7], lipoma can be distinguished from well-differentiated liposarcoma by the presence of thick septa, the presence of nodular/globular or non-adipose mass-like areas [8]. Fine-needle aspiration biopsy (FNAB), commonly performed in the diagnostic work-up for parotid mass, does not provide sufficient data for diagnosis [9]. During surgery, the facial nerve is identified and followed up to its peripheral branches, as far as necessary for tumour dissection. In our case, the facial nerve was compressed and displaced. This could explain the palsy of the inferior branch due to compression, corresponding to a first-degree injury described by Sunderland [10]. The neural block is created by increased intra-neural pressure and the nerve cannot conduct an impulse across the site of compression. If the compression is relieved, return of facial movement may begin immediately or within 3 weeks [10].

A correct clinical and instrumental evaluation of parotid gland masses, including both CT scan and MRI, can lead to a pre-operative diagnosis of lipoma. Imaging is also important to evaluate the location of the tumour and to programme the correct surgical approach.

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CASE REPORT

Pleomorphic adenoma of the lateral nasal wall: case report

Adenoma pleomorfo della parete nasale laterale: caso clinico

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SUMMARY

Pleomorphic adenoma is the most common tumour of the salivary glands. However, it is extremely rare for these to originate in the nose and even when they do so, it is most commonly in the nasal septum. It is important to be aware of the paucity of presenting symptoms (nasal obstruction and epistaxis), as the lesion may not be recognized immediately. Growth is generally restricted locally and the tumour is not known to spread to the neighbouring structures. Surgical resection is the treatment of choice. Recurrences and evolution to malignancy are not frequent, but long-term follow-up is recommended. The case is presented of pleomorphic adenoma arising from the lateral wall of the right nasal cavity, in a 34-year-old male, which was resected completely, endoscopically. Histological and immunohistochemical evaluation revealed the presence of a pleomorphic adenoma.

KEY WORDS: Nose • Nasal tumour • Pleomorphic adenoma • Diagnosis • Histopathology

RIASSUNTO

L'adenoma pleomorfo è il tumore benigno più comune delle ghiandole salivari. Comunque, la sua localizzazione nasale è molto rara e più comunemente origina dal setto. Importante è considerare che i sintomi di presentazione sono molto scarsi (ostruzione nasale e epistassi), per cui la lesione può decorrere a lungo misconosciuta. La crescita è generalmente locale e non sono noti casi di diffusione nelle strutture adiacenti. La resezione chirurgica è il trattamento di scelta. La recidiva e l'evoluzione maligna non sono frequenti, ma un lungo follow-up è da raccomandare. Presentiamo un caso di adenoma pleomorfo ad origine dalla parete laterale della fossa nasale di destra in un paziente di 34 anni, trattato chirurgicamente con resezione endoscopica completa. La valutazione istologica ed immunoistochimica hanno dimostrato la presenza di un adenoma pleomorfo.

PAROLE CHIAVE: *Naso • Tumori nasali • Adenoma pleomorfo • Diagnosi • Anatomia patologica*

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Introduction

Mixed tumour of the salivary gland or the pleomorphic adenoma is a benign tumour, arising mainly in the major salivary glands (65%), especially in the parotid and, less frequently, in accessory salivary glands (35%) [1]. Rare cases have been reported in the lip [2], the hard and soft palate [3], the lacrimal gland [4], and the external auditory canal [5]. It is extremely rare to find these in the respiratory tract [6-8]. The incidence is even lower in the upper respiratory tract, such as the nasal cavity, maxillary sinus and nasopharynx [8 9]. The largest reported case series of intra-nasal pleomorphic adenomas are those of Spiros et al. [10] with 40 cases, Compagno and Wong [11] with 40 cases and, more recently, Suzuki et al. [4] with 41 cases.

Intranasal pleomorphic adenomas generally arise in the nasal septal mucosa (reported incidence varies between 82.5% [11] and 90% [12]), even though the seromucosal glands are mainly located within the lateral nasal wall, in particular in the turbinates [13 14].

Various theories have been proposed to explain this observation. According to Stevenson [15], remnants of the vomeronasal organ, an epithelium-lined duct in the cartilaginous nasal septum degenerated in early foetus, could be the reason for the appearance of these tumours in this particular region. According to Ersner and Saltzman, in 1944, the precursors of the septal pleomorphic adenoma are ectopic embryonic epithelialised cells on the nasal septum mucosa, found during the migration of the nasal buds [16]. According to Evans and Cruikshank, it originates directly from the matured salivary glandular tissue [6]; Dawe, in1979, proposed a viral aetiology from polyoma virus [17].

Case report

A 34-year-old male, non-smoker, presented at our Department, in January 2003, reporting an isolated episode of epistaxis from the right nasal cavity. He also complained of worsening of a right nasal obstruction which had been present

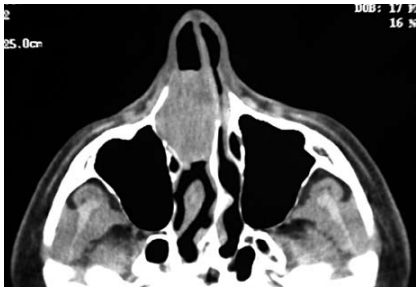

Fig. 1. Axial CT scan showing soft density mass in anterior portion of right nasal fossa with thinness of nasal process of maxillary bone.

for 10 years, frontal cephalalgia and anosmia. External clinical examination showed a mass arising from the lateral wall of the right nasal cavity and filling the naso-facial furrow.
Anterior rhinoscopy revealed a smooth, pink-grey, translucent, painless mass, obstructing the nasal cavity, not bleeding on touch, and a deviated nasal septum to the left. The rest of the ear, nose, and throat examination was normal and there was no evidence of cervical lymphadenopathy. Computed Tomography (CT) scan revealed a soft tissue mass in the right nasal cavity, not involving the paranasal sinuses, with thinning of the nasal process of the maxilla (Fig. 1). Endoscopic surgery, under general anaesthesia, confirmed the mass (2 cm in diameter) to be arising from the lateral wall of the right nasal cavity and extending from the anterior end of the inferior turbinate to the *agger nasi*. We excised the tumour completely, including the sub-periostal layer and a healthy margin of mucosa.
Histopathological analysis of the tumour showed a mixed epithelial and myxoid stromal appearance. Epithelial structures displayed different solid, trabecular and cystic growth patterns (Fig. 2). Immuno-histochemical stainings for smooth muscle actin (Fig. 3) and S100 (Fig. 4) highlighted the presence of an abundant myoepithelial component. The histo-morphological and immunophenotypical features observed were consistent with the diagnosis of pleomorphic adenoma. There is no endoscopic evidence of recurrence after 4 years' follow-up.

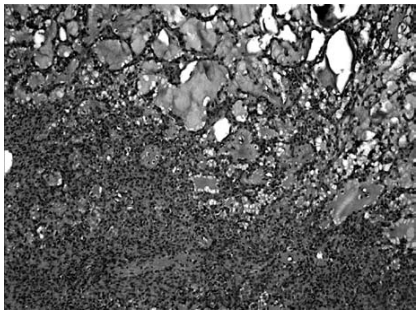

Fig. 2. Epithelial structures showing solid, trabecular and cystic patterns intermingled with myxoid stroma (H&E, x250).

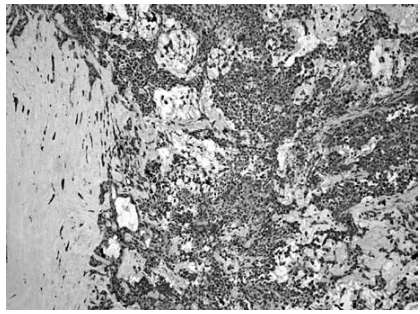

Fig. 3. Immunostaining for smooth muscle actin (x 250).

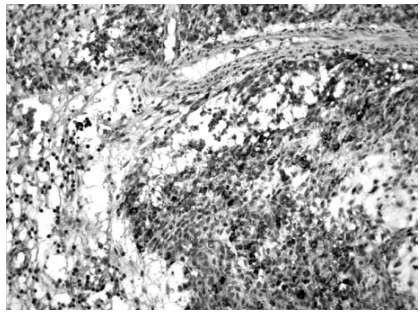

Fig. 4. Immunostaining for S100 protein (x 400).

Discussion

Nasal pleomorphic adenoma is seen predominantly in females [4-11] usually between the third and fifth decades of life [18]. There is no reported correlation with occupational exposure or inhaled toxic chemical compounds. It is generally known to be a slow-growing tumour and, therefore, clinical symptoms appear after a long silent period. Patients commonly present with gradual worsening of monolateral nasal obstruction and occasional epistaxis. Less commonly, when the tumoural mass reaches a relatively large size, to that of the nasal cavity, external swelling of the nasal pyramid as well as pain may be present.
Clinically, it appears as a polypoid, unilateral, sessile, translucent, pinkish-grey mass, with smooth surface and soft consistency. Tumours can range in size from < 0.7 cm to > 7 cm.
The clinical features, such as absence of superficial ulceration, no bleeding either on touch or spontaneously and lack of invasion of surrounding structures suggest a benign nature of the mass.
Histologically, all pleomorphic adenomas have a collagenous thin capsule, with a clear-cut distinction of the tumour tissue from the surrounding normal connective tissue. The tumours consist of three main structures: tubuloductal structure, solid area, and myxoid area. The tubuloductal structure presents ducts with double cell layers: cuboi-

dal-shaped epithelial cells at the inner layer, and spindle-shaped myoepithelial cells at the outer. Predominantly the solid areas consist of the spindle-shaped cells with high cellularity; the myxoid areas are characterised by their low cellularity [18].

The intra-nasal pleomorphic adenoma shows a predominance of epithelial rather than stromal elements, as compared with major salivary gland tumours. The epithelial cells are small, oval-shaped and often arranged in cordons; sometimes, they are organized in small acinous structures [13].

Immunohistochemical stains prove positive for various cytokeratins, S100 protein, glial fibrillary acid protein (GFAP), Vimentine, a smooth muscle actine (SMA). This describes the "mixed" nature of the tumour, namely, the stromal and the epithelial line [19].

Differential diagnosis of intra-nasal pleomorphic adenoma includes both malignant and benign tumours such as squamous cell carcinoma (the most common intra-nasal malignancy), adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, melanoma, olfactory esthesioneuroblastoma [20], polyps, papillomas (including inverted papilloma), angiofibromas and osteomas.

Differential diagnosis can also be difficult in the presence of a "neuroestesioepithelioma" (even though the site of origin of such a lesion, i.e., the ethmoid plate, should suggest its nature, since the lateral nasal wall is extremely rare), as, in the early stage, it presents a small cell proliferation organized like a "rosette", positive for S100 protein. Diagnosis is possible on account of the lack of an extracellular neurofibrillar structure, neurotubules, neurosecretive granules and due to the presence of mucinous material and the rarity of malpighian lobules disseminated on the pleomorphic adenoma [21].

Regardless of where the lesion originates, the main treatment modality should be surgical. While complete excision of the tumour with histologically clear margins is mandatory, the surgical approach will depend upon the size, location and extension. A radical and wide resection lowers the risk of recurrence, especially when the capsule is interrupted and a direct contact with the surrounding normal tissue is present. Approaches include lateral rhinotomy [22-24], transnasal or mid-facial degloving [13-18] and intra-nasal excision. The present patient underwent endoscopic resection since the tumour was small enough to observe under the endoscope. The advantages of endoscopic resection include no external scar, less blood loss. In the presence of large masses, the mid-facial degloving approach is preferred, since it has the advantage of wide exposure of the mass and direct approach to the nasal cavity.

Recurrences are not frequent, Compagno and Wong reported 3 cases of local recurrences in 40 patients (7.5%) [11], probably, as they thought, due to the amount of myxoid stroma of the tumour, which could be split into the surgical field.

The potential risk of malignant transformation of the pleomorphic adenoma is about 6% and is predominantly seen in the female patients [25]. The risk is increased by delay in diagnosis.

A histopathologically confirmed case with adenoid cystic and squamous carcinomatous differentiation has been reported [26].

There has also been a report of metastasis to the submandibular lymph-node, in a recurrent septal pleomorphic adenoma, 17 years after the first diagnosis. Even in this case, the microscopic features of both the primary and metastatic lesion were benign. In this regard, a iatrogenic theory has been proposed. This theory suggests that the metastasis occurs as a result of incomplete excision or inadvertent disruption of the tumour with consequent spread through haematogenous or lymphatic routes. Pulmonary, hepatic and bone metastasis have also been reported [27].

Long term follow-up is therefore necessary for early diagnosis of loco-regional recurrences by endoscopic examination followed by imaging (CT or MR) in case of clinical evidence of disease.

Conclusions

In the presence of a slow-growing unilateral mass of the nasal cavity, it is important to consider, among the various diagnoses, the presence of pleomorphic adenoma, even if it is not frequently encountered. Early diagnosis offers the possibility of a more complete excision with adequate care being taken not to disrupt the tumour in order to prevent local and distant spread of neoplastic cells. The endoscopic approach is preferred, as it allows complete control of the margins under direct vision and reduces the post-operative recovery period when compared to open surgery. Long-term follow-up, both endoscopic and radiologic, to exclude malignancy is mandatory, even if the tumour appears to be clinically benign and resected completely.

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CASE REPORT

Meningioma of the Cerebellopontine Angle Mimicking Benign Paroxysmal Positional Vertigo

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Benign paroxysmal positional vertigo (BPPV) is the most common cause of peripheral vertigo.[1] It accounts for approximately 24% of all cases of peripheral vestibular disorders.[2] This type of vertigo is generally seen in individuals aged 40 years and older, with the highest age distribution between 50 and 70 years.[3] The exact etiology of BPPV is still under debate. Over 50% of all reported cases are idiopathic in nature.[4] The signs and symptoms of BPPV are generally thought to arise from the peripheral vestibular system, although a conclusive demonstrable lesion at this level has not been confirmed.

Diagnosis of BPPV is based mainly on a history of characteristic positional vertigo along with the classic clinical signs. The nystagmus typically has a latency of a few seconds and is of limited duration, transient, fatiguable, and reversible on return to an upright position.[5] Classic BPPV involving the posterior semicircular canal (PSC) is the most common type of BPPV.[5] The Dix-Hallpike manoeuvre induces nystagmus, which is typically torsional, upbeating with the torsional component beating toward the lowermost ear.[6] The liberatory or Semont manoeuvre[7] and other canalith repositioning manoeuvres[8,9] are used in the treatment of canalolithiasis of the PSC.

Central vertigo is most commonly secondary to cerebellopontine angle (CPA) tumours, cerebrovascular disease (transient ischemic attack or stroke), migraine, multiple sclerosis, and other demyelinating diseases.[10] In central vertigo, the nystagmus is typically spontaneous; purely vertical, horizontal, or torsional; uninhibited by visual fixation; and direction changing.[5,11] It is usually rare for a patient with a central lesion to present with symptoms and signs typical of BPPV. In this report, we present a case of CPA menigioma presenting with signs and symptoms similar to those of BPPV.

Case Report

A man aged 51 years presented with a 1-month history of transient, episodic spells of vertigo, lasting for a few seconds and brought on by sudden movements of the head. There was no associated history of nausea, vomiting, tinnitus, or aural fullness. Also, there was no history of previous vertiginous spells, head trauma, cerebrovascular accidents, or metabolic diseases.

Otoscopy showed an intact and normal tympanic membrane. Audiologic assessment revealed a high-frequency bilateral symmetric sensorineural hearing loss between 4000 and 8000 Hz with bilateral speech discrimination scores of 100%. A Romberg test was normal, and an Unterberger stepping test showed minimal deviation to the left. Clinically, the cerebellar system was normal. A head shake test revealed a second-degree horizontal right-beating nystagmus that was unaffected by visual fixation. On performing the Dix-Hallpike manoeuvre in the left head-hanging position (30° below horizontal and 45° head turned to the left), a clockwise torsional nystagmus was observed after 5 to 6 seconds and extended up to 20 to 25 seconds. The nystagmus was reversed on bringing the patient back to the sitting position. Videonystagmography did not show any spontaneous nystagmus.

A provisional diagnosis of BPPV of the left PSC was made based on the Dix-Hallpike diagnostic manoeuvre. Subsequently, a left PSC-BPPV Semont manouevre was performed. This therapeutic manoeuvre did not evoke a liberatory nystagmus (nystagmus was similar in character to that obtained during the Dix-Hallpike test, indicating movement of otoconia in an ampullofugal direction toward the common crus and the utricule). Postmanoeuvre, the patient continued to

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have vertigo without any improvement in symptoms. Electronystagmography revealed a normal caloric response. Pursuit saccade and optokinetic nystagmus were within normal limits. As the symptoms were persistent, we performed an auditory brainstem response (ABR) examination. This revealed an abnormal interpeak latency between waves I and V (> 4.4 milliseconds in accordance with the criteria of Marangos and colleagues[12]) in the left ear (Figure 1). This finding suggested a not exclusive labyrinthine pathology.

Contrast-enhanced magnetic resonance imaging (MRI) (gadolinium) done in axial and coronal planes showed a mass of 1.7 cm occupying the left CPA (Figure 2). T_1-weighted, postcontrast images revealed homogeneous enhancement of the mass. The lesion was suspected to be a meningioma of the left CPA based on the MRI findings as described above, along with the presence of a characteristic dural tail. The tumour was completely excised by the translabyrinthine approach. Histopathology confirmed the diagnosis of menigioma. Postoperatively, the patient had appreciable relief of his vertigo.

Discussion and Conclusion

Vertigo is a common and frustrating symptom for which patients seek help from an otolaryngologist. The history, findings from a clinical neuro-otologic examination, characteristic pattern of nystagmus, and audiometric results provide the clue in differentiating peripheral from central vertigo.[1] Nystagmus seen in peripheral vertigo is either spontaneous or provoked, horizontal or torsional, fatiguable, reversible, and inhibited by visual fixation.[9,13]

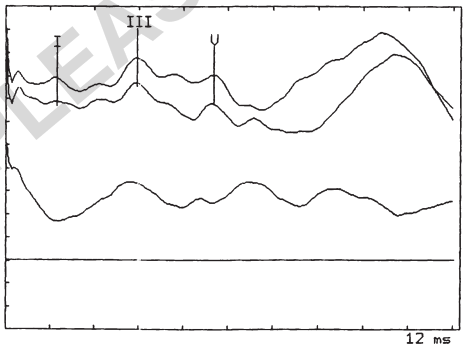

Figure 1. Auditory brainstem response examination showing an abnormal I–V interpeak latency in the left ear.

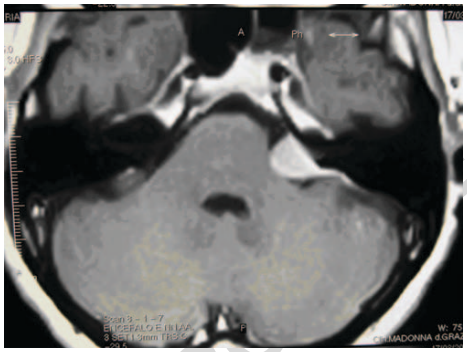

Figure 2. Magnetic resonance image axial section showing a gadolinium-enhanced mass in the left cerebellopontine angle with the characteristic dural tail.

BPPV is the most common cause of peripheral vertigo.[2] Vertigo is brought on by sudden changes in head position, lasting for a few seconds or minutes and associated with paroxysmal symptoms.[14]

In central positional vertigo, the nystagmus is often spontaneous; purely vertical, horizontal, or torsional; direction changing; and uninhibited by visual fixation.[5,11] Common causes of central vertigo are cerebrovascular insults, CPA tumours, multiple sclerosis, and other demyelinating neurologic conditions.[10] Among the lesions of the CPA, vestibular schwannoma (VS) accounts for up to 90% of the lesions, with meningiomas (10–15%)[15] being the second most common neoplasm.[16]

Meningiomas commonly present with unilateral tinnitus (87%) and unilateral hearing loss (75%) followed by dizziness or vertigo (62%).[17] These lesions demonstrate similar density and intensity patterns on computed tomography and MRI and can usually be distinguished from VS by their shape and position.[15] Meningiomas in the CPA appear as a sessile mass on the posterior surface of the petrous bone, with its axis eccentric to the internal auditory canal.[15] In addition, intratumoral calcification occurs in 25 to 35% of cases and an associated dural tail is seen on contrast-enhanced MRI in 50 to 70% of the cases.[15] Both calcifications and a dural tail may be present in VS, albeit rarely.[16]

Froehling and colleagues in 1991 and Franco-Vidal and colleagues in 2005 explained the pathophysiology of this paroxysmal positional vertigo secondary to a CPA mass.[18,19] It is present when the tumour is involving and eroding the labyrinth, when the endolymphatic sac is attached or compressed by the tumour, or when the lesion

injures or stretches the vestibular nerve, as in VSs or meningiomas.

In our patient, vertigo was probably related to the external compression or traction on the vestibular nerve by the tumour. Marangos and colleagues in 2001 showed that in CPA tumours, the oto-neurologic evaluation, electronystagmography, and caloric response testing can be normal.[12] The ABR evaluation was pathologic in the present case, but prospective studies comparing ABR and MRI for the screening of CPA tumours suggest abandoning the ABR as a screening test for CPA tumours.[20] Further, Ruckenstein and colleagues in 1996 showed that the sensitivity of the ABR is only 63%.[21] Gizzi and colleagues indicated that the probability that a patient with dizziness has a CPA mass is 0.004 or only 1 in 2500 cases.[22]

However, the repeated failure of repositioning manoeuvres and the persistence of the signs and symptoms of vertigo, along with unilateral hearing loss, warranted exclusion of a CPA tumour presenting with peripheral positional vertigo. MRI is the best option in suspected cases of intracranial tumours because of its superiority in visualizing the CPA, where most central nervous tumours causing vertigo exist. Once the lesion is identified to be a possible meningioma, complete removal of the tumour is desirable. Even though the coexistence between intracranial tumours and BPPV is reported,[23] our patient's postoperative improvement in vertigo after surgical treatment may exclude this aspect.

Intracranial tumours may occasionally present as peripheral positional vertigo. Failure to conclusively treat such conditions by repositioning manoeuvres, even in the presence of normal otoneurologic and audiologic evaluations, warrants further radiologic investigation to exclude any intracranial pathology.

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Management of benign paroxysmal positional vertigo of lateral semicircular canal by Gufoni's manoeuvre

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Abstract Benign paroxysmal positional vertigo (BPPV) of lateral semicircular canal (LSC) is one of the rarer forms of BPPV as compared to posterior semicircular canal BPPV. Various particle repositioning manoeuvres have been described in the literature as a mode of treating this condition.

Purpose: Evaluation and discussion of the procedure of the Gufoni's manoeuvre and its advantages in the treatment of BPPV of LSC.

Material and methods: Prospective study of 58 patients affected by LSC BPPV who were office-treated with Gufoni's manoeuvre.

Results: Seventy-nine percent of the patients so treated had complete resolution of symptoms, and 6.9% did not show any improvement in their symptoms. The remaining 13.8% had a conversion into posterior semicircular canal BPPV during treatment and were successfully treated with Epley's or Semont's manoeuvre.

Conclusions: Gufoni's manoeuvre is effective in treating patients suffering from BPPV of LSC; it is simple to perform; there are not many movements to execute, it needs low time of positioning, and positions are comfortable to the patient.

1. Introduction

Any patient presenting with history of vertigo is a challenge for the ear, nose, and throat (ENT) specialist. Vertigo affects the patients both physically and psychologically as it becomes impossible for the patient to go through daily routines of life without external help from others. Many of these patients are usually managed by primary care physicians medically for a long time before they are referred to an ENT surgeon. Because of this reason, they have to go through several unnecessary diagnostic procedures before arriving at a diagnosis or being referred further to a specialist centre. Fortunately, in patients affected by vertigo crisis due to benign paroxysmal positional vertigo (BPPV), correct diagnostic evaluation and appropriate management allows, in the great number of cases, to solve the problem quickly, without the need for any medical treatment.

Benign paroxysmal positional vertigo is the most common cause of peripheral vertigo [1]. It accounts for approximately 24% of all cases of peripheral vestibular disorders [2]. This type of vertigo is generally seen in individuals aged 40 years and older with the highest age distribution between 50 and 70 years [3]. The exact etiology of BPPV is still under debate. More than 50% of all reported cases are idiopathic in nature [4]. Classic BPPV involves the posterior semicircular canal (PSC) and represents the most common type of BPPV [3,5-7]. Lateral semicircular canal (LSC) BPPV accounts approximately for only 10–20% of all the patients presenting with BPPV [8]. In addition, treatment

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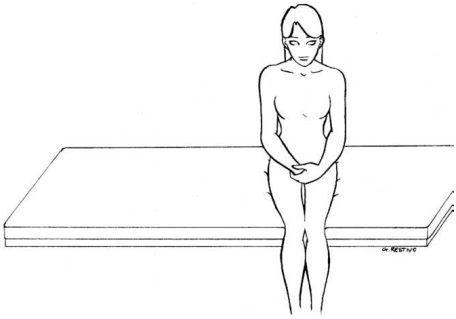

Fig. 1. Position 1, patient seated on the examination couch with both the legs hanging out from the same side, arms held close to the body and hands resting on the knees.

of LSC BPPV has got a lower success rate of between 60% and 90% as compared to PSC BPPV. Nuti et al [7] reported a success rate of 71% with barbecue rotation and 73% with forced prolonged position in patients with LSC-BPPV. Fife showed that 75% in 24 patients responded to the canalolith repositioning maneuver [8,9].

Diagnosis of BPPV is based mainly on a history of characteristic positional vertigo along with the classical clinical signs. Symptoms are similar for BPPV of LSC and PSC characterized by rotating vertigo with nausea and vomiting, elicited by movements of the head (when rising up or when lying down). The nystagmus typically has a latency (of few seconds) and is of limited duration, transient, fatigable, and reversible on return to upright position [5].

Patients of LSC BPPV have traditionally been treated with various particle repositioning manoeuvres. Therapeutic head-shaking, as suggested by Vannucchi et al [10], Lempert's so called "barbecue rotation" [11], Baloh's modification of the same with 360° rotation [3], Vannucchi's forced prolonged position or FPP [12], Epley's 360° rotation suggested in 1995 [13] and modified Semont's manoeuvre are few of the various treatment modalities currently being followed in treating this condition [14]. Gufoni [15] proposed a repositioning manoeuvre based on the hypothesis of the presence of free-floating debris with a higher density than endolymphatic fluid in the anterior arm of the horizontal semicircular canal [16]. This manoeuvre has the advantage of simplicity while maintaining the efficacy in treating this condition. We studied 58 patients having horizontal semicircular canal BPPV who were treated with Gufoni's manoeuvre.

The aim of our study was to evaluate the efficacy of Gufoni's manoeuvre in office management of patients affected with BPPV of LSC.

2. Materials and methods

We prospectively studied 58 patients (23 men and 35 women), aged between 27 and 81 years, presenting with BPPV secondary to LSC in the period 2001–2004. The inclusion criteria were as follows: first-time diagnosis of BPPV of LSC, no previous medical treatment for vertigo, no history of chronic ear disease. We study only geotropic variant of LSC BPPV. All patients diagnosed and managed in the emergency department were excluded from the present study.

All the patients underwent ENT and head and neck examination, posture evaluation, pure tone audiometric test, impedance, and stapedial reflex study. Spontaneous nystagmus was assessed with Frenzel's glasses in the seated position, with head rotated to right and to left, in the supine position, and in the Rose' position (patient lay in supine position with the head falling down over the end of a table). Evoked nystagmus was evaluated by Dix-Hallpike's

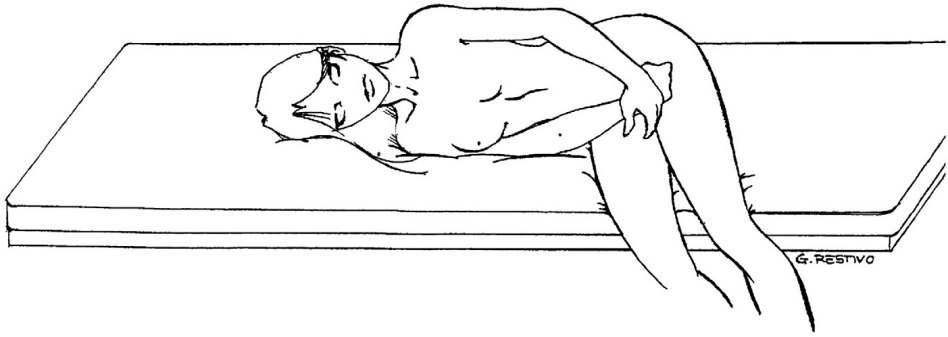

Fig. 2. Position 2, patient is then made to lie down on the uninvolved lateral side with a quick lateral movement and maintained in this position for 2 minutes until the end of evoked geotropic nystagmus.

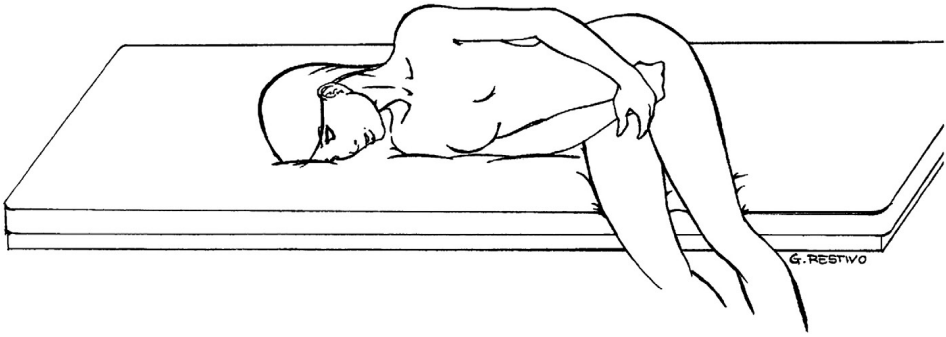

Fig. 3. Position 3, quick 45° rotation of the head towards the floor, position being maintained for 2 minutes.

manoeuvre [17] and by Pagnini's manoeuvre (patient in supine position and quick rotation of the head to right and to left) [10] in order to identify the involved semicircular canal. After ruling out other possible causes for the patients' symptoms, a diagnosis of LSC was arrived at.

Once the patients were diagnosed with BPPV of LSC, they were managed by Gufoni's manoeuvre.

Before performance of the treatment, an informed consent was obtained from each patient and the institutional ethical commission approved the procedure. This included putting

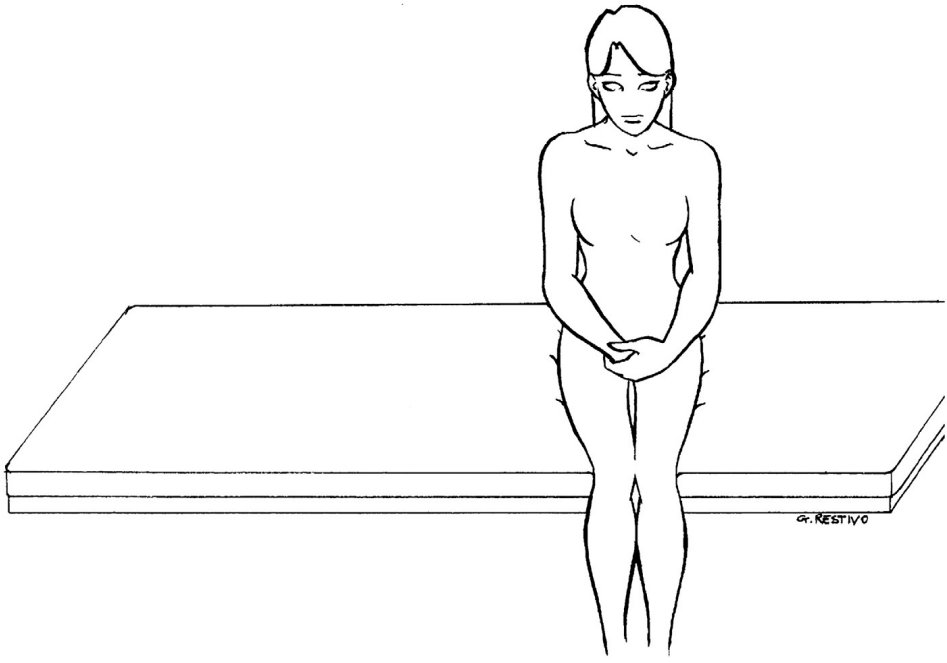

Fig. 4. Position 4, slow return back to the starting position.

Table 1
Outcome of treatment of BPPV of LSC by Gufoni's manoeuvre

Patients	Outcome
46 (79.3%)	Complete resolution
8 (13.8%)	BPPV of PSC conversion
4 (6.9%)	No benefits
58	

BPPV: benign paroxysmal positional vertigo; LSC: lateral semicircular canal; PSC: posterior semicircular canal.

the patients through the following positions: (1) patient seated on the examination couch with both the legs hanging out from the same side, arms held close to the body, and hands resting on the knees (Fig. 1); (2) patient is then made to lie down on the uninvolved lateral side with a quick lateral movement and maintained in this position for 2 minutes until the end of evoked geotropic nystagmus (Fig. 2); (3) quick 45° rotation of the head towards the floor, position being maintained for 2 minutes (Fig. 3); (4) slow return back to the starting position (Fig. 4).

Gufoni's manoeuvre was executed twice, and after this, the patients were reevaluated. The presence of attenuated vertigo, or persistence of nystagmus, implies the need for a repetition of the manoeuvre. At the end of the treatment, patients were discharged home. Postural restriction, even during night, was not advised. First clinical follow-up was 3 days after the procedure. Patients were further followed up on 2 more occasions, at the end of the first week and again at 3 months after the initial procedure.

Our institutional review board reviewed and approved the present study, and an informed consent was obtained from all patients before treatment.

3. Results

In 46 patients (79.3%) we obtained a complete resolution of vertigo and nystagmus after the first session (Table 1). This improvement was maintained up to the last clinical review. In all these patients a slight sensation of unsteadiness was present for two weeks after the treatment, which however resolved completely, spontaneously. Eight patients (13.8%) had a conversion to PSC canalolithiasis during the treatment, and those patients were managed promptly with Epley's manoeuvre (6 cases) or Semont's manoeuvre (2 cases) with resolution of symptoms. Four patients (6.9%) did not have any benefit after the treatment. They were advised Vannucchi's positions with resolution of symptoms subsequently, after several weeks.

4. Discussion

Etiology of BPPV is not always related to a definite cause and may be a sequelae of several inner ear diseases such as posttraumatic, viral, and vascular causes, as is described in the literature [18]. However, 70% of cases are thought to be idiopathic. Currently, the hypothesis that is widely accepted is that of displacement of otoliths from the utricular macula and consequent deposition of these fragments in the LSC or PSC. These otoliths provoke a piston-like mechanism of action on endolymph flowing from or toward the ampullae, causing activation or inhibition of the canals respectively [19]. Diagnosis of LSC BPPV is based on the history and features of the positioning nystagmus provoked by a quick turn of the head to either side with the patient lying supine. The characteristics of the positioning nystagmus leading to a diagnosis of LSC BPPV have been well summarized by Ciniglio Appiani et al [16] as having the following features typically: (1) very short latency (a few seconds), (2) paroxysmal character, (3) duration <1 minute, (4) purely horizontal (geotropic or apogeotropic direction changing) position and greater intensity on one side, and (5) not fatigable with repeated positioning.

Various manoeuvres have been proposed for the treatment of LSC BPPV. Most of these manoeuvres constitute quickly rolling the supine patient towards the unaffected side. This is thought to shift the otoconial debris out of the nonampullated end of the horizontal canal into the utricle [16]. Gufoni introduced a manoeuvre for treating LSC BPPV in 1998. The advantage of this manoeuvre was that, apart from showing very good results in geotropic LSC BPPV, it can be conducted even in patients with cervical spondylosis and obesity. This brisk deceleration manoeuvre was based on the rationale that the otoconial debris is moved from the lateral semicircular canal to the utricle, exploiting its inertia and correct disposition in the canal outlet, obtained by correct positioning of patient's head [12].

Based on this theory, the lateral decubitus position on the affected side should give rise to migration of otolithic debris to the posterior end of the lateral semicircular canal with a concomitant flow of endolymph toward the ampulla. This, in turn, causes activation of the hair cells with resultant vertigo and geotropic nystagmus. The rotation of the patient to the unaffected side should give rise to a reversal of flow with posterior migration of the otoliths and an inhibitory endolymphatic flow. In this case, the vertiginous symptoms are not as severe as in the precedent one, and also, the nystagmus is less intense. This pathophysiologic mechanism has 2 possible explanations: (1) Pagnini, in accordance with the Ewald's laws, suggested that after intense accelerations the excitatory stimulus is much more strong respect to inhibitory one [18]; (2) Baloh et al [4] hypothesized that otoliths present in the posterior arm of the LSC are placed in an asymmetric fashion and, consequently, the amplitude of its movement is different on assuming lateral decubitus posture on the affected and unaffected side, symptoms and nystagmus being much more intense on the affected side.

Gufoni's manoeuvre consists of the following steps (1) the patient sits on the edge of the bed; (2) the patient is made to lie down suddenly on one side: for geotropic LSC-BPPV, the patient lies on the healthy side, in the apogeotropic form on the affected side; (3) patient's head is rotated 45°

Table 2
Treatment and outcome of patients with benign paroxysmal positional vertigo of LSC with conversion to PSC after Gufoni's manoeuvre

Patients with PSC conversion	Treatment	Outcome
6	Epley's manoeuvre	Resolution 100%
2	Semont's manoeuvre	Resolution 100%

LSC: lateral semicircular canal; PSC: posterior semicircular canal.

downward and held for 2–3 minutes; (4) patient returns to sitting position; (5) outcome of the manoeuvre is checked. Vannucchi et al. [12] quoted a success rate of 96% for geotropic LSC BPPV and 77% for apogeotropic LSC BPPV. No side effects were observed in any of the 174 cases studied by them. Ciniglio Appiani et al [16], in their case review, quoted 100% success in 32 patients of geotropic LSC BPPV, treated with this manoeuvre, after 2 attempts. In comparison, we had an overall success of 93.1% in our patient population studied. In the first instance, 48 patients (79.3%) improved. The 8 patients (13.8%) whose vertigo was converted into a PSC BPPV had their vertigo corrected with Epley's manoeuvre or Semont's manoeuvre (Table 2). The remaining 4 patients (6.9%) who did not benefit from this manoeuvre were advised Vannucchi's forced prolonged position with which their symptoms resolved subsequently. All the patients complied well with our treatment, and there were no dropouts. In addition, we didn't observe any adverse effects of this manoeuvre on any of our patients.

Gufoni's manoeuvre is believed to clear the nonampullary arm of the LSC from otoliths using gravity and inertia of the particles. The quick variation from seated position to lateral decubitus on the unaffected side, putting the LSC on a vertical plane, causes movement of otolithic debris towards the nonampullary end of the canal. The subsequent 45° downward head rotation moves the otoliths, by inertia, into the utricle [15]. One of the main advantages of this manoeuvre is its acceptability to the patients. This is because the patients are made to roll on to the unaffected side, making it more readily acceptable. This also helps to keep the dropout rates very low [12]. It is possible to execute the Gufoni's manoeuvre under videonystagmographic control in order to evaluate step by step the nystagmus and verifying the efficacy of the several positions as suggested by Asprella et al [2]. In situations where the patient is having neck pain/stiffness and severe neurovegetative symptoms such as vomiting, causing them to refuse this treatment; in very elderly patients; and also in severe obesity, repositioning the manoeuvre may be difficult to perform. In these patients who are unable to tolerate the positional manoeuvres or in whom the treatment is unsuccessful, vestibular suppressant drugs and vestibular rehabilitation may be used [14].

5. Conclusion

Gufoni's manoeuvre is effective in treating patients suffering from BPPV of LSC and offers significant advantages. It is simple to perform; there are not many movements to execute, it needs low time of positioning, and positions are comfortable to the patient. Because of these favorable features, there are not many contra-indications for its reasonable application in any patient. In our experience, we obtained good results in 79% (overall 93.1% after including the PSC-PPV converted patients) of the patients studied, and only 6.9% of patients did not have any benefit with this treatment. The clinical evidence, from the application of Gufoni's manoeuvre, allows considering its use as the treatment of first choice in cases of BPPV of LSC.

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Imaging Case of the Month

Imaging of Cervical Lymph Node Metastases in Malignant Jugular Paraganglioma

Imaging of Paraganglioma Metastases

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Tympanojugular paragangliomas are the most common tumors of the skull base. Magnetic resonance imaging is the gold standard for radiologic study, with a characteristic salt-and-pepper pattern on T1-weighted images with gadolinium enhancement. Angiography is needed to visualize the feeding vessels to perform preoperative tumor embolization. The typical angiographic appearance of a paraganglioma is that of a hypervascular mass with enlarged feeding arteries, intense tumoral blush (due to intratumoral vascular shunts), and early draining veins (1).

Metastases from jugular paragangliomas are relatively rare, in contrast with vagal paragangliomas (incidence varies between 1–4%), and are the main manifestation of malignant behavior (2). The metastases show the same angiographic pattern as that of primary tumor.

The present case describes a patient with left tympanojugular paraganglioma and a left-sided mass in the neck.

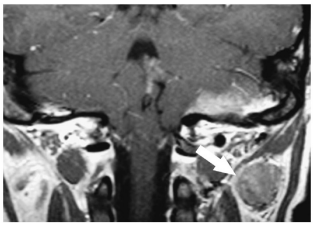

FIG. 1. Magnetic resonance coronal image T1 weighted with gadolinium enhancement displays a left-sided neck mass (*white arrow*) between the posterior belly of the digastric muscle and the sternocleidomatoid muscle, with a mild contrast enhancement.

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Magnetic resonance imaging T1-weighted images after gadolinium enhancement revealed a primary lesion involving the left jugular foramen with dura involvement and a neck mass located between the posterior belly of digastric and the sternocleidomastoid muscles (Fig. 1).

The common carotid artery arteriography showed a blush of the jugular foramen mass and of the neck lump with similar features (Fig. 2A). A selective arteriography of occipital artery was performed, revealing an enlarged branch of occipital artery as the main feeding vessel of the metastases (Fig. 2B).

The histopathologic diagnosis was malignant paraganglioma with lymph node metastases.

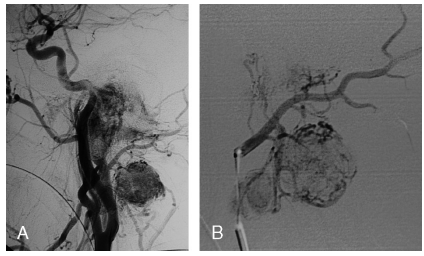

FIG. 2. *A*, Arteriography of the left common carotid artery shows a blush in the lesion of the left jugular foramen and also of the neck mass. *B*, Selective arteriography of the left occipital artery that demonstrates the enlarged feeding vessel of the neck lesion.

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Imaging Case of the Month

Imaging of Vestibular Schwannoma With Prevalent Cystic Component: Cystic Vestibular Schwannoma

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Cystic vestibular schwannomas (VSs) are described as behaving in a more aggressive fashion, with shorter periods of documented symptoms, poorer responses to radiotherapy, and worse outcomes from surgical intervention (1).

These factors include higher rates of engulfment of neurovascular structures, the association with hypervascular solid components, and the absence of an adequate subarachnoid dissection plane.

Recommendations from "New and Modified Reporting Systems from the Consensus Meeting on Systems for

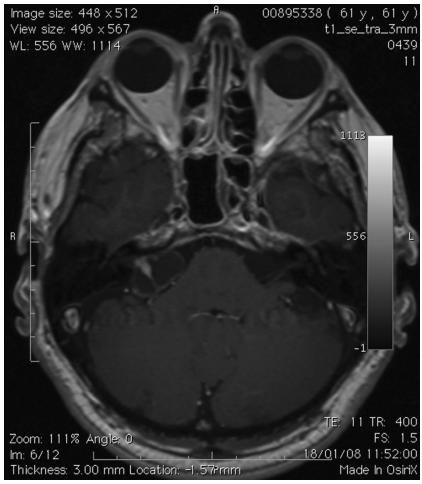

FIG. 1. T1-weighted image of the right cystic VS of the internal auditory canal and cerebellopontine angle. The solid portion of the tumor is hyperintense after Gd administration. The cyst content is hypointense as compared with the brain. Enhancement of the cyst capsule is noticeable.

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Institution where work was done was Gruppo Otologico Piacenza.

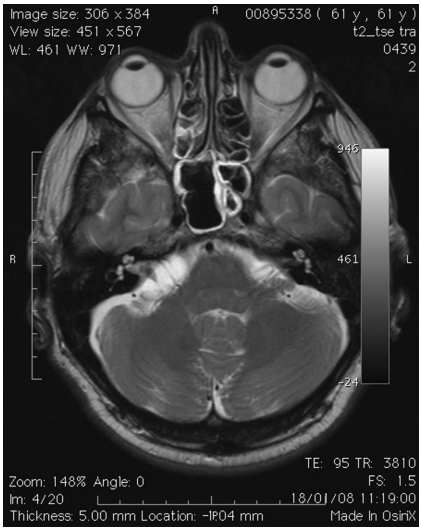

FIG. 2. T2-weighted image with standard TR. The cyst content is displayed with the same intensity as the CSF. The solid portion seems isointense as the brain.

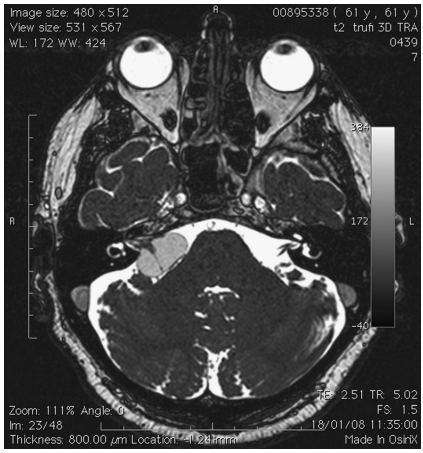

FIG. 3. T2-weighted image with modified TR. The cyst content seems hypointense as compared with CSF, allowing differential diagnosis with arachnoid cysts.

Reporting Results in Vestibular Schwannoma" suggested that multicystic tumors with a cystic component on the surface of the tumor be documented to facilitate clinical studies (2).

We report a case of right-sided cystic VS of the internal auditory canal and cerebellopontine angle with prevalent cystic component.

Magnetic resonance imaging represents the best choice to diagnose and visualize the VSs. Cystic VSs consist of 2 components: 1) a solid portion and 2) a single or multiple cysts. Intravenous administration of gadolinium (Gd) allows visualization of tumoral solid component.

The solid portion of the tumor seems hyperintense in T1-weighted images with Gd (Fig. 1) and hypointense in T2-weighted images (Fig. 2). The cystic component is displayed hypoisointense in T1-weighted images with Gd (Fig. 1) and hyperintense in T2-weighted images (Fig. 2). The cyst content can be distinguished from cerebrospinal fluid (CSF) by variation of the time of repetition (TR) value in T2-weighted slice. This variation has an important effect on the control of image contrast characteristics (Fig. 3).

Tumors with cystic component have to be differentiated from CPA epidermoids and subarachnoid cysts. These latter 2 lesions are hypointense in T1 and hyperintense in T2 and do not enhance after Gd administration.

Fluid-attenuated inversion recovery and echo-planar diffusion imaging are 2 kinds of sequences that can distinguish between epidermoids and arachnoid cysts (3).

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Otoneurological management of petrous apex cholesterol granuloma

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Abstract

Objective: The aim of the study is to review the management of petrous apex cholesterol granuloma. The surgical approaches for drainage or total removal and the wait and see policy were analyzed, and outcomes were evaluated.

Methods: Retrospective charts of 27 patients managed for petrous apex cholesterol granuloma with a minimum follow-up of 12 months were analyzed in a quartenary skull base center. Presenting symptoms and signs were recorded, and radiologic imaging was evaluated. Management options included wait and see policy and surgery by several approaches.

Results: The mean age of patients affected by the lesion was 38.8 years. The mean follow-up was 56.7 months. Patients complained of hearing loss, vertigo, tinnitus, diplopia, hemifacial spasm, trigeminal neuralgia, and facial paresthesia. Twelve patients were managed by wait and see policy, and in this category, only one lesion showed growth during the follow-up. Depending upon size and location, 15 patients were surgically treated by infralabyrinthine approach (9 patients), infratemporal type B approach (3 patients), combined infratemporal type B transotic approach (2 patients), and transotic approach (1 patient). One recurrence was recorded during the follow-up.

Conclusions: Radiologic evaluation is required for diagnosis and management. Patients with good hearing can be treated by infralabyrinthine approach. Infratemporal fossa type B approach is advocated in patients with extensive disease and internal carotid artery involvement. Wait and see policy is recommended for asymptomatic cases. Drainage and permanent ventilation are the goals of treatment. Complete removal is indicated in selected cases where placement of drainage tube is not feasible.

1. Introduction

Cholesterol granuloma (CG) of the petrous apex (PA) is a rare, benign expanding lesion, which was defined by Graham [1] as a distinct clinical entity. This lesion has been reported throughout the temporal bone—middle ear, mastoid, and PA [2]. It consists of a cyst with a thick fibrous capsule filled with a brown fluid formed by degradation of blood elements as follows: globular material, lipids, and cholesterol crystals. In literature, 2 mechanisms to explain the possible origin are described, having a common basis—a foreign body giant cell reaction. The first theory is based on extravasation of intravascular fluid into the mucosa of the air cells, leading to occlusion of pneumatized temporal bone cells. The gas present in the cells are gradually reabsorbed leading to a vacuum, negative pressure leads to hemorrhage into the air cells and the following degradation of hemosiderin, and cholesterol stimulate an inflammatory granulomatous reaction [3,4]. The progressive expansion of the mass results in erosion of the surrounding bone. This theory was reviewed by Jackler et al [3], who described an alternative mechanism of subacute hemorrhage based on

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Table 1
Surgical approaches reported in the literature

Authors	Year	Pts	Age, mean	FU, mean, mo	Surgery										Rec	WS
					IL	IC	TM	MCF	P	TO	TL	SO	TS	IFTB		
Gherini	1985	9	49	NA	5			1			3				1	
Graham	1985	4	36	NA			3	1								
Thedinger	1989	12	47	47	3					2		1	4		5	2
Goldofsky	1991	9	45	NA	7						1	1			1	
Brodkey	1996	17	47	29	8	2					1					6
Eisenberg	1997	14	39	36				8	2							4
Cristante	2000	8	45	60				8								
Brackmann	2002	34	41	60	7	18		7		1	1				5	
Mosnier	2002	12	36	18	5	2				1						4
Sanna*	2008	27	38	56	9					3†				5†	1	12

Pts indicates patients; FU, follow-up in months; TM, transmastoid; P, petrosal approach (not specified); SO, suboccipital; TS, transsphenoidal; Rec, recurrences; WS, wait and see policy.

* Present study.

† In 2 cases, IFTB was combined with TO.

erosion of marrow-filled cavities of PA by the development of air cells, particularly in highly pneumatized petrous apices. This hypothesis supports better the more aggressive form of CG of the PA, in which a significant hemorrhage is necessary to explain the rapid growth [5].

The clinical presentation of patients having PA CG may vary depending on the extension; the symptoms do not occur until it has become relatively large. Hearing loss and vertigo are present in one third of cases, followed by tinnitus and otalgia. Frequently, trigeminal neuralgia and diplopia are present. Abnormal facial sensation and facial spasm are also reported [6,7]. Other symptoms encountered are headache and, occasionally, seizures. Surgery by means of different approaches described [7] represents the mode of elective management in large cases with or without symptoms.

The aim of this article is to present our series of patients affected by PA CG and to discuss surgical management with the review of the literature.

2. Materials and methods

Of almost 2500 skull base procedures performed in our quaternary referral center, we retrospectively reviewed 29 charts of patients affected by PA CG, managed between 1998 and 2007. Patients included in the study had at least 12 months of follow-up. Two patients were excluded from the study because of incomplete follow-up. The presenting symptoms were recorded in all cases. All patients underwent head and neck examination and audiological evaluation. Pure tone average (PTA) (0.5, 1, 2, 4 kHz) was recorded for air and bone conduction. Computed tomography (CT) and magnetic resonance imaging (MRI) with and without gadolinium were obtained in all cases preoperatively and postoperatively and during follow-up. In all surgically managed cases, a lateral skull base approach was adopted. Facial nerve function was assessed preoperatively and postoperatively and at the last visit and was reported in accordance with House-Brackmann (HB) grading scale [8].

The English literature review was conducted through PubMed engine search. In the literature search, we included all studies concerning PA CG (Table 1). We excluded work

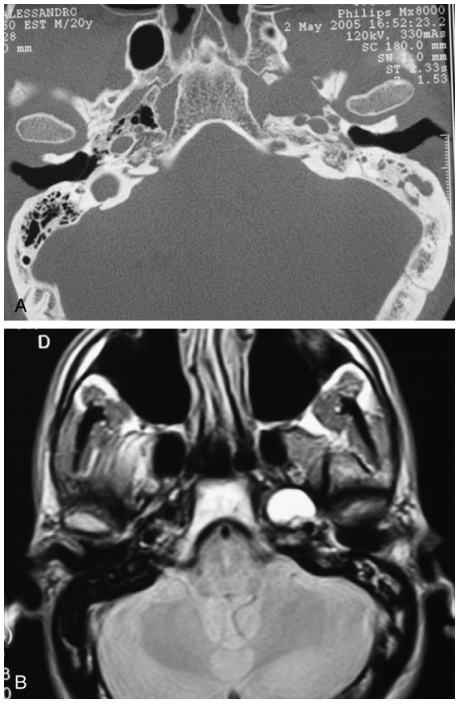


Fig. 1. Magnetic resonance fast spin echo sequences of patient affected by left PA CG, managed by wait and see policy. (A) Computed tomography of year 2005. (B) Magnetic resonance scan of year 2008.

done in the same institute and case reports, to avoid duplication of cases. Our institutional review board approved the present study, and an informed consent was obtained from each patient.

3. Results

The study includes 27 patients. Left side was involved in 15 cases and right side in 12 patients. Thirteen patients were male and 14 were female, with mean age of 38.8 years (range, 12–57 years) at the time of diagnosis. The mean follow-up was 56.7 months (range, 15–112 months).

In 12 of 27 patients, imaging was done for symptoms not related with PA CG (10 patients had chronic rhinosinusitis), and its diagnosis was incidental. All patients at diagnosis were asymptomatic and were managed conservatively. During follow-up with imaging, no evidence of growth was noted in all but one patient (Fig. 1A, B). One patient, who had growth of lesion on follow-up, refused surgical management. All patients to date are free of symptoms.

The hearing loss was the most common symptom and was present in 9 patients. Four patients had vertigo and tinnitus. Four patients complained of headache. Symptoms due to cranial nerve deficit were also present. Six patients had diplopia, and hemifacial spasm was present in 1 patient. Trigeminal neuralgia occurred in 1 case and facial paresthesia in 2 cases. One patient who underwent 2 previous operations in other center had otorrhea.

The audiological assessment of patients having hearing loss revealed that 2 patients did not have functional hearing preoperatively and in the remaining 7 patients, who had sensorineural hearing loss, the mean PTA was 55 dB (range, 25–80 dB).

The diagnosis of PA CG was done after radiologic investigation with CT scan and MRI with and without gadolinium (Table 2). In all patients, CT scan showed a PA lesion, isodense with brain, with a variable degree of bone erosion of the petrous bone and the clivus. The MRI scans were obtained in all patients showing the typical characteristics of hyperintensity on T1-weighted with and without contrast enhancement and T2-weighted images (Fig. 2A).

Table 2
Differential diagnosis on imaging of nonenhancing cystic lesion of cerebellopontine angle and PA

	CT	MR		
		T1	T2/FSE	FLAIR
Epidermoid cyst	Hypodense or isodense	Hypointense	Hyperintense	Hyperintense
Arachnoid cysts	Hypodense	Hypointense	Hyperintense	Hypointense
Cholesterol granuloma	Isodense	Hyperintense	Hyperintense	Hyperintense

T1 indicates T1-weighted images; T2, T2-weighted images; FLAIR, fluid attenuated inversion recovery; FSE, fast spin echo.

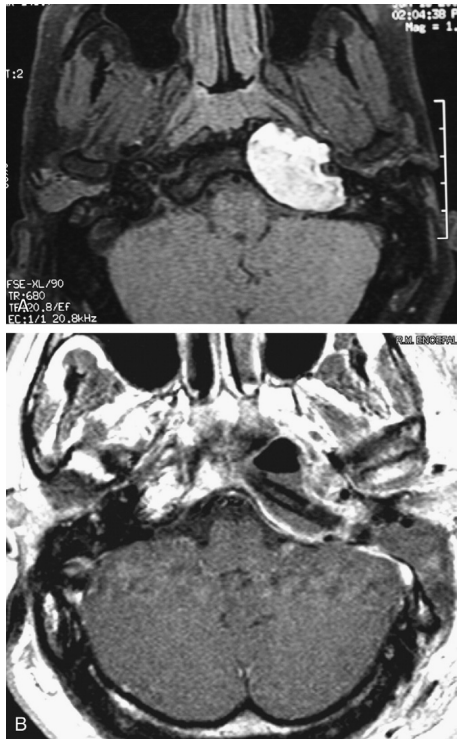


Fig. 2. Representative case with preoperative and immediate postoperative MR. (A) Magnetic resonance fast spin echo sequence displaying a high-signal image of a left expanding lesion of the PA. (B) Immediate postoperative MR T1-weighted image displaying a correct position of the drainage tube and presence of some postoperative secretion, which can be differentiated from CG because of low-signal intensity. The high-signal rim around the cavity, which represents the capsule of the CG, is seen.

The mean size of largest diameter was 27.6 mm (range, 20–45 mm). Fifteen patients were treated by surgery as summarized in Table 3.

An infralabyrinthine (IL) approach was performed in 9 patients (Fig. 2A, B). In 2 patients, complete removal of the cyst was achieved by combined transotic (TO) and infratemporal type B (IFTB) approaches (Fig. 3A, B). Three cases were treated by an IFTB approach because of extension of disease toward intrapetrous carotid artery and serviceable hearing. In 2 of these patients presenting with 3.8 and 3-cm lesions, respectively, extending from the internal auditory canal to the sphenoid sinus, medially to the ICA, the IFTB approach was combined with a temporal-zygomatic craniotomy. This approach was used to control the intrapetrous carotid artery, which was

Table 3
Clinical and surgical details of patients surgically treated in the present study

Patients				Clinical evaluation		Surgery		Follow-up		
	Age	Sex	Side	Symptoms	PTA (dB)	Approach	Complications	Months	Symptoms	PTA (dB)
1	19	M	R	HL	25	IL		110		25
2	36	M	R	Diplopia	20	IL	Intraoperative CSF leak	106		20
3	48	M	R	Diplopia, HL, hemifacial spasm	80	IFTB TO	Intraoperative ICA bleeding, FN palsy HB grade VI	22	FN palsy HB grade II, diplopia	DE
4	25	M	L	Headache, diplopia	20	IL		112		20
5	22	F	L	Diplopia	20	IL		93		20
6	44	M	L	Vertigo, HL, tinnitus	45	IL		60		45
7	42	M	R	Facial numbness	20	IFTB*	FN palsy grade 5 HB at discharge	45	FN HB grade I	20
8	28	F	R	DE	120	IFTB TO		70		DE
9†	38	F	L	Otorrhea, tinnitus, DE	120	TO	Intraoperative CSF leak	40		DE
10	52	F	R	HL, tinnitus, vertigo	45	IL	FN palsy grade 2 HB at discharge	68	FN HB grade I	45
11	40	F	L	Diplopia, headache, vertigo	25	IL	Cochlear acqueduct injury	34		25
12	41	M	L	Headache, vertigo	20	IFTB		20	Dizziness	20
13	51	M	R	HL, tinnitus, facial numbness	75	IFTB*	FN palsy HB grade V	31	FN palsy HB grade II	DE
14	57	M	L	HL	65	IL		25		65
15	34	M	L	Diplopia, headache, trigeminal neuralgia, HL	45	IL		15		45

M indicates male; R, right; HL, hearing loss; CSF, cerebrospinal fluid; FN, facial nerve; DE, dead ear; L, left; f, female.
* IFTB enlarged with temporal-zygomatic craniotomy.
† Two previous operations by IL approach in another center; an iatrogenic cholesteatoma was found.

displaced anteriorly to allow complete removal of the cyst from the clivus and sphenoid sinus.

One patient had undergone 2 previous surgeries in another hospital—an IL drainage and a revision procedure 1 year later; the patient after the second operation had total hearing loss and had ear discharge and tinnitus in following 3 years. He was surgically treated in our center by a TO approach, to drain the PA lesion, and iatrogenic cholesteatoma of the mastoid was found during the operation.

Intraoperative cerebrospinal fluid leak occurred in 2 cases, managed by IL approach. In one case, a small posterior fossa dura lesion was managed by the cavity obliteration with abdominal fat at the time of the surgery; in another case, cerebrospinal fluid leak occurred due to accidental opening of the cochlear acqueduct. This was managed by the obliteration of the duct with muscle and periosteum.

In one case managed by TO + IFTB approach, a small opening of internal carotid artery (ICA) wall, at the anterior foramen lacerum, occurred. Because of difficulty in controlling the distal portion of the ICA, we opted for immediate packing of the whole cavity with surgery. An evaluation of the efficacy of the collateral circulation in maintaining the perfusion of the areas that would be affected by the manipulation of the ICA was done, and the definitive closure of the vessel was made by endovascular balloon 2 days later.

Immediate postoperative facial nerve palsy was noted in 4 patients. In 2 patients managed by IFTB approach, HB grade V palsy was present. In 1 patient after IL drainage, HB grade II deficit was noted, and in another patient with balloon occlusion of the carotid artery, a HB grade VI was noted. After 31 months of follow-up, HB grade II facial deficit was noted in 2 patients managed by IFTB; in other patients, facial nerve was normal at last follow-up.

The hearing results were good in patients managed by IL approach, with no change between preoperative and postoperative PTA. In 3 patients managed by IFTB approach, we could save sensorineural hearing in 2 patients, whereas it was lost in the other. In all patients managed by IFTB, the masticatory function was normal.

Of 5 patients, presenting with preoperative diplopia and managed by IL approach, 2 had complete recovery of cranial nerve VI function, in the immediate postoperative period. Two cases had complete recovery of nerve VI after 1 year of operation.

One patient with more than 3-cm lesion, which was managed by IFTB approach, complained of disequilibrium even after 35 months of follow-up.

Only one recurrence was noted during follow-up, but the patients refused reintervention, and he is being managed with wait and scan policy.

4. Discussion

The term *cholesterol granuloma* indicates a foreign body, giant cell inflammatory reaction to blood degradation products. It can be found inside air cells of temporal bone, that is, middle ear, mastoid, and less commonly into PA air cells.

Petrous apex CGs must be differentiated from the disease of middle ear and mastoid. There is no evidence of association of middle ear obstructive disorders and development of this pathologic condition. Furthermore,

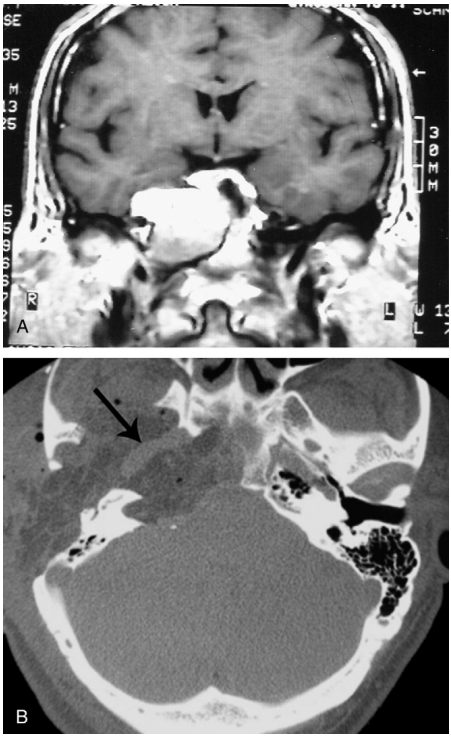


Fig. 3. Image of representative case of patient managed by IFTB approach. (A) Magnetic resonance coronal T1-weighted scan showing a huge right hyperintense expanding lesion spreading into sphenoid sinus and in direct contact with brain. (B) Three-year postoperative CT showing the cavity obliterated by soft tissue. The black arrow shows the ICA.

many patients with persistent eustachian tube dysfunction and middle ear effusion have early arrest of development of pneumatization and thus do not have apical air cells.

Table 4
Symptoms present in patients affected by PA CG reported in literature and percentage

Symptoms in PA CG	n	%
Hearing loss	60	50
Vertigo	58	48.3
Tinnitus	44	36.6
Headache	39	32.5
Trigeminal symptoms	30	25
Diplopia	20	16.6
Facial weakness	21	17.5
Patients evaluated	120	

Petrous apex CG arise in extensively pneumatized temporal bone [9].

Presenting symptoms are related to size and structures involved. In the series of Brodkey [10], dizziness was the main symptom. Trigeminal nerve and cranial nerves VI and VII may be also involved, causing facial paresthesia, diplopia, and facial weakness, respectively. The cranial nerve VIII is involved by extension of the disease into IAC (Table 4).

Differential diagnosis of PA lesions includes PA effusion, petrous bone cholesteatoma (apical location according to the classification by Sanna [11]), chondromas, chondrosarcomas, arachnoid cysts, and vascular malformations. Diagnosis requires imaging studies with both CT scan and MR with gadolinium enhancement. Cholesterol granuloma is nonenhancing in both imaging methods (Table 2). In CT images, the margins of the lesions are sharp with bone erosion present frequently. The loss of the trabeculae of the air cells differentiates CG from PA effusion [12]. The contralateral PA is often well pneumatized in PA CG. The MR is diagnostic with high signal on T1-weighted images, on T2-weighted images, and in all spin echo sequences, with few exceptions due to maturity of the granuloma, which helps in differential diagnosis with cholesteatoma and other tumors [13-16].

There are 2 strategies to treat PA CG as follows: wait and see policy and surgical treatment (Tables 5 and 6). The first option is recommended to asymptomatic patients who are diagnosed incidentally by imaging, for those symptomatic who have poor general conditions or elderly age. Patients managed conservatively undergo serial radiologic evaluation with MR/CT imaging. The surgical treatment is advised to patients with symptomatic disease and patients having

Table 5
Flow chart of our treatment algorithm for asymptomatic PA CG

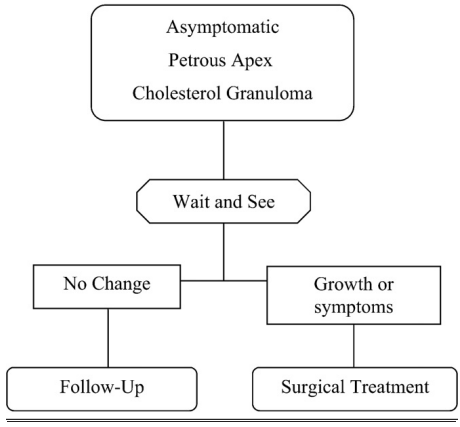
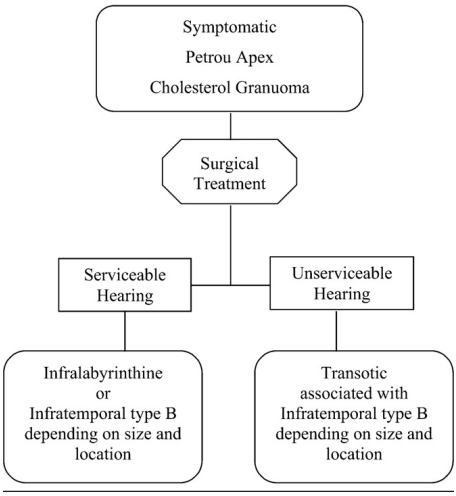


Table 6
Flow chart of our treatment algorithm for symptomatic PA CG



cranial nerve deficit and/or extensive lesions. Several approaches have been proposed in literature through lateral skull base and transnasal-transsphenoidal route [7,17,18]. However, the choice of surgical approach is based on preoperative hearing status, location, extension of the lesion, relationship with neurovascular structures, and anatomical variations (eg, high jugular bulb).

Eisenberg [19] proposed the total cyst wall removal by middle cranial fossa (MCF) approach and obliteration of the cavity with pedicled temporalis muscle flap to avoid recurrences. Cristante et al [6] described a "key-hole" MCF approach to drain or remove CGs (Table 1). We do not advocate these approaches because of limited control of the ICA and difficulty to place a drain through this approach to establish a permanent aeration of the cavity if total removal is not realized. Furthermore, the "keyhole" MCF approach limits the surgical field, putting at risk a dehiscent ICA with subsequent difficulty to control bleeding.

The suboccipital approach has been advocated by some authors [17,20,21]. This approach does not provide permanent drainage and ventilation; thus, it becomes mandatory that the total removal of the cyst should be accomplished. Chemical meningitis is a risk, due to contamination of the subarachnoid spaces by the fluid content of the cyst. This approach is not generally recommended but was adopted by some authors for the lesion isolated in the area near to the internal auditory canal with high possibility of complete excision [20].

Keeping in mind that the objective of operation is drainage and the ventilation of the cavity, in case of preoperative serviceable hearing, IL and infracochlear (IC) approaches are suggested because of low complication rate and good postoperative hearing. In 1982, House and Brackmann [22] were first to report results using a transmastoid approach to drain a PA CG into middle ear cleft. Infralabyrinthine approach requires a postauricular incision with a complete mastoidectomy. Infralabyrinthine cells, which are limited by sigmoid sinus, third portion of the facial nerve, posterior semicircular canal, and jugular bulb, are opened. In our opinion, the IL approach is the best option because of no work on ossicular chain, the drainage tube is positioned in the mastoid cavity far from eardrum, no risk for the ICA and revision surgery is easy by postauricular incision. Reported complications include sensorineural hearing loss and facial nerve injury [20]. Infracochlear approach was strongly supported by House Ear Institute in Los Angeles (CA) [7,23,24] (Table 1). This approach provides adequate access to the PA, but requires maneuvers on tympanic membrane, enlargement of external auditory canal with following reconstruction of the tympanic plate with bone patè [7]. A significant step of this procedure is exposure of the ICA, which may be injured during drilling. The catheter is positioned close to the tympanic membrane and eustachian tube; revision surgery requires the elevation of the tympanic membrane. The main problem regarding IL and IC approaches is the presence of a high jugular bulb. In IC approach, if the jugular bulb is two thirds anterior to the mastoid tract of the facial nerve, it reduces the working window without possibility of putting a drainage tube. To avoid injury to the jugular bulb, particularly when it is dominant, we prefer to approach the lesions via IFTB as described by Fisch [25]. This approach presents adequate space for operation and preserves sensorineural hearing. These patients could be fitted with bone-anchored hearing aid to aid conductive hearing.

The IFTB consists of the following steps, which lead to some morbidity: (1) the blind sac closure of the external auditory canal with loss of conductive hearing and (2) exposure and retraction of mandibular condyle with section of V_3 branch of the trigeminal nerve, leading to some difficulty in mastication. The main advantages of this approach are direct vision and complete control of the intrapetrous ICA and the possibility of complete cyst removal from clivus and sphenoid sinus [26]. After tumor removal, the cavity is obliterated with abdominal fat. To avoid injuring the ICA, a detailed evaluation of radiologic investigations is done to estimate the relationship between tumor and carotid artery and to plan an eventual endovascular stent positioning [27]. In all cases with intrapetrous ICA involvement, the evaluation of cerebral circulation should be done preoperatively, and the possibility of the permanent ICA closure in case of intraoperative injury should be kept in mind [28].

The translabyrinthine (TL) and TO approaches are reserved for patient without serviceable hearing [7] and huge lesions. These 2 approaches allow a wide and direct exposure of the PA. We advocate combining the IFTB with the TL or TO approach for those lesions spreading anteriorly, which are in contact with the ICA and erode the clivus, to achieve the whole cyst wall removal and avoid recurrences.

If the PA CG extend into sphenoid sinus or abuts its posterior wall a transnasal endoscopic approach can be performed [18]. The transsphenoidal endoscopic approach is less invasive than those by lateral skull base and allows hearing preservation. It is safer in patients with well-pneumatized sphenoid sinus, and the patient can be followed up with office fiber-optic examination [29]. We do not advocate this approach in case of wide erosion of carotid canal because it is difficult to remove the entire cyst wall and, in case of IAC and dura involvement, because of risk of dural opening and postoperative cerebrospinal fluid leak. This may lead to increased risk of meningitis.

Despite use of hearing preservation techniques in PA CG treatment, hearing loss has been reported in 16% to 44% of cases after lateral skull base approaches [9,10].

Petrous apex CGs is termed as *recurrent disease* when the disease becomes symptomatic again or it shows growth on imaging. The presence of fluid secretion into an aerated cavity is not considered as recurrent lesion. In the literature, 14% to 16% of the recurrence rate is reported [7,16,17,30]. Several authors attributed this failure to the closure of either drainage catheter or fenestration, and they postulate that drainage combined with a permanent aeration of the cavity is the effective long-term treatment of CGs of the PA. The pseudocapsule left in place does not seem to have any prognostic effect on recurrence [6]. When only subtotal excision without stable cavity ventilation is done, patients generally have to undergo more than one operation [10]. Revision surgery has to be considered in case of growth occurs or clinical symptoms reappear.

5. Conclusion

Petrous apex CG knowledge is required to make differential diagnosis among other lesions of this area. Imaging with both CT and MR is required for diagnosis and to plan correctly the management. The petrous apex can be widely exposed through lateral skull base approach; the choice depends on preoperative hearing status, location, and extension of the lesion. For patients with good preoperative hearing, we recommend drainage via IL approach (Table 6). In deaf patients and those with extensive disease, TO approach combined with IFTB is recommended. Infratemporal type B is also indicated in case of good hearing and for lesions spreading anteriorly toward intrapetrous carotid artery, clivus, and sphenoid sinus. The transsphenoidal approach is indicated only in selected cases, when the lesion abuts the posterior wall of the sphenoid sinus without ICA, dura, and/or IAC involvement. We advocate wait and see policy for asymptomatic patients (Table 5). The goal of the treatment should not be complete removal of the cyst but the permanent ventilation of the cavity through a drainage catheter. The complete removal of the cyst wall with obliteration of the cavity is required in selected cases when it is not possible to put a drainage tube. Recurrence seems to be related with obstruction of the airflow in the cavity. If complete excision is accomplished, the cavity may be obliterated with fat, and the risk of recurrence is very low.

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GLUT-3 expression in laryngeal carcinoma: is really a prognostic indicator?

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Aim. **We describe our experience about cellular membrane glucose transporters (GLUT) as prognostic factors in laryngeal cancer through a retrospective evaluation of presence of GLUT 1-3 in specimens of squamocellular cancer of larynx**
Methods. **We assessed the expression of GLUT1 and GLUT3 in 50 formalin fixed, paraffin embedded biopsy specimens of laryngeal carcinoma. The antibodies used were anti-GLUT1 MYM and anti-GLUT3 MYG. Specimens were considered positive only when strong membrane-associated immunoreactivity was observed. Positive controls for MYM were erythrocytes present in each section, and for MYG were sections of human testis.**
Results. **Strong positive result for GLUT1 on 100% of cases and no positive issue for GLUT3.**
Conclusion. **Our results indicate that GLUT-3 is not useful as prognostic factor in this kind of tumor.**

KEY WORDS: Laryngeal neoplasms - Prognosis - Laboratory techniques and procedures.

In oncological research the main objective of several scientists is the identification of biomolecular markers as prognostic factor. The results are often controversial and only positive data are reported leading to incorrect evaluations.

Laryngeal cancer accounts for 25% of all head and neck cancers and 1% of all cancers. One-third of patients will eventually go on to die of their disease. This neoplasm is most prevalent in the sixth and seventh decades of life and has a 4:1 male predilection. This is thought to be due to the changing public acceptance of female smoking. This cancer is also more prevalent among lower socioeconomic classes, in whom it is usually diagnosed at more advanced stages, particularly in supraglottic carcinoma. Glottic cancer makes up 59% of laryngeal cancers, supraglottic 40%, and the rare subglottic carcinoma the rest. When observable, subglottic masses are most likely direct extensions of glottic carcinoma. The management of laryngeal cancer is actually based on clinical and radiological evaluation. The identification of prognostic factors could lead to a more appropriate and individualized treatment.

GLUTs are a family of cellular membrane glucose transporters, expressed in different normal tissues in several forms: GLUT1 is mainly expressed in erythrocytes and vascular tissues as well as in several malignant neoplastic tissue; it plays a very important role in the growth of some kind of tumors, including head and neck squamous cell carcinoma (HNSCC). GLUT3 is expressed in brain tissues and inflammatory cells. This markers were studied for several tumors and once also for larynx with promising results.[1] We tried to study our patients with the same protocol.

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Material and methods

A retrospective evaluation of 50 laryngeal specimens by immunohistochemistry was performed. We assessed the expression of GLUT1 and GLUT3 in 50 formalin fixed, paraffin embedded biopsy specimens of laryngeal squamocellular carcinoma (divided in three subgroups based on grading: 20 G1, 17 G2, 13 G3). The antibodies used were anti-GLUT1 MYM and anti-GLUT3 MYG. The adopted protocol was: deparaffinization of sections in xylene, rehydratation through reprising decreasing concentration of alcohol ending in phosphate-buffered saline (PBS), and microwaved in 10 mmol/L citrate-buffered, pH 6.0 for 15 minutes. Incubation in of sections with 2% normal goat serum in 1% bovine serum albumine (BSA) in PBS for 30 minutes at ambient temperature, washed in PBS, and incubation with MYM and MYG antibodies diluted 1:3000 and 1:1000, respectively, in 0.1% BSA in PBS for 60 minutes at ambient temperature. Sections were washed in PBS, and bound antibody was detected using Vectastain Elite ABC rabbit kit, with 3.3' diaminobenzidine as chromogen. Sections were counterstained with hematoxylin, dehydrated and mounted. Also negative control specimens were immunostained as described before, but instead of incubation with MYM or MYG, the section were incubated with the same concentration of the primary antibodies that were preincubated overnight at 4° C with 0.3 mg/ml of the immunizing peptides. Specimens were considered positive only when a strong membrane-associated immunoreactivity was observed Positive controls for MYM were erythrocytes present in each section, and for MYG were sections of human testis. Our Institutional Review Board approved the present study.

Results

We found a strong positive result for GLUT1 on 100% of cases: more than 50% of tumor cells in 70% of specimens. On the other hand we didn't find any positivity for GLUT3 among all specimens. No clinical/prognostic correlation was possible.

Discussion

The tissutal distribution of human GLUT3 protein is highly restricted (brain and testis) [2] and very low levels of GLUT3 are detectable in heart, placenta, liver and kidney.[3] A small amount of malignant tumors show GLUT3 over-expression (high grade gliomas,[4] testicular germ cell tumors, non-small cell lung carcinomas and rare cases of ovarian and gastric carcinoma).[5] Baer *et al.* reported GLUT3 expression in about 62% of their laryngeal carcinoma cases, with a percentage of positive case ranging from 1% to more than 75% of the neoplastic cells population.[1] Moreover, they underline an association with poor survival. Our results are in accordance with the only two studies we were able to find in the literature about GLUTs protein expression in HNSCC both reporting no positive immunostain for GLUT3.[6, 7] Only the presence of GLUT3 m-RNA is reported by Mellanen *et al.*[7] and this observation has been referred by Reisser *et al.* to the impossibility of distinguishing the inflammatory component-related mRNA from the tumor-cell related one in tissutal extracts.[6]

Conclusions

Even if a negative result was founded in our study, we believe that this may contribute to exclude some erroneous prognostic factor among the great number of those present in literature.

We agree with the consideration that GLUT3 immunostain couldn't be used to evaluate either prognosis or survival in laryngeal carcinoma, but further study will be useful to confirm these results.

Riassunto

Espressione GLUT-3 nel carcinoma della laringe: è realmente un indicatore prognostico?

Obiettivo. Gli autori descrivono la loro esperienza sui trasportatori di membrana cellulare del glucosio (GLUT) quali fattori prognostici nel cancro della laringe, attraverso una valutazione retrospettiva della presenza di GLUT 1-3 nei campioni di cancro a cellule squamose della laringe.

Metodi. E' stata valutata l'espressione di GLUT1 e GLUT3 in 50 campioni bioptici di carcinoma della laringe fissati in formalina e inclusi in paraffina. Gli anticorpi utilizzati sono stati anti-GLUT-1 MYM e anti-GLUT-3 MYG. I campioni sono stati considerati positivi solo quando si è osservata una forte immunoreattività membrana-associata. I controlli positivi per MYM erano gli eritrociti presenti in ogni sezione, mentre per MYG erano sezioni di testicolo umano.

Risultati. Si è avuta una forte positività per GLUT-1 nel 100% dei casi e nessun risultato positivo per GLUT-3.

Conclusioni. Gli autori concludono che i loro risultati indicano che, in questo tipo di tumore, GLUT-3 non è utile quale fattore prognostico.

PAROLE CHIAVE: Neoplasie laringee - Prognosi - Tecniche e procedure di laboratorio.

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Management of naso-septal deformity in childhood: Long-term results

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Abstract

Objective: The classical teaching advocates a conservative approach for children presenting with various naso-septal deformities. It may not be appropriate especially when it causes nasal obstruction to the growing child. This study has two main purposes: to contribute in identifying the correct selection criteria for surgical management of pediatric patients and in selecting the most appropriate surgical technique.
Material and method: We reviewed a series of 46 cases of post-traumatic septal and naso-septal deformity not managed promptly or with recurrence of nasal deviation, following bones fracture correction alone. The mean follow-up was 10 years.
Results: Patients with naso-septal deformity managed only by septoplasty had accentuation of nasal pyramid deformity; those treated by septorhinoplasty showed a good aesthetic and functional result after long-term follow-up.
Conclusion: Our series results demonstrated that the best results were obtained when we correct all evident alterations of nasal septum and pyramid at a single stage. Unsuccessful results seen in our first group suggest that immediate correction of septum alone with delayed management of nasal pyramid deformity leads to a poorer outcome.

Keywords: Septoplasty; Rhinoplasty; Childhood nasal deformity; Nasal trauma; Septal deviation

1. Introduction

Surgery for deformities of the nasal pyramid and septum during childhood is shrouded with controversies. Every surgical procedure of the nose at this young age may cause developmental arrest [1]. Even the results may not be long lasting in time, as the nose is a growing structure. A review of literature showed that there is neither any solution to this problem nor any guidelines for management, yet [2–5]. True incidence of septal deviation in childhood is unknown. Gray reported that in 58% of 2380 children studied a septal deviation was present [6]. Trauma is the most common cause for naso-septal deviation during childhood. Apart from this, cranio-facial growth irregularity may also cause the formation of a ridge between septal cartilage and vomeral bone, often associated with turbino-septal contact. Connate septal deformity due to trauma during intrauterine life or during transit in birth canal has also been reported as a cause for septal deviation, in the literature [7]. Surgical correction of septal deviation is indicated, irrespective of age, if such deformity causes nasal stenosis and oral breathing. Conservative management may worsen the nasal morphology, because deviated nasal septum may exert traction during growth, to normal alar and triangular cartilages not involved in previous trauma. Natural history of nasal trauma in early years demonstrates that, effect of a misdiagnosed trauma can appear during developmental age, and a nasal deformity due to unmanaged fracture becomes worse during growth. Cartilaginous arch involvement may cause narrowing of the nostril and height and/or length asymmetry of nasal pyramid. Delayed management of these alterations requires difficult surgical procedures with not always good results. Moreover the impaired nasal patency may exert negative effect on other systems and organs that play a role in the somatic and psychic development of the little patient.

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Such effects are seen mainly on the maxillo-facial skeleton and rib cage, but also seen as dysventilatory syndrome of middle ear and paranasal sinuses, vocal tract disorders and difficulty in sleep. This study has two main purposes: to contribute in identifying the correct selection criteria for surgical management of naso-septal deformities in pediatric patients and in selecting the most appropriate surgical technique for such patients.

2. Material and method

The study was designed as a retrospective review of charts of 46 patients with post-traumatic naso-septal deviation, not managed promptly or with recurrence of naso-septal deviation following initial bone fracture correction alone. The ethical committees of our institution have approved this study and subjects gave informed consent to the work.

Sixteen patients out of 46 affected by septal deviation, without nasal pyramid alterations, underwent septoplasty and were excluded from results evaluation.

Remaining 30 patients with naso-septal deviation were divided in two groups depending on surgical procedure performed (Table 1).

The first group included 16 patients suffering from septal deviation and nasal pyramid deformity. These patients too underwent septoplasty alone. The second group had 14 patients in them affected, as those in the first group, by nasal septum and nasal pyramid deformation. These patients were managed by septoplasty and partial rhinoplasty (i.e. reopening of old fracture lines and reduction). Patients were followed up post-operatively to see for any recurrence of septal deviation as well as the overall effect on the nasal pyramid. The senior author (CD) performed all operations.

The long-term efficacy of treatment was determined by: (1) evidence of residual septal deviation, (2) symmetry of nasal pyramid, and (3) subjective satisfaction of patients for both respiratory function and aesthetic appearance.

2.1. Surgical technique

The key in performing a conservative septoplasty is to obtain good visualization of the deviated segment of nasal septum during surgery. Unless we do this, there is always a risk of removing normal septal segments, apparently causing the deformity, using unnecessarily complex surgical techniques. Cottle's maxilla–premaxilla approach allows good exposure of all the septal segments [2,3]. We sometimes adopt the more extensive form of this approach, in children, which entails the formation and reunion of four tunnels. Sometimes it is sufficient to do just one anterior tunnel and one or two posterior tunnels (Fig. 1). The mucoperichondrium is dissected from quadrangular cartilage maintaining its integrity. Deformity of nasal septum can be due to parallel, perpendicular or oblique fractures with respect to the maxillary plane (Fig. 2). Occasionally parallel and oblique fractures coexist. Deformity due to parallel fractures can be usually corrected by inferior and posterior chondrotomy, leaving the quadrangular cartilage in situ (Fig. 3). This way we can maintain the articulation with triangular cartilage intact. Next step is to remove the inferior part of quadrangular cartilage, if it exceeds or is luxated towards the floor of nasal cavity. Later, depending on whether they are deviated or not, vomeral bone and perpendicular lamina of ethmoid are corrected. While performing all these steps, adequate care is taken to avoid any superimposition of septal segments (Fig. 3). Deviations due to perpendicular/oblique fractures with coexistent nasal pyramid deformities and obstruction of the valvular area, often requires total removal of the quadrangular cartilage, remodelling it outside the body and replacing it back in its place with external guide stitches (Figs. 4 and 5). These stitches are positioned in order to sustain the point where septum, nasal bone and triangular cartilage join together

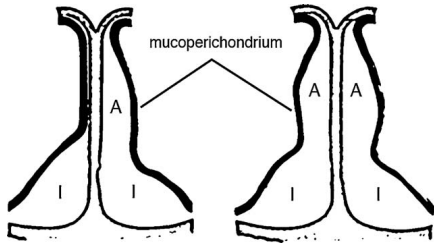


Fig. 1. Scheme of tunnels in nasal septal dissection. The mucoperichondrium is dissected from quadrangular cartilage forming three or four tunnels. (A) Anterior tunnel and (I) inferior tunnel.

Table 1
Groups of patients enrolled in this study depending on nasal septum and pyramid alterations and on surgical procedure performed with results obtained.

Groups	Number of patients	Mean age	Mean duration of observation	Deformity	Technique	Outcome
I	16	9 years (range 6–12 years)	12 years (range 8–15 years)	Naso-septal	Septoplasty	In 25% of cases recurrence of septal deviation Nasal pyramid deformity accentuated in 100%
II	14	9 years (range 6–12 years)	14 years (range 10–20 years)	Naso-septal	Septorhinoplasty	In 2 cases asymptomatic recurrence of septal deviation Good aesthetic result in all cases with symmetric nasal pyramid and growth of face

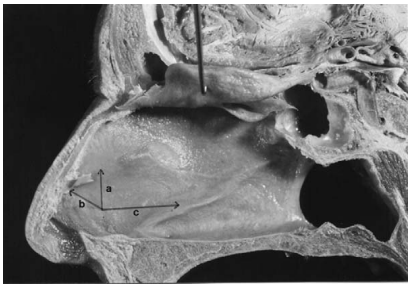


Fig. 2. Schematic draw on a cadaver nasal septum of fracture lines. (a) Vertical fracture, (b) oblique fracture, and (c) horizontal fracture.

(Cottle's ''K area''), the nasal tip and columella. Correction of posterior deviation is achieved by targeted removal of deviated bony segments, following posterior chondrotomy. Sometimes the deviated segment needs to be replaced back between the mucoperichondral/mucoperiosteal layers after proper remodelling, in order to reduce empty segments of the septum, thereby giving it better stability. If there is deviation of either bony or cartilaginous arch, we prefer to do a partial rhinoplasty. This latter is done by opening the old fracture lines with a thin osteotome, performing low to high basal osteotomies. Disarticulation of triangular cartilages from the quadrangular is the next step. This approach allows good correction of oblique septal deviations, that often include deformity of bony-cartilaginous junction, and helps in restoring normal valvular angle. The nasal dorsum is never lowered. If there is any caudal dislocation of the septum, a columellar pouch is created to receive the inferior aspect of quadrangular cartilage.

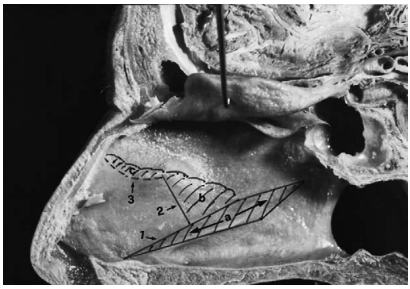


Fig. 3. Correction scheme: (1) inferior chondrotomy, (2) posterior chondrotomy, and (3) detachment of quadrangular cartilage and perpendicular ethmoidal lamina contact; (a) removal of deviated vomeral bone (spurs and ridge), (b) removal of posterior portion of quadrangular cartilage, and (c) correction of perpendicular ethmoidal lamina, to avoid any superimposition of septal segments.

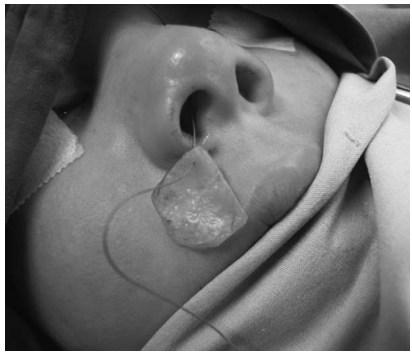


Fig. 4. Total removal of the quadrangular cartilage, remodelling and replacing it back in its place with external guide stitches–stitch in the ''K area''.

3. Results

The patients were aged between 4 and 12 years, and had a follow-up period of 7–20 years (mean follow-up 10 years).

The 16 patients suffering for isolate septal deviation had no objective growth deficit of the nasal pyramid during follow-up after operation. The subjective functional results in this series were also good. Only one patient (6.3%) had sub-luxation of inferior aspect of quadrangular cartilage.

The first group included patients aged between 6 and 12 years. Four patients (25%) presented with a recurrence of septal deviation. Nasal pyramid deformity was accentuated in all patients (Figs. 6 and 7).

The second group consisted of children aged from 6 to 12 years. All patients had acceptable aesthetic results (Figs. 8 and 9) and two patients (14.7%) presented with asymptomatic recurrence of septal deviation (Table 1).

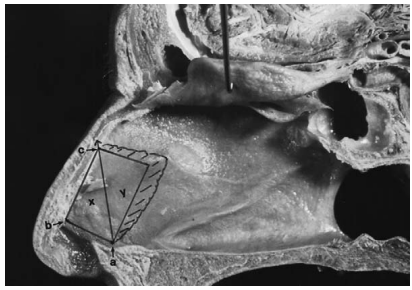
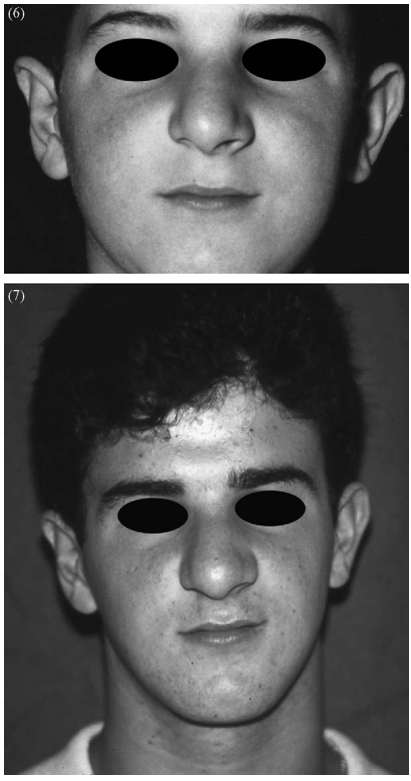
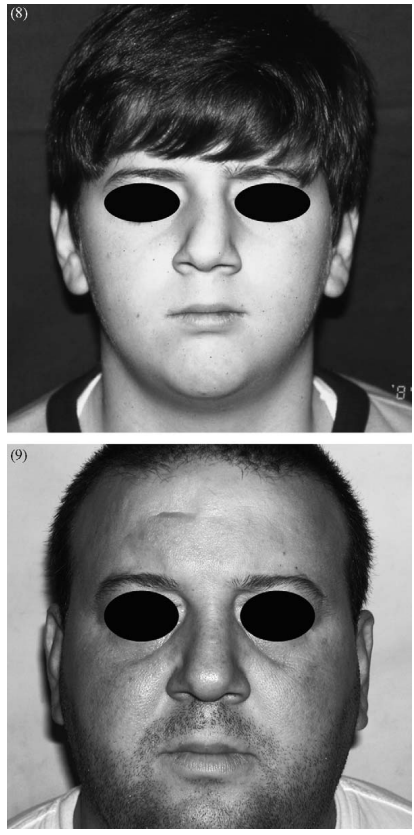


Fig. 5. Scheme of replacing the remodelled quadrangular cartilage. The cartilage may have a triangular (x) or quadrangular (y) shape. The new quadrangular cartilage have to: lay on nasal spine (a), sustain the nasal tip (b), and sustain the ''K area'' (c).



Figs. 6 and 7. Group I: 9 years follow-up; evidence of accentuated nasal pyramid deformity.



Figs. 8 and 9. Group II: 20 years follow-up; no deformity of nasal pyramid is present.

4. Discussion

It is known that nasal septum plays an important role in the harmonic growth of the face. Compelled oral breathing due to nasal obstruction during childhood, disrupts the normal development of skull base angle and consequently the normal maxillo-facial growth. This in turn can cause malocclusion and protrusion of maxillary bone, leading to a condition called as class II skeletal deformity, comparable to ''facies adenoidea'' [8,9]. If septal deviation occurs during the rapid phase of development, it may cause irregular growth of cartilaginous structure of the nasal vault including in those structures that were not originally affected by the trauma. Trauma may involve fracture of either bony or cartilaginous vault. If such injuries are not corrected at an early stage, it will lead to consolidation of the defect, thereby affecting the aesthetics and function of the facial skeleton. Because of all these reasons, if on the one hand surgical management seems indicated in cases of difficult nasal breathing, on the other hand there are still controversies about the timing of management, the surgical technique and the extent of surgical approach. It is our opinion that timing of the intervention should not be related to age but to the grade of nasal obstruction. There are different opinions regarding surgical approach and surgical technique to be used in these patients, they are: early correction of septal deviation and scheduling the rhinoplasty after the development is complete; or performing septorhinoplasty at a single stage. In our

opinion treatment of nasal septum and pyramid deformity have to be done at the same time. Just like how a fractured nasal bone has to be treated promptly, a fractured nasal bone consolidated in abnormal position should also be replaced in the correct position after reopening the old fracture lines. If we follow this protocol, long-term results on completion of nasal development should be the same as with prompt treatment of fractured nasal bones. Cottle's approach (maxilla–premaxilla) is the best option, in our experience. This is because, it allows us to perform targeted dissection of deviated nasal septum and, if necessary, a complete exposure of the entire septum. Jugo reported that the conservative Cottle's technique caused a high incidence of recurrent deviation due to limited surgical field and incomplete linkage between quadrangular and alar cartilages [10]. Such observations imply poor adherence of quadrangular cartilage to the surrounding structures and, during the cicatrisation process, may favour recurrence of the deviation. As a solution to such problems, he proposed, a total reconstruction of nasal septum by an external approach defined as ''decortication'', adopted first time by Hage [11]. Such techniques demand long surgical time and extensive dissection. Therefore, it should be reserved only for those rare cases having severe deformity of nasal septum [10]. Another technique reported in literature, used by Halstead in 1910 for approaching pituitary gland, is done through a sublabial incision [12]. Healy proposed an open septoplasty by sub-labial approach to manage nasal bone fractures, preserving as much cartilaginous part of the septum as possible [13]. Cases reported in their study showed good reduction of fracture without any disturbance in growth, during follow-up. In a study based on anthropometric measurements of 28 patients affected by severe anterior septal deviation and managed by external septoplasty (removal, remodelling and repositioning of quadrangular cartilage), Bejar reported that such technique had no effect on naso-facial growth, but may disturb the length and development of the nasal dorsum [14]. In our experience [15] reconstructive septal surgery does not cause significant growth retardation in children if the mucoperichondrium is preserved. El-Hakim et al. reported the same opinion using an open approach [16].

Yilmaz was of the opinion that external technique for septoplasty offers no additional advantage as against the hemitransfixion–transfixion incision, but also is more traumatic for the nasal growth [17]. Therefore the less traumatic hemitransfixion–transfixion incision should be preferred in every condition of nasal septum, except in cases of severe septal deviations coexistent with nasal tip deformity. We advocate the hemitransfixion incision approach maintaining the mucoperichondrium integrity as described before.

The objective outcome evaluation by rhinomanometry and acoustic rhinometry has not yet proven to be diagnostically useful, despite fervour of some centers [18]. For this reason we believe, in accordance with other authors [18,19], that patients subjective feelings is the main outcome measurement of surgery success.

5. Conclusion

Obstructing deviation of nasal septum in childhood is an absolute indication for surgical correction. Our series results demonstrated that the best results were obtained when we correct all evident alterations of nasal septum and pyramid at a single stage, irrespective of age. Unsuccessful results seen in our second group suggest that immediate correction of septum alone with delayed management of nasal pyramid deformity leads to a poorer outcome. In such cases the septum, even when adequately corrected, continues to lie between deviated structures and during growth follows a deviated course. Moreover, during the rapid developmental phase (pubertal period) the growth itself can cause additional alteration of already deviated structures. The patients subjective feelings is the main outcome measurement of surgery success.

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Uvulopalatopharyngoplasty with tonsillectomy in the treatment of severe OSAS

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Key-words. Snoring; obstructive sleep apnea; tonsillectomy, uvulopalatopharyngoplasty; surgery

Abstract. *Uvulopalatopharyngoplasty with tonsillectomy in the treatment of severe OSAS. Objective*: To establish the efficacy of uvulopalatopharyngoplasty with tonsillectomy for treating selected patients with severe obstructive sleep apnea syndrome.
Methodology: Retrospective study of patients who underwent clinical/instrumental evaluation and surgical treatment.
Setting: University ENT division with a tertiary snoring referral center.
Participants: Twenty-two patients with normal body mass index affected by severe obstructive sleep apnea syndrome.
Main outcome measures: Pre- and post-operative cardiopulmonary monitoring during sleep, daytime sleepiness evaluation, post-treatment complication recording.
Results: Complete response to therapy was obtained in 78% of patients. Four patients had relief of symptoms but retained apnea/hypopnea index scores greater than 5.
Conclusions: Uvulopalatopharyngoplasty associated with tonsillectomy can be employed safely to treat patients with normal body mass index who suffer from severe obstructive sleep apnea.

Introduction

The prevalence of habitual snoring in adult males and females is about 24% and 14%, respectively.[1] Among these, obstructive sleep apnea syndrome (OSAS) affects 4% of men and 2% of women. The pathophysiology of this condition is thought to be excessive narrowing of pharyngeal airway that also collapses during inspiration, resulting in increased negative intrathoracic pressure, which in turn exacerbates the condition. When complete obstruction occurs, the drastic reduction in airflow to the lungs arouses the patient from sleep.

Symptoms of OSAS are generally vague. Neurocognitive symptoms such as memory and learning deficits may be present, and patients can exhibit daytime fatigue due to loss of sleep or hypoxia itself. In these patients, cardiovascular diseases, such as hypertension and stroke, are related to sleep apnea secondary to increased intrathoracic pressure.[2]

As initial therapy, life-style modifications, such as avoiding alcohol and drugs and weight reduction, are encouraged. When medical treatment is indicated, continuous positive airway pressure (CPAP) therapy during sleep or the use of jaw/tongue advancement devices may be effective. If these prove unsuccessful, surgical options are available. The choice of surgical procedure depends on the site and degree of obstruction. Uvulopalatopharyngoplasty (UPPP) is one of the most common surgical interventions used to treat OSAS. Originally proposed by Ikematsu,[3] it was popularized in 1980 by Fujita *et al.*[4]

The aim of the present work was to establish the efficacy of UPPP with tonsillectomy in the treatment of selected patients with severe OSAS.

Materials and methods

We retrospectively reviewed the charts of all patients with OSAS who were treated surgically in our department between January 2000 and December 2005. A detailed history of all patients was recorded. All patients underwent a complete head and neck examination, static and dynamic endoscopic evaluation of the upper aerodigestive tract, Muller maneuver evaluation, body mass index (BMI) calculation, and cardiopulmonary monitoring (CPM) during sleep. The parameters evaluated during CPM were 1) apnea/hypopnea index (AHI),

Table 1

Tonsillar Hypertrophy, Friedman's grading

Grade	Clinical Features
0	Previous tonsillectomy
1	Tonsils inside the tonsillar fossa hidden behind the anterior palatal pillar
2	Tonsils partially outside the tonsillar fossa occupying 25% of the oropharynx
3	Tonsils occupying 50% of the oropharyngeal space
4	Tonsils occupying more than 75% of the oropharynx, almost meeting in the midline

Table 2

Grading of oropharyngeal (retropalatal) obstruction on Muller's maneuver

Grade	Endoscopic Features
1	Minimal movement of pharyngeal wall with space reduction between 0-49%
2	Pharyngeal wall movement with space reduction between 50-74%
3	Pharyngeal wall movement with space reduction between 75-99%
4	Complete occlusion of pharyngeal lumen

calculated as the summation of total events per hour; 2) oxygen desaturation index (ODI); and 3) saturation value reached during sleep. Apnea was considered as cessation of breathing for at least 10 seconds and hypopnea was defined as reduction of breathing effort with 4% desaturation. We evaluated the daytime sleepiness in all patients based on the Epworth's sleepiness scale questionnaire.

Patients were selected for the study based on the following parameters: 1) OSAS grade severe (AHI > 30) on CPM; 2) Palate position grade I-II according to Friedman's classification[5]; 3) Palatal tonsillar hypertrophy grade 2-4 in accordance with Friedman's grading[6] (Table 1); 4) Oropharyngeal (retropalatal) collapse grade 3 (50-75% of space reduction) to grade 4 (collapse > 75%) on Muller's maneuver (Table 2); 5) BMI < 28. Patients who did not meet the above criteria were excluded from the study. Patients receiving CPAP therapy were excluded from the study.

Twenty-two patients were included in the study. All 22 patients had been treated surgically with UPPP plus tonsillectomy under general anaesthesia. CPM during sleep was repeated three months after the surgical intervention. Post-operative apnea/hypopnea index and ODI scores below 5 indicated a complete response to therapy. An improvement in AHI exceeding 50% and an AHI less than 20 was considered successful treatment.[7,8] Post-operative complications and chronic adverse effects (hemorrhage, palatal insufficiency, rhinolalia, and disgeusia) were recorded.

Our institutional review board approved the study protocol. Informed consent was obtained from all patients.

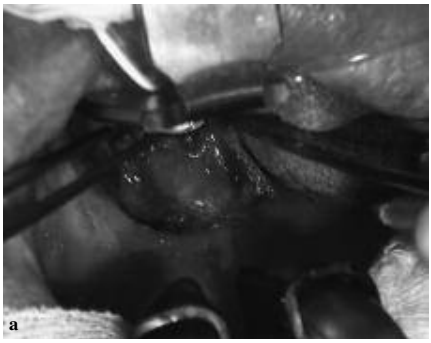
Surgical technique

Tonsillectomies were performed using the cold dissection method. The oropharyngeal aspect of the soft palate mucosa was incised 25-mm distal to the posterior end of the hard palate. The mucosa was then dissected off the underlying muscle up to the free edge of the soft palate and then removed, leaving a myo-mucosal flap of the soft palate mucosa on the nasopharyngeal side (Figure 1). The free soft palate mucosal edge of the nasopharyngeal side was then sutured to the original incision line on the palatal side (Figure 2). This process increases the velopharyngeal inlet.

Results

Sixteen males and six females affected by OSAS were included in the study. The mean age of the patients was 47 years (range 24-58). The median pre-operative and post-operative scores are shown in Table 3. Mean follow up was 31 months (range 20-38; Figure 3). According to Friedman's staging system,[5] 18 patients were stage I and four were stage II. All of the patients classified as stage II presented with tonsil size grade 2 and palate position 1-2.

Complete response to therapy was obtained in 17 patients (78%). Four patients had relief of symptoms but retained AHI and ODI scores greater than 5 (Table 3). Thus, treatment was successful in 21 of 22 patients (96%). One patient (4%) was classified as not deriving any benefit from treatment because their post-operative AHI score was 21. All patients were discharged on the second post-operative day. Subjective pain and swallowing discomfort disappeared in all patients by the eighth post-operative day (median 6; range 6-8). Return to normal diet was used as an index of swallowing improvement. No patients complained of velopharyngeal insufficiency.



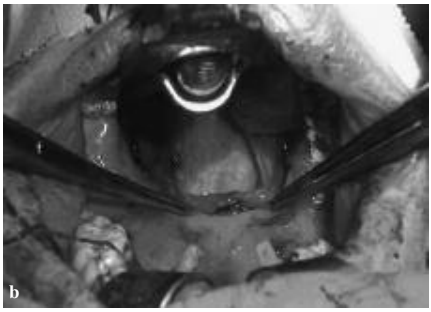


Figure 1
Dissection of the mucosa off the underlying muscle up to the free edge of the soft palate, creating a myo-mucosal flap of the soft palate mucosa on the nasopharyngeal side.

Figure 2
Suturing the palatal flap using an absorbable suture

Three patients experienced persistent dry mouth for a mean of 13 months. Two patients had a slight subjective taste disturbance, which recovered spontaneously six months after surgery.

Discussion

In the last decade, attention to persistent snoring, particularly when associated with apnea syndrome, has increased tremendously. OSAS is a relatively common disorder that affects about 4% of adults.[1] It is often ignored by the patients, which can result in serious complications and even endanger the patient's life. Quality of life in such patients is generally poor as compared to that of the general population, because of daytime somnolence and its associated consequences, such as increased risk of accidents while driving and at work. Male sex is known to be a major risk factor for rhonchopathy, this is well explained by the higher prevalence of OSAS in men.[9]

Until 1990, the procedures used to diagnose OSAS were inadequate for establishing the precise site of obstruction. Therefore, patient selection for surgery was not accurate, which affected the eventual outcome of surgery.

Currently, there are various therapeutic options for managing OSAS. The first approach is to encourage the patient to reduce their body weight, improve their sleep hygiene, and avoid alcohol and sedative consumption just before sleep. Medical treatments consist of CPAP devices and oral appliances that advance the mandible to allow the airway to remain patent. Patients show a low compliance with CPAP use and often discontinue or interrupt the treatment for various reasons.

Surgery is generally considered a second-line option. Several techniques have been described in literature, based on the grade of OSAS. Surgery can be performed on either an inpatient or an outpatient basis, depending on the severity of sleep apnea and the surgical procedure chosen.

Historically, lack of understanding of the pathophysiology of OSAS contributed to the erroneous application of some surgical techniques, such as removing

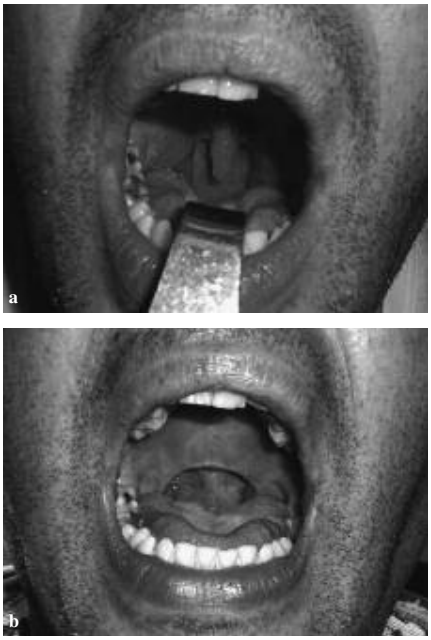


Figure 3
A patient affected by severe OSAS stage II who was treated with UPPP and tonsillectomy. a) Pre-operative photograph. b) Post-operative features after 6 months of follow-up.

muscles of the soft palate along with its mucosa in order to debulk the soft palate, which invited poor results. Implementation of these types of procedures was likely main reason behind the high prevalence of complications and failure in the treatment of OSAS. Advances in diagnostic devices have allowed for more precise evaluation of patients who suffer from snoring. Endoscopic evaluation of upper respiratory tract collapse on Muller's maneuver and its grading have enabled more effective surgical approaches by excluding those patients with hypopharyngeal (retroglossal and lateral wall) collapse from UPPP.[10]

For young patients in good general health, we propose surgical correction of the predominant cause of OSAS. Accurate patient selection and use of the least invasive technique that gives the best success rate are paramount for success. UPPP is a procedure with a reasonably short post-operative recovery period that is characterized by swallowing difficulty and pain.[7] In our series, all patients had complete resolution of pain and improvement in swallowing discomfort by the eighth post-operative day. The long-term success rate of UPPP ranges from 50% to 80%.[11-14] In a recent meta-analysis, Sher *et al.*[11] found an overall success rate of 40.7%. The success rate was related to the level of obstruction and was 52.3% in patients with only palatal narrowing or collapse, dropping to just 5.3% in patients with a retro-glossal obstruction with or without palatal component.[11] Because this surgery is performed in patients who have experienced labored breathing for a very long time before surgery, they should be observed closely following surgery. However, the views regarding post-operative observation vary. Spiegel and Raval[15] suggested monitoring patients for only 2-3 hours after surgery and then discharging them home. Kezirian *et al.*[16] reported a nonfatal complications rate of 1.5% and mortality of 0.2% in a series of more than 3000 cases of UPPP.

Great care should be exercised when intubating and extubating these patients for general anaesthesia, because patients with OSAS typically have difficult

Table 3
Cardiopulmonary monitoring and daytime sleepiness variations

	Pre-operative median score (range)	**Post-operative median score (range)**
Apnea/Hypopnea index	45 (40-56)	4 (3-21)
Oxygen desaturation index	39 (36-43)	4 (4-24)
Sleeping oxygen saturation	71% (68-80)	92% (80-95)
Epworth sleepiness scale	15 (12-17)	5 (5-9)

airways. Riley *et al.*[17] reported that most post-operative complications were related to hypertension and at that only six of 182 patients had a post-operative saturation less than 90% (possibly attributable to narcotics used for general anaesthesia). It is mandatory that regular CPM be performed during surgical follow up in order to assess for residual disease and evaluate treatment efficacy. Indeed, the risk of developing cardiovascular complications in patients with unresolved OSAS is nearly 50%.[18]

UPPP is associated with both short-term and long-term complications. However, as noted by Sher *et al.*,[11] it is impossible to determine the true rate of complications because of the majority of papers on UPPP have not reported the presence or absence of complications. The more common complications described in literature are velopharyngeal insufficiency, post-operative bleeding, nasopharyngeal stenosis, and voice change. In our study, the main complications encountered were taste disturbance in two patients and mouth dryness in three patients. Damage to taste buds on the soft palate during UPPP might be a factor in post-operative taste function impairment, which is observed in 7-10% of patients.[19] However, taste function may recover over time, as was observed in our patients.

UPPP is contraindicated in those patients with only retroglossal obstruction. In a previous report, negative predictors of outcome were combined palatal and retroglossal obstruction and previous tonsillectomy.[13] A pharyngeal surgical approach may be recommended for patients with severe grade OSAS. As demonstrated by our data, a greater than 50% reduction of the pre-operative AHI was obtained in 96% of patients with severe OSAS, indicating good efficacy of UPPP plus tonsillectomy. These data coincide with those reported by Friedman *et al.*,[6] who obtained an 80% success rate in stage I patients managed with UPPP. In our opinion, tonsillectomy should be performed during the same surgical session in a day-surgery regimen.[20] Friedman *et al.*[21] asserted that in patients with palatal obstruction who have undergone previous tonsillectomy, it might be better to perform a Z-palatoplasty during UPPP.

It is known that a BMI greater than 27 drastically reduces the efficacy of UPPP, even with combined genioglossus advancement and hyoid suspension. Symptomatic relief by UPPP is known to deteriorate during long-term follow-up. In a survey of patients at 17-20 years post UPPP, the percentage of symptomatic relief had decreased significantly.[18] Weight gain was the main predisposing factor for recurrence of symptoms.

Conclusions

Patients suffering from OSAS should be evaluated using a multidisciplinary approach. Determining the site and grade of obstruction is mandatory for selecting the appropriate treatment strategy. Although surgery remains a second-line option, it can help to reduce snoring and the frequency of sleep apnea episodes. Our data suggest that UPPP associated with tonsillectomy can be safely employed to treat even those patients with severe OSAS with stage I-II disease and normal BMI.

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Cystic Vestibular Schwannoma: Classification, Management, and Facial Nerve Outcomes

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Objective: Review of postoperative morbidity and facial nerve outcomes of cystic vestibular schwannoma (CVS) patients compared with solid vestibular schwannoma (SVS) patients and a proposal for a new CVS classification system.
Study Design: Retrospective review.
Setting: Tertiary care facility.
Patients: Ninety-six patients with surgically treated CVS (1998–2008). Outcomes were assessed in a subpopulation of 57 patients with greater than or equal to 1-year follow-up compared with 57 SVS patients.
Intervention: Fifty-six CVS patients underwent the enlarged translabyrinthine approach with transapical extension (Type I), and 1 patient underwent a transcochlear/transzygomatic approach.
Main Outcome Measure: Preoperative and postoperative (at least 1 yr) House-Brackmann facial nerve (HBFN) grade evaluation.
Results: Favorable HBFN grades (I–III) were observed in 46 (81%) CVS patients, and unfavorable HBFN grades (IV–VI) were seen in 11 (19%) CVS patients. Comparison of tumor size and 1-year HBFN grades showed significant, moderate to strong, Pearson correlation (0.38). Comparison of long-term facial nerve outcomes with a sample of 57 matched SVS patients showed no significant difference ($p = 0.74$). When the tumor was adherent to the facial nerve and a dissection plane could not be developed between the cyst wall and the nerve, only subtotal resection could offer the CVS patients a normal facial nerve outcome.
Conclusion: In most CVS cases, complete resection should be foreseen. Central and thick-walled tumors can be removed in almost all cases. However, when peripheral thin-walled, adherent, cystic tumors are confronted and the cysts are medially or anteriorly located, we recommend subtotal resection, leaving portions of the cyst walls on neurovascular structures and on the facial nerve. This surgical strategy allows us to improve facial nerve outcomes and to reduce complications. **Key Words:** Acoustic neuroma—Cystic vestibular schwannoma—Facial nerve outcomes—Translabyrinthine approach—Vestibular schwannoma.
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Vestibular schwannomas account for 6 to 8% of all intracranial tumors and 80% of tumors that arise in the cerebellopontine angle (CPA) (1). These lesions can be divided into 3 groups: homogeneous, heterogeneous, and cystic. Cystic vestibular schwannomas (CVS) differ from solid schwannomas by their rapid growth, frequent involvement of facial nerve, and somewhat unpredictable biologic behavior. Cystic vestibular schwannomas have been estimated to represent anywhere from 5.7 to 48% of all vestibular schwannomas, with more recent studies in favor of numbers closer to 10% (2–5). However, the true incidence is debatable because there are various descriptions of what constitutes a CVS. (2,5–7).

Preoperatively, CVS can be identified with magnetic resonance imaging (MRI). Fluid-filled portions of these lesions seem hyperintense on T2-weighted images, whereas solid portions are isointense or hypointense with the brain on T1-weighted imaging. The solid tumor component and the cystic wall are enhanced with gadolinium (8,9) (e.g., Fig. 1B and D). Enhancement of the cyst wall is an imaging characteristic that can be used to differentiate CVS from arachnoid cysts and epidermoids (8).

In the absence of a cystic component, the growth rate for these tumors is known to range from approximately 2 to 6 mm/yr (10). Some authors think that only a limited number of solid vestibular schwannomas (SVS) grow

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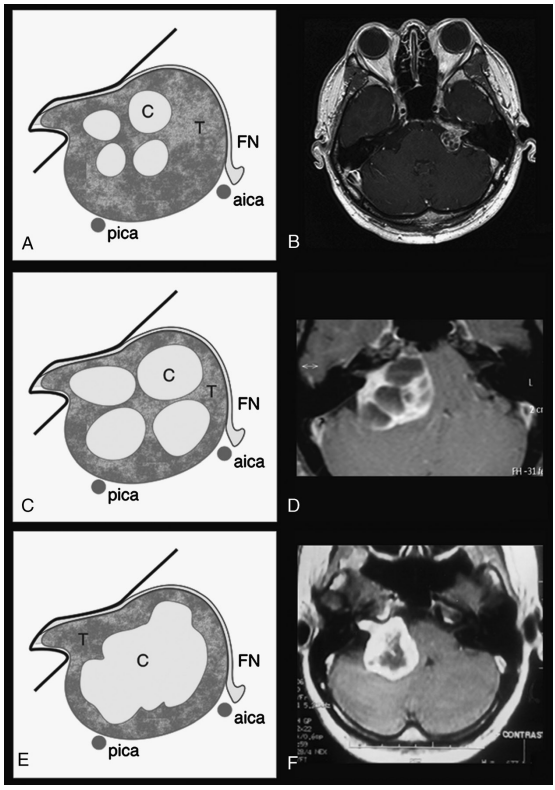

FIG. 1. Schematic illustrations and representative MRI examples of each subtype of Type A CVS according to the proposed classification in Table 1. Type A1 (*A*, *B*). Type A2 (*C*, *D*). Type A3 (*E*, *F*). Cyst (*C*), solid tumor (*T*), facial nerve (*FN*), *PICA*, and *AICA*. Images *B*, *D*, and *F* are T1-weighted axial images with contrast.

continuously (11). In the presence of a cyst, there can be rapid expansion of the lesion, brainstem compression, and hydrocephalus associated with neurologic symptoms (12). Rapid CVS enlargement can also occur as a consequence of intratumoral hemorrhage (13). In addition, cyst expansion and neurologic impairment have also

TABLE 1. *Proposed classification for CVS is first based on overall cyst location (central or peripheral) and cyst wall thickness (thick or thin)*

Type	Overall cyst location/cyst wall thickness	Subtype	Definition
A	Central and thick wall	1	Polycystic (multiple small intratumoral cysts with a thick cyst wall)
		2	Polycystic (multiple moderate size intratumoral cysts with a thick cyst wall)
		3	monocystic (single large cyst with a thick or thin cyst wall)
B	Peripheral and thin wall	1	Anterior
		2	Medial
		3	Posterior
		4	Combined

Type A lesions are further subdivided by the cyst characteristics (polycystic or monocystic) and size. Type B lesions are further classified according to cyst orientation with respect to the internal auditory meatus (anterior, medial, posterior, or a combination of these locations).

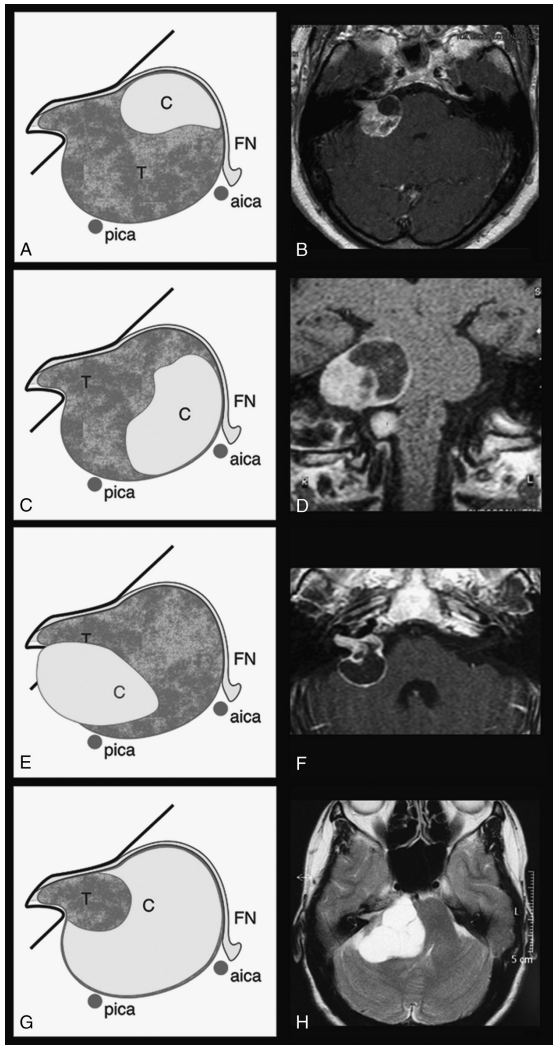

FIG. 2. Schematic illustrations and representative MRI examples of each subtype of *Type B* CVS according to the proposed classification in Table 1. Type B1 (*A*, *B*). Type B2 (*C*, *D*). Type B3 (*E*, *F*). Type B4 (*G*, *H*). Cyst (*C*), solid tumor (*T*), facial nerve (*FN*), *PICA*, and *AICA*. Magnetic resonance images *B*, *D*, and *F* are T1-weighted axial images with contrast. Magnetic resonance image *H* is a T2-weighted image.

been documented after attempted treatment with radiosurgery (12,14).

Contemporary treatment options for CVS include observation, surgery, radiosurgery via one of a number of modalities, and/or a combination of surgery and radiosurgery. Because of the unpredictable growth patterns and reported cases of cyst enlargement after radiosurgery, complete or subtotal microsurgical resection is often recommended for CVS (5,15). However, literature suggests that facial nerve outcomes after CVS resection have been less favorable in comparison to results after removal of SVS (3,5,16,17).

In this study, we present our series of surgically treated CVS. We review postoperative morbidity and facial nerve outcomes and compare these results with those from SVS resected during the same period at our institution. Finally, we propose a classification system for CVS that might be used to guide surgeons in the management of these tumors to optimize surgical results.

MATERIALS AND METHODS

We retrospectively reviewed all cases of vestibular schwannomas operated in our center between January 1998 and May 2008. Patients were included in this study if they had a CVS and were treated at our institution during this period. A tumor was labeled as a CVS if it satisfied 2 requirements: presence of hypodense/hypointense areas on MRI and intraoperative identification of cystic elements. All CVS patients treated at our institution during this period underwent surgery by the same surgeon (M.S.). Of 1,416 patients that underwent vestibular schwannoma resection during this period, we identified 96 with CVS. Fifty-seven of these CVS patients had greater than or equal to 1 year of documented follow-up. Ninety-six SVS patients were randomly selected from our vestibular schwannoma database for comparison on facial nerve outcomes, morbidity, and mortality in the following manner. To compare CVS with SVS, solid tumors were first stratified according to size and later selected through random computer assignment. Tumor size was stratified as less than 1.0, 1.1 to 2, 2.1 to 3, 3.1 to 4, and 4.1 to 5 cm. The number of SVS patients selected from each tumor size group equaled the number of CVS patients in each group.

In 1998, we began to photographically record preoperative and postoperative MRI scans and preoperative and postoperative facial nerve function of all vestibular schwannoma patients. The photographic MRI record allowed us to accurately identify patients for this study, develop a proposed classification system for CVS, and separate tumors based on this classification system. To evaluate facial nerve function, photographs were taken of patients with their face at rest, closing their eyes, raising their eyebrows, and smiling. Analysis of facial nerve results was limited to those patients with greater than or equal to 1 year of follow-up.

The following variables were recorded from each chart: patient demographics, tumor size and location, cyst position, cyst wall thickness, surgical strategy, operative findings, and complications. Preoperative and postoperative House-Brackmann facial nerve (HBFN) grade were also recorded (18). Any statistical analysis was completed using GraphPad Instat.

All patients underwent preoperative gadolinium-enhanced MRI of the brain and internal auditory canals. These images were used to determine tumor size, cyst position, and cyst wall thickness. Tumor size was measured at the largest extrameatal tumor diameter on the preoperative MRI (6). Tumors were first classified based on overall cyst location and cyst wall thickness: central and thick-walled (Type A), or peripheral and thin-walled (Type B). Type A lesions were then subdivided by cyst characteristics (polycystic or monocystic) and size. Type B lesions were classified according to cyst orientation with respect to the internal auditory meatus (anterior, medial, posterior, or a combination of these; Table 1). According to the proposed classification, schematic illustrations and representative MRI examples of each subtype of CVS are provided in Figures 1 and 2.

The amount of tumor removal during initial operation was used to divide CVS patients into 2 groups: complete or subtotal resection (>5% of tumor left; Fig. 3) (6). In cases of subtotal resection, the location of adherent remaining tumor was recorded at the time of the operation at 1 or a combination of up to 3 locations: facial nerve, brainstem and intracranial vessels (anterior inferior cerebellar artery [AICA]), posterior inferior cerebellar artery, or superior cerebellar artery. The type of resection was determined preoperatively or intraoperatively. If the operative goal was complete tumor resection and the involved portion of facial nerve was accidentally interrupted, an attempt was made at facial reanimation. This was accomplished with either an interposition nerve graft or a hypoglossofacial anastomosis (19,20). If the operative goal was subtotal

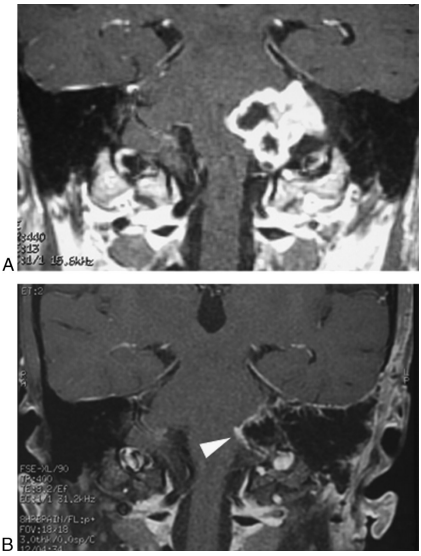

FIG. 3. Subtotal left CVS resection example on coronal and axial MRI. *A*, Preoperative coronal T1-weighted image with contrast showing left CVS. *B*, Postoperative T1-weighted image with contrast, showing subtotal resection, left cystic tumor remnant is marked with the *white arrowhead*.

TABLE 2. *Summary of all CVS patients that underwent surgery at our institution during the period from January 1998 to May 2008*

CVS patients, n			
Period	1998–2003	2004–2008	1998–2008
Patients	26	70	96
Male	12	34	46
Female	14	36	50
Right-sided tumors	13	34	47
Left-sided tumors	13	36	49
Complete resection	26	51	77
Subtotal resection	0	19	19
Nerve graft	1	8	9
Hypoglossofacial anastomosis	1	2	3
>1 yr of follow-up	16	41	57

The patients are grouped according to date of operation. After 2004, there is a tendency toward subtotal resection (to leave the cyst wall in place).

TABLE 3. *Summary of all SVS patients randomly selected from groups of patients stratified for tumor size (January 1997 to February 2007)*

SVS patients, n	
Period	1998–2008
Patients	96
Male	42
Female	54
Right-sided tumors	44
Left-sided tumors	52
Complete resection	80
Subtotal resection	16
Facial nerve graft	4
Facial nerve end-to-end anastomosis	1
Hypoglossofacial anastomosis	4
>1 yr of follow-up	96

The mean tumor size was 2.7 cm (range, 0.2–5 cm).

tumor resection, portions of the cyst wall were left in place when it was not possible to develop a dissection plane between the facial nerve, brainstem, and/or major vessels.

RESULTS

Patients

Between 1987 and May 2008, we completed 1,750 vestibular schwannoma resections. Among 1,416 patients that underwent vestibular schwannoma resection at our institution during the period ranging from January 1998 to May 2008, 96 (6.8%) patients underwent some form of CVS resection. Preoperatively, all CVS patients had normal facial nerve function. A summary of all surgically treated CVS patients from this period is provided in Table 2. This table shows patients grouped according to date of operation, demonstrating a tendency from 2004 on toward more subtotal resections.

Complications

Table 3 provides a summary of the SVS group. Postoperative complications that were identified among the group of 96 CVS patients and the 96 SVS patients are listed in Table 4. There was no mortality in either group of patients. The total percentage of all complications directly related to the schwannoma resection was only slightly greater in the CVS group (6.25%) compared with the SVS group (5.21%).

1-Year Follow-Up

Fifty-seven CVS patients had greater than or equal to 1 year of documented follow-up at our institution. The bulk of the analysis presented here is based on these 57 patients unless otherwise stated. Of the 57 CVS patients, 29 were men and 28 were women, whereas the average age was 51 years (median, 50 yr; range, 27–80 yr). Fifty-seven SVS patients with greater than or equal to 1-year follow-up were randomly selected from the group of 96 SVS, first according to CVS tumor size and later by computer assignment. Of the 57 SVS patients, 22 were men and 35 were women, whereas average age was 49 years (median, 47 yr; range, 25–79 yr).

Tumors

The average CVS size was 2.8 cm (median, 3 cm; range, 0.8–5 cm). Cystic vestibular schwannomas were grouped according to the proposed classification system presented in Table 1: Type A, 25 (44%; Type A1, 15 [26%]; Type A2, 6 [11%]; Type A3, 4 [7%]) and Type B, 32 (56%; Type B1, 3 [5%]; Type B2, 8 (14%); Type B3, 5 (9%); Type B4, 16 [28%]). Average SVS size was 2.8 cm (median, 3 cm; range, 0.8–5 cm).

Surgical Strategy

Fifty-six CVS patients underwent the enlarged translabyrinthine approach with transapical extension (Type I), and 1 patient underwent a transcochlear/transzygomatic approach (21,22). Forty-seven CVS (82%) patients underwent complete resection, whereas 10 (18%) underwent subtotal resection. Among patients that underwent complete tumor resection, 7 required interruption of the facial nerve and grafting, and 2 required hypoglossofacial anastomosis. Among patients that underwent subtotal resection, the tumor was left in contact with the facial nerve in 8 cases (2 facial nerve, 5 facial nerve and brainstem, 1 facial nerve, brainstem, and vessels). The tumor

TABLE 4. *Cystic vestibular schwannoma versus SVS complications and mortality*

Complication	CVS (n = 96)	SVS (n = 96)
Abdominal fat graft site hematoma	1	0
Cerebrospinal fluid leak	1	0
Intracranial hemorrhage	1	0
Lower cranial nerve deficit	2	1
Sigmoid sinus thrombosis with concurrent ipsilateral vision loss	0	1
Sixth nerve palsy	1	1
Subdural hematoma	0	2
Transient ischemic attack	1	0
Mortality	0	0
Total complications directly related to the schwannoma resection, n (%)	6 (6.25)	5 (5.21)

TABLE 5. *57 CVS patients with greater than or equal to 1-yr follow-up grouped by HBFN*

HBFN	n	%	Mean tumor size, cm
I	15	26	2.3
II	4	7	2.9
III	27	47	2.7
IV	6	11	3.9
V	4	7	3.8
VI	1	2	2.0
Total	57	100	

The number of patients (n), percentage of the total (%), and mean tumor size for each group are shown.

was left in contact in 1 case with the brainstem and in another with the intracranial vessels.

All 57 SVS patients underwent the enlarged translabyrinthine approach with transapical extension (Type I). Forty-eight (84%) SVS patients underwent complete resection, and 9 (16%) underwent subtotal resection. Among the SVS patients that underwent complete resection, none required nerve grafting, whereas 2 required hypoglossofacial anastomosis. One SVS patient underwent subtotal resection and required hypoglossofacial anastomosis.

Facial Nerve Outcomes

Among the 57 CVS patients with greater than or equal to 1 year of follow-up, favorable (Grades I–III) HBFN grades were observed in 46 (81%) CVS patients, and unfavorable (Grades IV–VI) HBFN grades were found in 11 (19%). These patients were further grouped by HBFN grade in Table 5 and Figure 4. Twenty CVS patients (80%) with Type A tumors had favorable outcomes, and 5 (20%) had unfavorable facial nerve outcomes. Twenty-six CVS patients (81%) with Type B tumors had favorable outcomes, and 6 (19%) had unfavorable facial nerve outcomes. A comparison of tumor size and 1-year facial nerve follow-up grades showed a significant, moderate to strong Pearson correlation (0.38). The long-term facial nerve outcomes from the sample of 57 CVS patients were compared with a sample of 57 matched SVS patients through Wilcox matched-pairs signed-ranks test. This test showed no significant difference in long-term facial nerve outcomes between these 2 groups ($p = 0.74$). This comparison is further demonstrated in Figure 5.

Furthermore, we compared the CVS facial nerve outcomes after complete resection with facial nerve reanimation (nerve graft or hypoglossofacial anastomosis) and subtotal resection. When the tumor was adherent to the facial nerve, not a single case in the complete resection group had a facial nerve outcome better than Grade III, and normal facial nerve function was only achieved after subtotal resection.

2-Year Follow-Up

Of the 96 CVS patients included in this study, 19 had greater than or equal to 2 years of documented follow-up at our institution. Of those 19 patients, 3 underwent subtotal resection, 1 of which developed a recurrence that required reoperation. The patient was a 60-year-old man with a 2.5-cm (Type B4) CVS. In March 2006, he underwent a translabyrinthine approach for resection of this lesion. Intraoperatively, significant bleeding developed that required additional retrosigmoid access for control. The surgeon ended the procedure prematurely due to blood loss. A small portion of solid tumor was left at the internal auditory meatus along the facial nerve, and a portion of the cyst wall was left attached to the brainstem. Postoperatively, his facial nerve function recovered to normal. An MRI showed no evidence of tumor regrowth 7 months after operation. Approximately 30 months after the operation, he returned to our institution with Grade III facial paralysis. Follow-up MRI showed regrowth of the residual tumor that seemed almost identical to the first lesion except for a more anterior location of the cystic component in the CPA. He underwent a transotic approach and subtotal resection of the recurrent CVS 31 months after his first operation. Thus far, he has done well postoperatively.

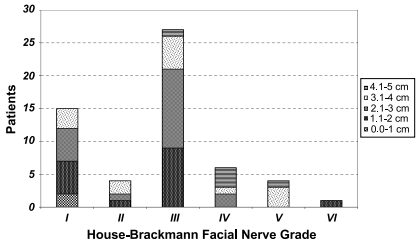

FIG. 4. Facial nerve outcomes in CVS patients with greater than or equal to 1 year of follow-up. Cystic vestibular schwannoma patients are separated into groups according to their 1-year HBFN outcome. Each column is further divide by tumor size.

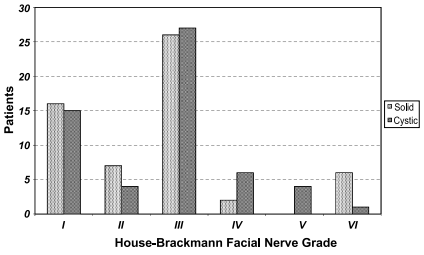

FIG. 5. Long-term facial nerve outcomes and tumor type. Facial nerve grades from 57 patients that had solid tumors are compared with 57 patients that had cystic tumors.

DISCUSSION

Cystic vestibular schwannomas are widely described as being more aggressive, having shorter symptomatic periods before presentation, poorer responses to radiosurgery, and worse outcomes from surgical intervention (3,5,15,16,23,24). Factors that lead to unfavorable surgical outcomes include engulfment of and adherence to neurovascular structures, hypervascular solid portions of the tumor, and the absence of an adequate subarachnoid dissection plane. Although each of these elements can be encountered during surgical removal of SVS, it seems they occur with increased frequency during resection of CVS. In large published series, they are typically only alluded to because they cannot be analyzed in a systematic, objective way. Analysis is further complicated because there are various descriptions of CVS, and there is a lack of a universal classification system for these tumors.

Fundova et al. (5), Yamakami et al. (7), Kameyama et al. (24), and Shirato et al. (25) have offered descriptions and/or classification systems for CVS. To facilitate clinical studies, a consensus meeting was held to discuss the reporting vestibular schwannoma results in 2003. It was recommended that multicystic tumors be identified as a separate group when reporting results. Tumors included in this group are those in which the cystic components are on the tumor's surface (6). To assist with preoperative surgical planning and to standardize the reports of surgical results, we propose a simple classification system based on preoperative imaging confirmed with intraoperative findings (Table 1, Figs. 1 and 2).

The pathogenesis leading CVS formation is unknown. Theoretically, CVS could form because of 1 or a combination of the following mechanisms: tumor growth and subsequent central necrosis, coalescence of microcysts formed in Antoni B tissue, and/or repeated intratumoral hemorrhage (26,27). Later, gradual cyst enlargement could be attributed to osmotic gradients set up by extravasation of serum proteins from an impaired blood-tumor barrier and/or the production of mucinous material within the cyst (3,26). Recently, high levels of proteolytic enzymes (matrix metalloproteinase 2) have been identified in CVS fluid and cyst walls. These enzymes are thought to play a role in cyst formation and enlargement in other cystic diseases. It has been inferred that these enzymes may play an important role in the pathogenesis of cyst formation and peritumoral adhesion in CVS (17).

Fundova et al. (5) conducted a comparison of CVS and SVS. Their study showed that patients with CVS had a significantly shorter initial duration of symptoms and worse facial nerve outcomes. However, CVS were subjectively evaluated to be "less" adherent to intracranial structures (brainstem, trigeminal nerve, lower cranial nerves, and dura, with no mention of adherence to the facial nerve) than SVS. They surmised that the less favorable surgical outcomes seen with CVS were due to rapid tumor growth and compression of posterior fossa structures. In contrast, Moon et al. (17) reported significantly increased adherence of cystic tumors to the facial nerve. Benech et al. (15) also reported increased adherence to neural structures with increased complications related to dissection of adhesions from the brainstem.

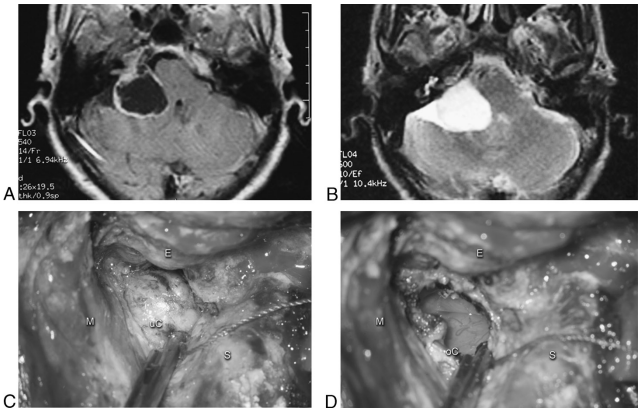

FIG. 6. Right Type B4 CVS that was recently operated at our institution through a translabyrinthine approach. *A*, Preoperative axial T1-weighted image with contrast showing a right CVS. *B*, Preoperative axial T2-weighted image of the same lesion. *C*, Intraoperative photograph showing the unopened CVS (*uC*) through a translabyrinthine approach. *D*, Intraoperative photograph showing the opened CVS (*oC*). The vessels lying between the thin cyst wall and the brainstem were visible (*D*). Middle fossa dura (*M*), boney external auditory canal (*E*), and sigmoid sinus (*S*).

In most studies, reported facial nerve outcomes after CVS resection have been less favorable in comparison to results after removal of SVS (Table 5) (3,5,16,17,23,28). Benech et al. (15) showed a trend toward worse facial nerve outcomes after CVS resection in comparison to solid tumors that did not reach statistical significance. However, Jones et al. (2) found no significant difference in facial nerve outcomes when they compared their series of CVS and SVS.

Our comparison of long-term facial nerve outcomes from 57 CVS patients and 57 matched SVS patients showed no significant difference. However, we think CVS are more adherent to neurovascular structures, and we attribute the similar facial nerve outcomes to familiarity with the intraoperative management of CVS, using subtotal resection when necessary and overall surgical experience. We agree with Samii et al. (29) that the predictive factors for facial nerve preservation include not only tumor size and extension, cystic tumor consistency, previous surgery, or radiosurgery, but also a surgeon's operative experience.

Vascular complications constitute a relatively rare but significant problem seen after resection of vestibular schwannomas. Hegarty et al. (30) reported a 2.1% rate of distal AICA territory infarcts. Samii and Matthies (23) reported an overall rate of symptomatic postoperative hemorrhage of 2.2%. Sade et al. (31) reported a 2.7% rate of vascular complications in their series of 391 vestibular schwannomas. We reported a hemorrhagic complication rate of 1.3% without analysis of solid versus cystic tumors in a series of 707 patients (32). In our present series, 1 patient (~1%) had a transient ischemic attack on postoperative Day 4, and 1 patient (~1%) developed postoperative intracranial hemorrhage that required surgical intervention.

In 2004, we reported the surgical volume of vestibular schwannoma resected at our institution between 1987 and 2001 (32). In the current study, we found that 6.8% of surgically treated vestibular schwannoma patients had CVS. Using this percentage to estimate the number, we think an additional 23 CVS patients were treated at our institution in the 10 years before 1998. Therefore, based on senior authors' experience of 119 CVS, the following recommendations are made.

Three factors need to be considered before CVS resection: thickness of the cyst wall, position of the cyst, and extrameatal size of the lesion, including cystic and solid components. In the senior authors' experience, vestibular schwannomas with centrally located cysts and thick cyst walls or tumors with intratumoral cystic change (both Type A) tend to be less difficult to remove.

Thin-walled, Type B tumors can present a more formidable challenge. Subtotal resection is frequently warranted when tumors of this nature are encountered. Figure 6 is an example of a thin-walled Type B CVS that was recently operated at our institution. Preoperative axial MRI images and intraoperative photographs demonstrate the degree of tumor adherence to the brainstem. In this case, the vessels lying between the thin cyst wall and brainstem were visible (Fig. 6D). Unable to develop an adequate subarachnoid plane, the surgeon left a portion of the cyst wall in place. There was no immediate postoperative morbidity.

Although many important neurovascular structures are encountered during the resection of any lesion in the CPA, to simplify the resection of CVS, we recommend that surgeons focus their attention on the brainstem, the facial nerve, and the vessels in the posterior fossa. One should correlate cyst position with these structures and attempt to preoperatively plan their management of the tumor. For example, with anteriorly based cysts, one should consider subtotal removal leaving the capsule on the facial nerve. When medially or posteromedially based cysts are confronted, especially when that brainstem and the 4th ventricle are compressed, complete resection can be difficult. In these situations, consideration should be given to leaving a portion of the cyst wall on the brainstem and vital vessels. On the other hand, purely posterior cysts are typically less difficult to remove, and complete resection is often achieved. Careful dissection along the surface of the cerebellum is typically inconsequential.

We recommend looking for subarachnoid planes that lend themselves to blunt or sharp dissection. In addition to these conventional dissection methods, we have had success using a bipolar to detach the cyst wall. When activated at a safe distance from vital neurovascular structures, the bipolar current can spread across the surface of the cyst and begin to develop a subarachnoid plane. If the cyst wall is thin, lying over the facial nerve, the brainstem or vessels of the posterior fossa, we advocate subtotal resection in these areas, leaving portions of the cyst wall.

Finally, during the resection of any CVS, surgeons need to pay particular attention to the depth of their dissection because it is possible to pass through the cyst and unintentionally enter normal brainstem parenchyma. This is a crucial point in the resection of polycystic tumors due to the multiple layers of tissue that the surgeon encounters.

CONCLUSION

In most cystic vestibular scwhannomas, complete resection should be foreseen. Central and thick-walled tumors can be removed in almost all cases. However, when peripheral thin-walled, adherent, cystic tumors are confronted and the cysts are medially or anteriorly located, we recommend subtotal resection, leaving portions of the cyst walls on neurovascular structures and on the facial nerve. This surgical strategy allows us to improve facial nerve outcomes and to reduce complications.

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Localisation of mediterranean Kaposi's sarcoma in Morgagni's ventricle

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Key-words. Larynx; Kaposi's sarcoma; larynx surgery; histopathology; Morgagni's ventricle

Abstract. *Localisation of mediterranean Kaposi's sarcoma in Morgagni's ventricle. Objective*: Head and neck involvement in Kaposi's Sarcoma (KS) is not unusual. However, laryngeal involvement is a relatively infrequent manifestation and ENT specialists should consider it in differential diagnosis in laryngeal lesions of AIDS patients and/or subjects from the Mediterranean area.
Methods: Case report and review of the literature in English.
Clinical Case: Male patient presenting with a three-month history of cough and acute dyspnoea. Laryngoscopy identified a laryngeal mass occluding the glottic plane. Tracheotomy was then performed and the laryngeal lesion was removed.
Histopathology showed neoplastic spindle cells that were positive to immunostain with CD-31 and CD-34, and immunoreactivity for HHV-8 was present. A diagnosis of KS was then suspected and confirmed after dermatological inspection.
Conclusion: Purple vascular mass lesions should lead in ENT to a high index of suspicion to exclude systemic diseases. Laryngeal KS must be included in the differential diagnosis of pigmented laryngeal lesions to plan correct management.

Introduction

The first description of Kaposi's sarcoma (KS) was by Kaposi in 1872,[1] who reported an unusual tumour consisting of small brownish-red cutaneous nodules, mainly involving the skin of lower extremities in a multifocal fashion.

The development of KS is related to several factors: genetics due to race and geographical distribution and infection because KS is found principally in patients with acquired immunodeficiency syndrome (AIDS).

Infection by HHV-8, a new human herpes virus described by Chang in 1994,[2] was considered necessary but not sufficient for KS development after HHV-8 DNA was found in tissues of patients affected by KS. The development of KS also requires compromised immune status.

Head and neck involvement in Kaposi's sarcoma (KS) is not unusual.[3] However, laryngeal involvement is a somewhat infrequent manifestation. The literature describes about 50 cases of laryngeal KS.

There are four types of epidemiological KS: AIDS-related or epidemic, iatrogenic, African or endemic, and the classic or Mediterranean type. Three clinical forms of KS have been noted: localised nodular, locally aggressive and generalised. HIV-negative patients with KS of the larynx have been reported.[4,5]

Males seem to be affected most (91%). The majority of patients with laryngeal KS have advanced HIV infection and were antiretrovirally naive.

Presenting symptoms may include hoarseness, throat discomfort, cough, dysphagia, stridor and dyspnoea. Laryngoscopy may show laryngeal oedema or more often a purple vascular mass lesion.

We report on the first case in the literature in English of KS in Morgagni's ventricle.

Case report

A 65-year-old white male complaining of cough and hoarseness over the past three months attended the emergency room of our department for episodic dyspnoea and stridor. The history was negative for cigarette smoking and alcohol consumption. The patient presented with dysphonia and inspiratory stridor. The indirect laryngoscopy showed a reddish sessile mass arising from the superior aspect of the right true vocal cord. The diameter of the lesion at the largest point was 1.5 cm,

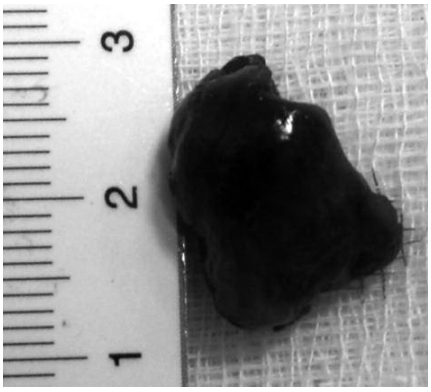

Figure 1
Laryngeal Kaposi's Sarcoma mass excised

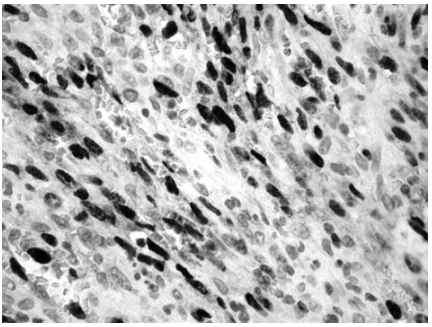

Figure 2
Neoplastic cells showing nuclear immunoreactivity for HHV-8. (Strept-ABC; original magnification 400×).

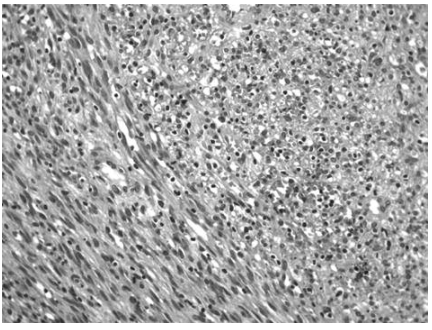

Figure 3
This section shows the proliferation of the neoplastic spindle cells arranged in intersecting fascicles which form slit-like vascular spaces of various dimensions containing red cells. (Hematoxilin-Eosin staining; original magnification 200×).

compromising the respiratory passage. Vocal cord motility was normal, as was the rest of the mucosa. Head and neck clinical examination did not reveal lymph node disease.

The patient underwent an urgent tracheotomy because of the stridor, low oxygen saturation (average of 93%) and severe dyspnoea.

Pre-operative routine blood tests results were normal, as were thoracic radiographs.

The patient underwent a direct microlaryngoscopy, revealing that the true origin of the lesion was above the arcuate line in the fundus of the right Morgagni's ventricle. The lesion was completely excised (Figure 1) by means of laser-assisted surgery. The tracheostomy was then closed in the same intervention.

Histopathology revealed the proliferation of neoplastic spindle cells arranged in intersecting fascicles, which form slit-like vascular spaces of various dimensions containing red cells (Figure 2). The specimens were positive to immunostain with CD-31 and CD-34. Nuclear immunoreactivity for HHV-8 was present, confirming the suspected diagnosis of KS (Figure 3).

The patient was then readmitted for further analysis and to evaluate the possibility of HIV infection. No signs of HIV infection were found. Blood tests were repeated and ELISA examination for HIV, CMV and EBV viruses were also performed. All values were in the normal range. No virus infection was found.

A total body dermatological examination was then conducted, showing typical KS nodular lesions on both feet (Figure 4). The definitive diagnosis of Mediterranean or classic KS was made.

The patient was then followed-up. After one year, no recurrent laryngeal lesions were detected,

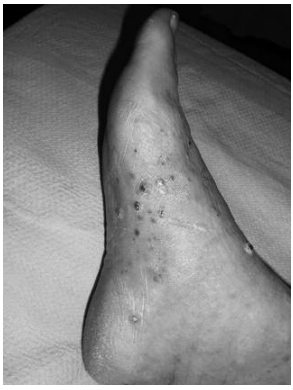

Figure 4
Nodular skin lesions on the right foot, typical of Classic Kaposi's Sarcoma.

and the skin lesion did not show any change.

Discussion

Mediterranean type or classic KS occurs in the older population of the Mediterranean area and it affects men 15 times more often than women. The nodular lesions are mainly situated in the lower extremities; they are indolent and infrequently cause morbidity. Conversely, the epidemic form of KS occurs in immunocompromised subjects (AIDS-related). The lesions in this form are aggressive and multicentric.

About 40% of AIDS patients will develop KS during the course of the disease, and two-thirds of these patients will have head and neck involvement.[6]

The lesions are reddish-purple, multicentric macules and nodules. Histologically, the typical features of KS are spindle-shaped cells with numerous vascular channels and extravasated erythrocytes. Deposits of haemosiderin are present in a collagen stroma. An inflammatory infiltrate may be present. Immunostain is performed with HHV-8 antibodies to confirm the viral infection and hence the diagnosis.

The two largest series of patients affected by laryngeal KS have been reported by Abramson *et al*.[7] in 1970 with 13 patients and by Mochloulis[8] in 1996 with 17 cases. Classic KS of the larynx is a rare

Table I
The literature relating to Kaposi's sarcoma, including the present case*

Author	Year	Cases	Site involved	Local treatment	Type
Reynolds[10]	1965	1	Arytenoids-Epiglottis	Tracheotomy	Classic
Coyas[11]	1983	1	Larynx	Tracheotomy	Classic
Abramson[7]	1970	13	Larynx		Classic
Moritsch[16]	1978	1	Larynx-Hypopharynx	Tracheotomy	Classic
Abemayor[3]	1983	1	Epiglottis		Epidemic
Gnepp[12]	1984	2	Anterior commissure (1) Larynx-Hypopharynx (1)	Excision (1) Tracheotomy (1)	Epidemic
Weidauer[17]	1986	1	Larynx	Excision	Epidemic
Levy[18]	1990	1	Glottic		Epidemic
Friedman[13]	1996	6	Larynx	Intralesional vinblastine (6) Tracheotomy (1)	Epidemic
Mochloulis[8]	1996	17	Supraglottic (11) Glottic (8) Subglottic (3)	Tracheotomy (1) Radiotherapy (5)	Epidemic
Schiff[19]	1997	2	Epiglottis (2)	Biopsy (1) excision (1)	Epidemic
Beitler[9]	1996	1	Larynx	Tracheotomy (1)	Epidemic
Gras[20]	1999	1	Supraglottic	Intralesional injection	Epidemic
Alkhuja[21]	2001	1	Larynx	Tracheotomy	Epidemic
Ares[22]	2005	1	Larynx	Tracheotomy	Epidemic
Angouridakis[4]	2006	1	Vocal cord	Excision	Classic
Ashurov[5]	2007	1	Larynx		Classic
Dispenza*	2008	1	Larynx	Tracheotomy and excision	Classic

entity with less than 20 cases reported in the literature (Table 1).

The clinical presentation of laryngeal KS is variable, depending on the site and the stage of the disease. The symptoms range from dysphonic voice to stridor and dyspnoea due to upper airway obstruction. In the literature, ten cases of laryngeal KS needed tracheotomy,[8-13] including the present case (Table 1).

Diagnostic biopsies were performed without complications in several patients, but biopsies of such vascular lesions have been associated with brisk and potentially fatal bleeding.[8]

The diagnosis of KS is generally made after histopathology, particularly in Classic KS, because of the lack of manifest extralaryngeal symptoms. In AIDS patients, the index of suspicion is higher than in other patients affected by the Mediterranean form.

Therapeutic options include: low-dose irradiation, intralesional chemotherapy, ablation and systemic therapy if there is disseminated disease. Obstructing laryngeal lesions require urgent intervention with tracheotomy. Depending upon the location of the lesion, a tracheotomy may contribute to mortality as a result of fatal haemorrhaging.[9] A tracheotomy is generally adopted in these patients when transoral intubation for general anaesthesia is difficult or impossible, and in cases of severe dyspnoea. Furthermore, surgeons should bear in mind that Kaposi's nodules may be bleeding lesions, and so intraoperative haemorrhaging during transoral surgery may be well managed if the airways are saved. Surgical excision is adopted for isolated lesions and for those obstructing the airway. The transoral modality for the surgical removal of the lesions is the first choice because it allows for the prompt and good visualisation of the glottic plane and rapid postoperative healing.

In our case the lesion was removed after airway patency was restored by tracheotomy. Tracheotomy may be closed once the lesion is removed.

Friedman *et al.* adopted the intralesional injection of Vinblastine sulphate, with an appreciable response in over 75% of cases. Only one patient required a tracheotomy for upper airway obstruction.[13]

The Mediterranean type of KS does not generally contribute to patient mortality and the treatment of asymptomatic laryngeal lesions may be conservative[8], as in other laryngeal lesions.[14,15] In the epidemic type, death is secondary to other AIDS-related disease processes.

Conclusion

Laryngeal KS is a rare clinical entity. To the best of our knowledge this is the first case reported in the English literature of KS affecting the laryngeal ventricle. The clinical investigation generally shows a mass without malignant features. The definitive diagnosis is established after histopathology, but the index of suspicion is high, especially in AIDS patients. It must be included in the differential diagnosis of pigmented laryngeal lesions. Urgent treatment may be required in cases of acute stridor due to an occluding mass. Classic KS is not an aggressive disease and patients usually die of other diseases, but follow-up is mandatory to prevent loco-regional recurrence or new primary lesions.

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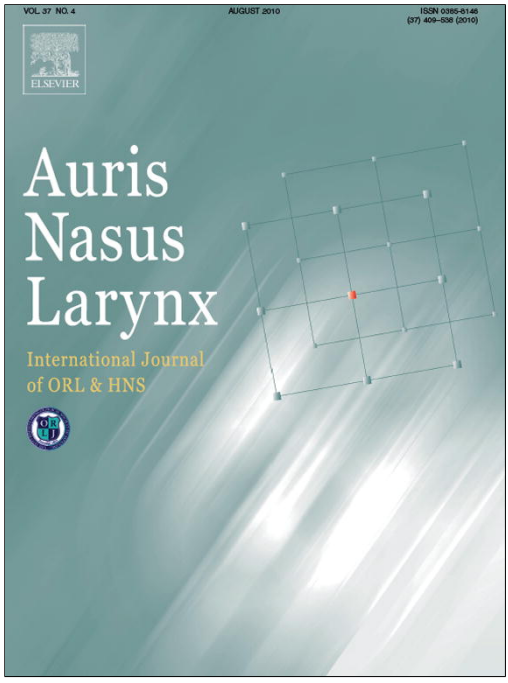

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Modified fronto-lateral laryngectomy in treatment of glottic T1(a-b) cancer with anterior commissure involvement

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Abstract

Objective: Evaluation of clinical and oncological safety of the modified fronto-lateral laryngectomy in the treatment of T1a-b glottic cancer.
Methods: Retrospective review of charts of patients managed with classical fronto-lateral laryngectomy or with our modified technique using a cervical fascia flap and a false cord flap to reconstruct the defect.
Results: No recurrence of cancer was observed in the present series and slight dysphonia was present in all cases. The patients managed with classical technique required a revision surgery for granulations or anterior synechia in 4 cases; those managed with modified technique did not need a second intervention.
Conclusion: The fronto-lateral laryngectomy should be present in the head-neck surgeon armamentarium. In T1a-b glottic cancer this technique gives a good oncological resection, but the postoperative period requires an intensive rehabilitation process. The modification of the classical technique reduces the incidence of a second intervention.

Keywords: Laryngectomy; Fronto-lateral laryngectomy; Glottic cancer; Larynx surgery; Vertical laryngectomy

1. Introduction

In the management of laryngeal cancer the choice of the conservative surgical technique depends upon the TNM staging, tumor location and laryngeal structures involved. The anterior commissure (AC) of the glottis is a ''risk region'' for two reasons: its anatomical structure and the difficulty in delineating the deep extension of the tumor, even with the help of radiological study. Anatomically the AC constitutes thin mucosa with absence of internal perichondrium of thyroid cartilage along with proximity of the crico-thyroid membrane and of the caudal end of the epiglottis. This may erroneously lead to clinical down staging of the tumor, as cT1, which after histopathological examination turns out to be pT4.

The role of the AC in the development of the tumor is a matter of debate. Several authors consider the AC as a low resistance area to neoplastic growth [1–4]. Others authors suppose that AC is a barrier (wall) against anterior spreading of the tumor in the early phases of the tumoral growth [5,6].

The Broyles's tendon acts as a barrier against the deep infiltration of the tumor in the early phases, but it does not restrict superficial spread either in the supraglottic or subglottic direction.

Carcinoma involving the AC is more aggressive than carcinoma arising in other sites, with the consequent worse prognosis. This observation led Fini-Storchi to add an anatomical-oncological classification to TNM staging of neoplasm involving the AC [7].

We present our oncologic and functional results in the patients affected by laryngeal cancer involving the AC treated with a modified frontal–lateral laryngectomy (FLL), a surgical procedure described by Leroux-Robert

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in 1956 [8] and popularized in Europe in 1970s [9], that today may be helpful in selected cases not well managed with endoscopic laser microsurgery or horizontal partial laryngectomies.

2. Materials and methods

A retrospective chart review of patients treated for laryngeal cancer with frontal–lateral laryngectomy in our department from 1994 to 2000 was conducted. History and symptoms were recorded in all cases. All patients underwent complete head and neck check up, including upper aero-digestive endoscopic examination. A computed tomography with contrast enhancement of the neck and standard X-ray chest projection were done in all patients. Patients were classified in accordance with TNM staging system. Biopsy of the laryngeal lesion was done under direct microlaryngoscopy in general anesthesia followed by FLL. Modified fronto-lateral technique was performed in about half of the patients since 1997, when we planned and introduced the variation from the classical technique. Complete information including all treatment options (i.e. surgery and radiation therapy) was provided to all patients and informed consent was obtained.

Surgical technique: the modification of the Leroux-Robert technique consists of two additional surgical steps: (1) the use of a superficial fascia flap, dissected at the beginning of the operation, to reconstruct the defect due to excision of thyroid cartilage (Figs. 1 and 2) and (2) a shifting flap of false cord to reconstruct the glottic defect (Fig. 3).

In all cases temporary tracheostomy was performed and a naso-gastric tube was positioned. The voice rehabilitation was done after tracheostomy closure by speech-language pathologist for a period of 3 months.

The minimum follow-up period was of 5 years. It was accomplished with endoscopic evaluation of larynx and head and neck clinical examination at 1, 2, 3, 6, and 9 months in the first year after operation, every 6 months in the second and third year and once every year thereafter.

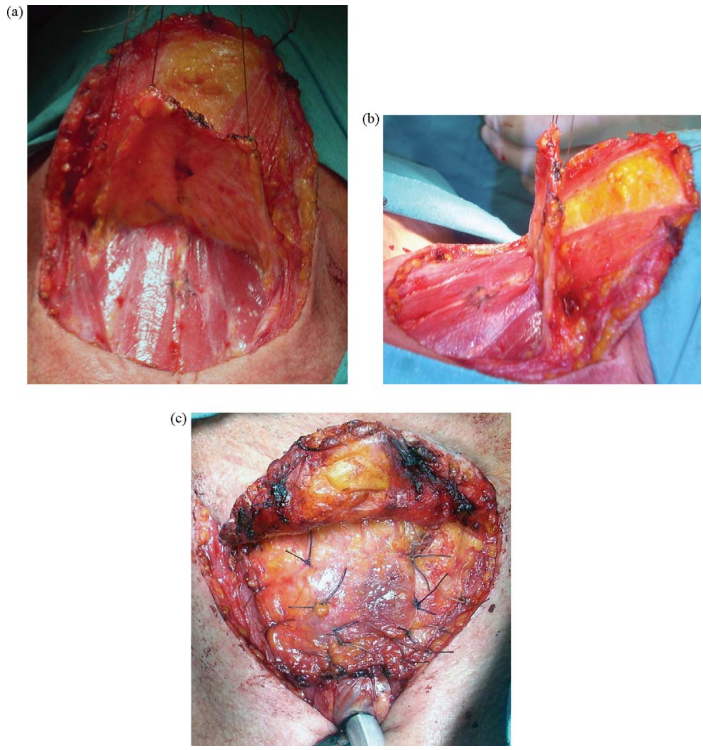

Fig. 1. The cervical fascia flap used in the reconstruction of anterior aspect of the larynx: (a) anterior view; (b) lateral view; (c) final reconstructive suture.

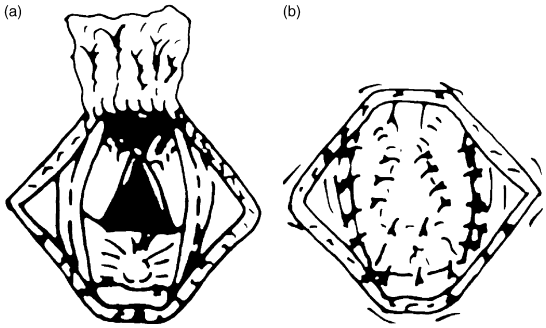

Fig. 2. Scheme of the cervical fascia flap suture: (a) the thyroid cartilage gap created after tumor removal will be covered by the cervical fascia flap elevated as first step of the operation; (b) the suture of the flap to the cartilage border and to the strap muscles, over the thyroid cartilage gap.

Our Institutional Review Board approved the present study.

3. Results

Twenty-one male patients with fronto-lateral laryngectomy were treated in our Department, from 1994 to 2000, to manage glottic cancer extending to the AC. All patients who underwent surgery refused radiation therapy as treatment. The mean age was 64 years (range 53–75 years). All patients were heavy smokers: 6 patients more than 20 cigarettes per day and 15 patients more than 30. In 13 cases more than 200 ml of daily alcohol consumption was associated with smoking. The symptoms recorded were: dysphonia in 21 cases, productive cough in 7 cases and dry in 3 patients, pharyngeal discomfort in 4 patients. The biopsy showed an infiltrating squamous cell carcinoma in all cases. The Leroux-Robert's fronto-lateral laryngectomy was performed in 8 cases until March 1997. Since June 1997 to December 2000 we performed the modified technique described above in 13 patients.

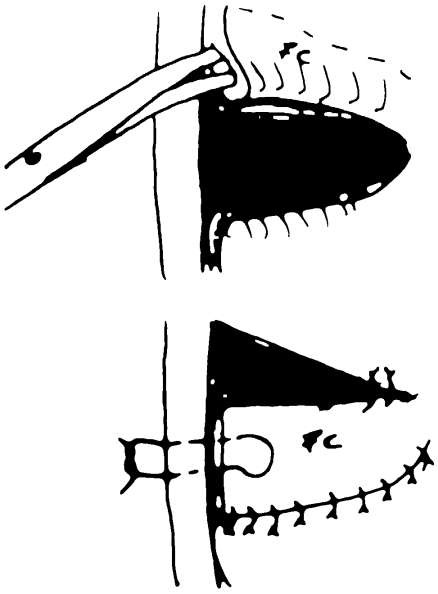

Fig. 3. Scheme of the false cord flap to reconstruct the glottic plane after tumor removal; the flap is dissected and rotated downward to fill the glottic plane gap and then sutured.

The definitive histopathological examination confirmed the presence of a squamous cell carcinoma in all series. In 5 (23%) out of 21 patients an early thyroid cartilage invasion was present, but always contained by the cartilage.

The naso-gastric tube was positioned for an average of 6 days (range 4–13 days). The deglutition was normal in all cases. The tracheostomy tube was kept for less than 10 days in 10 patients, between 10 and 20 days in 10 patients and 25 days in one case.

The mean follow-up was 9.5 years (range 7–15 years).

All patients presented with slight dysphonia. In 4 patients treated with the classical Leroux-Robert technique a revision microlaryngoscopic surgery was necessary to remove glottic granulations in 3 patients and anterior synechia in 1 (Fig. 4). In the patients managed with the modified fronto-lateral technique we noted glottic granulations only in one case. All patients are without recurrence till date (Fig. 5).

4. Discussion

The surgical treatment of T1a-b glottic cancer with AC involvement, extending to the anterior third of the

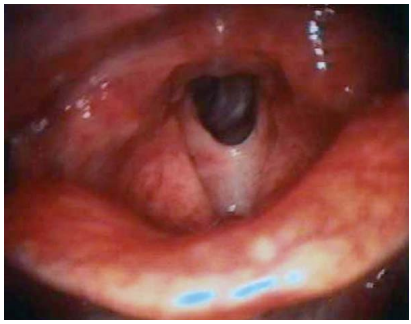

Fig. 4. Anterior synechia in a patient treated with the classical Leroux-Robert technique.

contralateral vocal cord, has two main objectives: (1) oncologically safe excision; (2) sparing of laryngeal functions. The less invasive techniques, such as endoscopic laser microsurgical approach, is often preferred because of few postoperative complications and it allows preservation of thyroid cartilage integrity thus leaving a natural barrier in case of recurrence.

Sometimes doubt exists about the deep extension of cancer involving the AC toward the thyroid cartilage. In this case choice of a less invasive technique (transoral surgery) may not be appropriate, while a supracricoid partial laryngectomy as cricohyoidoepiglottopexy may represent an overtreatment; therefore in our view the use of the vertical partial surgery such as the FLL offers a more effective control of the disease, with preservation of laryngeal function in case of only one vocal cord and AC involvement.

Leroux-Robert demonstrated that the FLL permits the excision of the vocal cord, the correspondent subglottic area, AC and subcommissural region. The technique includes resection of the dihedral angle of thyroid cartilage together with the lesion. According to Leroux-Robert the indication of FLL is a cancer that involves the vocal cord from the arytenoid cartilage to the AC, even if the motility of such a cord is impaired.

The Leroux-Robert's indication enjoyed wide popularity among several authors [3,10–13]. Other authors adopted the FLL in the vocal cord carcinoma that crosses the midline in the region of AC [14].

The posterior extension toward the arythenoid cartilage is not an absolute contraindication to perform FLL. De Campora and Radici limit the FLL application to vocal cord cancer that does not involve the vocal process of the arythenoid cartilage and disapproves this technique also in cases with contralateral vocal cord involvement, subglottic and ventricular extension [3].

The postoperative period after FLL requires hospitalization for about 6 days because of tracheostomy tube management and naso-gastric tube feeding. Tracheostomy tube was needed for a mean period of 11 days (only one case needed it for 25 days), until the healing of glottis was considered safe for breathing. It is noticeable that Brumund et al. reported a large series of patients treated with FLL without performing a temporary tracheostomy and without naso-gastric tube positioning. However, our data of post-operative care are in accordance with the length of time previously reported in literature [9,15,16].

The voice quality after a classic FLL is similar to that obtained after a cordectomy via laryngofissure. The anterior synechia seems to have a significant impact on the voice quality in patients treated with FLL [17]. As suggested by some authors, the reconstruction of the glottis with a false cord flap results in a better phonatory outcome, because of reduction of the risk of anterior synechia [18,19]. The cervical fascia or mucochondral nasal septum free flap [20] gives a good support to the pre-laryngeal tissues, avoiding its herniation in the laryngeal space, and facilitating the glottic healing (Fig. 5). In our experience the cervical fascia and the false cord flap give a good functional result and for this reason we adopted such technique in all patients since 1997.

The rate of complications in our patients was low. No patients had infection of wound or fistula formation. The modification of the classical technique allowed, in our

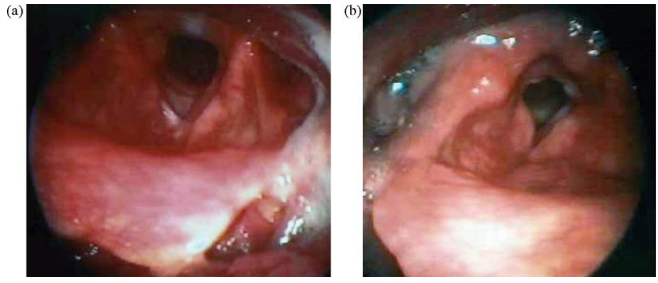

Fig. 5. Postoperative examination of cases treated with our modified fronto-lateral laryngectomy, the triangular shape of the new glottic plane obtained with suggested modifications is noticeable.

series, a drastic reduction of laryngeal granulation development in the postoperative period.

We did not observe any problem in swallowing in our series of patients; the nasal-gastric tube was removed in all patients in about 6 days from operation.

The absence of local recurrence in our series is probably due to strict selection of patients; we performed FLL only in patients with a glottic cancer T1a-b with AC involvement. Fiorella et al. showed that FLL was not sufficient for advanced tumor involving AC [13]. We usually advocate a supracricoid partial laryngectomy (i.e. cricohyoidoepiglottopexy) for glottic T2 stage, because of high risk of recurrence noted in the other centre [21,22].

In the last decade we performed less FLL due to practice of endoscopic CO_2 laser surgery that permitted excision of T1a-b glottic tumors. We reserve the modified FLL for patients with AC involvement who have contraindication to laser surgery, inadequate laryngeal exposure for endoscopic surgery, and for patients with low performance status in which reconstructive laryngectomy procedures are contraindicated.

5. Conclusions

Head and neck surgeons should consider fronto-lateral laryngectomy for selected patients that choose surgical therapy and are not well manageable with CO_2 laser surgery. In T1a-b glottic tumor with AC involvement this technique gives a reasonable oncological safe resection. The recurrence rate is comparable with other procedures for T1a-b glottic cancer, but the postoperative period is longer and needs an intensive rehabilitation process. From the time when we adopted the modified FLL we observed optimal results in disease treatment and functional outcome. The modified technique reduces the postoperative risk of synechia and granulation tissue development thus improving the quality of the voice.

Conflict of interest

None.

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Benign paroxysmal positional vertigo following whiplash injury: a myth or a reality?

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Abstract

Objective: The aim of the study was to evaluate the true incidence, diagnosis, and treatment of benign paroxysmal positional vertigo (BPPV) arising after whiplash injury and to distinguish this type of posttraumatic vertigo from other types of dizziness complained after trauma.
Methods: This was a retrospective study comprising patients referred to our center after whiplash injury. The patients were evaluated with neurotologic examination including bedside and instrumental tests. A Dizziness Handicap Inventory evaluating the symptoms of patients was submitted before and after treatment and was evaluated. The BPPV patients were separately evaluated from those with cervicogenic vertigo, and a comparison between our data about idiopathic BPPV was done.
Results: Eighteen patients of whiplash who had BPPV were evaluated. The mean age was 38.2 years. BPPV was the cause of vertigo in 33.9% of total whiplash patients. In 16 cases, the posterior semicircular canal was involved; the lateral semicircular canal was involved in 2 cases. The instrumental neurotologic assessment did not show any alteration of either vestibulospinal reflexes or dynamic ocular movements. Duration of symptoms before treatment ranged from 3 to 26 days. A total of 55.5% of patients had relief from their symptoms after first repositioning maneuver. The Dizziness Handicap Inventory score improved in all patients treated with repositioning maneuvers, but no difference emerged with idiopathic BPPV data.
Conclusion: BPPV after whiplash injury could be unveiled with a simple bedside examination of peripheral vestibular system, and a treatment could be done in the same session. The diagnosis of posttraumatic BPPV is not different from the idiopathic form, but the treatment may require more maneuvers to achieve satisfactory results.

1. Introduction

The equilibrium is the result of a perfect integration of input from eyesight, proprioceptive receptors, and labyrinths. The whiplash injury is a traumatic lesion due to rapid flexion-extension movement of the cervical column. This causes disturbance signals reaching from the cervical proprioceptive system to the central vestibular system and thus has an adverse effect on equilibrium. Balance problems affect 5% to 50% of patients of whiplash injury [1,2]. The whiplash injury is generally due to car collision and is the first cause of insurance claims. About 15% to 20% of cases develop the so-called late whiplash syndrome with persistent complaints including headache, vertigo, instability, nausea, and tinnitus [2].

The cervical trauma may increase the discharge of muscles' proprioceptive receptors of the neck [3] and may

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interfere with normal activity of vestibular system, resulting in an alteration of vestibular-ocular reflexes [4,5]. The neck pain, and related balance impairment, is the most common symptom and may be the cause of the symptoms complained by patients that is generally called *cervicogenic vertigo*.

The quantification of vestibular damage is difficult in forensic cases. For these reasons, it is mandatory to detect maligners and distinguishing them from patients with true disequilibrium disturbance [6].

Labyrinthine vertigo and auditory disturbances are present in 25% and 17% of subjects, respectively [7]. The incidence of dizziness with even mild head injury ranges from 15% to 78%, probably because of an unclear definition of the trauma and of the concept of dizziness [8-10].

Benign paroxysmal positional vertigo (BPPV) is the most frequent cause of peripheral vertigo [11]. It accounts for approximately 24% of all cases of peripheral vestibular disorders [12]. This type of vertigo is generally seen in individuals 40 years and older, with the highest incidence between 50 and 70 years [13].

The exact etiology of BPPV is still debatable. More than 50% of all reported cases are idiopathic in nature [14]. Adler [15] was the first to describe manifestations of BPPV in posttraumatic cases. Classic BPPV involves the posterior semicircular canal (PSC) and represents the most common type of BPPV [13,16-18].

Diagnosis of BPPV is based mainly on history of characteristic positional vertigo along with the classic clinical signs. Symptoms are characterized by rotating vertigo with nausea and vomiting, elicited by movements of the head. The nystagmus typically has a latency (of few seconds) and is of limited duration (10–20 seconds), transient, and fatigable [16].

In patients of BPPV, correct diagnostic evaluation and appropriate management, in the great number of cases, solve the problem quickly, without the need for any medical treatment [19].

Our work's aims were to analyze the patients affected by BPPV after whiplash injury and to evaluate differences between idiopathic BPPV and so-called cervicogenic vertigo.

2. Materials and methods

A retrospective study of patients of whiplash injury who visited our department between January 2008 and September 2009 was conducted. Patients with a diagnosis of BPPV following the trauma, occurring within 1 week before presentation, were evaluated. The exclusion criteria were history of vertigo before the whiplash injury, history of ear diseases or hearing loss, central nervous system pathology, psychiatric diseases, and history of vascular diseases. The evaluation included clinical history, complete head and neck examination, clinical vestibular tests, pure tone audiometry, and videoculography/videonystagmography with infrared system (ULMER, Synapsis Inc, Marseille, France). The smooth-pursuit function was evaluated by following an oscillating lighted target on a 29-in screen. The target velocity was regular (18°/s); and the oscillating movements were from center to right, back to the center, and center to left. Each trial was of 20 cycles of 57 seconds each. The saccadic test was performed by watching the target on a horizontal plane; the frequency was 0.4 Hz, and the amplitude was ±20°. The parameters analyzed in saccadic movement evaluation were latency, velocity, and accuracy. Our cutoff parameters to consider results as pathologic were as follows: value more than 200 milliseconds for latency, a score less than 77% for accuracy, and a highest velocity less than 530°/s. The smooth-pursuit movement analysis was evaluated measuring the gain (eye velocity/target velocity), and the parameter of normality was a value of 0.88 ± 0.2.

The same operator performed all instrumental tests.

The Dizziness Handicap Inventory (DHI) was used as reference for clinical improvement and was submitted at first contact and during the follow-up.

The clinical vestibular tests used to investigate the positioning nystagmus were the Dix-Hallpike and McClure-Pagnini tests (nystagmus observed in a supine position while turning the head to the left and right). The vestibulospinal function was evaluated by the Romberg test, index deviation test, and Unterberger test [20]. The dynamic ocular bedside examination included the head-shaking test and Halmagyi test. The evaluation of nystagmus and vestibular reflexes was done after a period of at least 5 days from last dosage of vestibular suppressant drugs.

Imaging is generally included in those patients with uncommon clinical presentation or those with lack of response to treatment [21].

After diagnosing BPPV, all patients were promptly treated with canalith repositioning maneuver (CRM) according to the affected semicircular canal. The Semont maneuver or the Epley maneuver was used to treat a PSC BPPV; the Gufoni maneuver was used to manage the lateral semicircular canal (LSC) BPPV [19] The persistence of nystagmus and vertigo spells after CRM was indicative of treatment failure, and repetition of maneuver was done in the same session or in the following 3 days. No medical treatment was prescribed to patients after CRM. The follow-up was done at 1 week, 3 weeks, and 1 month; the patients were examined, and a DHI questionnaire was submitted at the second and sixth months after the treatment.

The patients with cervicogenic vertigo were treated with a combination of physiotherapy, habituation exercises, and analgesics.

Finally, the data where matched with our result in treating idiopathic BPPV [19,22] and with patients complaining a "cervicogenic vertigo" following a whiplash injury to evaluate the differences.

Our Institutional Board reviewed and approved the study.

3. Results

Out of 53 patients of whiplash injury who were referred to our department, 33 were male. The mean age was 40.77 (range, 18–66) years. In all patients, the head trauma occurred within 1 week before presentation.

In 20 patients, the history revealed the presence of rotating vertigo after trauma. An unspecified imbalance or dizziness was the chief complaint in 33 patients, which were labeled as having cervicogenic vertigo. These patients did not show any alteration on neurotologic examination. The hearing was normal in all patients.

In 18 of 20 patients, the vertigo was related to head position and movement on the bed. In the remaining 2 cases, a labyrinthine concussion was diagnosed; and these 2 patients were excluded from present analysis. No patient reported history of vertigo before the head trauma.

The result of the Dix-Hallpike diagnostic maneuver was positive in 16 of 18 patients, whereas the result of the McClure-Pagnini maneuver for the LSC was positive in 2 cases.

Out of 18 whiplash patients with BPPV, 11 were male. The mean age of the group was 38.2 (range, 25–66) years. The BPPV was the cause of vertigo in 33.9% of whiplash patients. In 16 cases, PSC was involved, the right side in 9 patients and left side in 7 cases. The left LSC was involved in the remaining 2 cases. The neurotologic assessment did not show any alteration of either vestibulospinal reflexes or dynamic ocular movement (Table 1).

Symptoms duration before treatment ranged from 3 to 26 days. A symptoms-free period was present in all cases, with recurrence of vertigo spells after a period ranging from 1 week to 1 month.

The DHI score improved in all patients treated with CRM, as shown in Table 2. Although the improvement was remarkable if compared with cervicogenic vertigo results, no difference emerged with DHI after treatment of idiopathic BPPV.

Table 1
Analysis of eye movement results of the patients

	Idiopathic BPPV (110 cases)	Cervicogenic vertigo (33 cases)	Posttraumatic BPPV (18 cases)
Smooth-pursuit gain (SD)	0.87 (±0.04)	0.86 (±0.03)	0.87 (±0.04)
Saccadic velocity, °/s (SD)	571 (±34.1)	572.05 (±24.35)	565.9 (±27.47)
Saccadic latency, °/s (SD)	155.3 (±13)	161.73 (±13.07)	155.4 (±14.35)
Saccadic accuracy, % (SD)	0.83 (±0.06)	0.83 (±0.06)	0.84 (±0.06)

The patients with cervicogenic vertigo and posttraumatic BPPV due to whiplash injury.

Table 2
Dizziness Handicap Inventory in the patients pre- and posttreatment

	DHI pretreatment	DHI posttreatment (last)
Idiopathic BPPV	Severe: 75	Severe: 0
	Moderate: 33	Moderate: 1
	Low: 2	Low: 109
Posttraumatic BPPV	Severe: 15	Severe: 0
	Moderate: 3	Moderate: 0
	Low: 0	Low: 18
Cervicogenic vertigo	Severe: 9	Severe: 3
	Moderate: 18	Moderate: 15
	Low: 6	Low: 11

The patients with cervicogenic vertigo and posttraumatic BPPV due to whiplash injury. The score of DHI is as follows: severe (100–70 points), moderate (69–40 points), and low (39–0 point).

A total of 55.5% (10 cases) of patients had relief from their symptoms after first CRM. Two CRMs were necessary in 6 (33.3%) patients, including the 2 patients with LSC BPPV. The remaining 2 (11.1%) patients required 3 sessions of CRM to achieve satisfactory results. Comparing these results with the treatment of idiopathic BPPV, we noted that the posttraumatic variant requires more maneuvers to reach curative repositioning of otoliths (Table 3).

4. Discussion

The effect of trauma on cervical column was first described by Crowe [23] in 1928 and followed by Gray and Abbott [24] in 1953. Significant injuries can occur following even low-speed collision, but simulated accidents have shown that a 5-mph rear-end car crash can result in a positive acceleration of 8.2 G of the head [25].

The whiplash injury is a biomechanical event that produces a distortion of the cervical column causing lesions of several cervical sites, such as the muscles, ligaments, vertebral joints, vessels, and nerves. The typical acute symptoms after whiplash injury includes neck pain, headache, paraesthesia of upper cervical dermatomes, dizziness or imbalance, and tinnitus [26,27]. The majority of patients recover spontaneously after few months of symptomatic treatment. In some patients, the symptoms may persist.

Pathophysiologically, there is central nervous system weakness following a whiplash injury. With respect to inner ear pathology due to whiplash, the exact nature of the lesion

Table 3
Canalith repositioning maneuver needed to reach the curative repositioning of otoliths

	Idiopathic BPPV	Posttraumatic BPPV
1 CRM	81%	55.5%
2 CRMs	17%	33.3%
>2 CRMs	2%	11.1%

is not known; but some possible explanations are transient ischemia by vertebral artery compression, hemorrhage into labyrinth, direct labyrinthine concussion, and noise of the collision.

A neurotologic evaluation should be performed to find a possible cause of symptoms. The examination includes the assessment of peripheral labyrinth and vestibulo-ocular reflex system by means of clinical vestibular tests, caloric test, and videoculography/videonystagmography.

Previous studies have scarcely demonstrated any relationship between peripheral dysfunction and trauma. Some studies present in the literature have shown positional nystagmus and unilateral hyporeflexia in patients of whiplash injury [9,28-33]. Ettlin et al [34] reported peripheral vestibular deficits in only 2 cases among 18 cases after whiplash injury. However, all these reports have not used the standard value as benchmark or any proper control group. In a previous study, we did not find any correlation between trauma and eye movements in patients with recent trauma.

However, the whiplash injury is considered to be a direct cause of the BPPV [35,36] especially when head trauma is associated. The pathophysiology of the classic BPPV as a disorder of otoliths was suspected first by Barany and later supported by Schuknecht [37,38]. Following the trauma, the otoliths are detached from the utricle and displaced within the labyrinth. Generally, patients affected by idiopathic BPPV are older than those due to trauma.

The patients experience severe vertigo when rolling in one particular direction in bed and, less frequently, may also report dizziness with head motion. For dizziness occurring at times other than in bed, cervicogenic vertigo must be considered after a whiplash trauma. Head injury may equally affect both labyrinths; thus, bilateral BPPV is expected to occur more frequently in the posttraumatic cases [35,39], although we have not noted a high incidence of bilateral cases in our series.

There is consensus on the incidence of posttraumatic BPPV that accounts for 15% to 20% of all cases [40,41].

The diagnosis is confirmed by positional tests (Dix-Hallpike [38], McClure-Pagnini [42]). Establishing a diagnosis of BPPV is beneficial because it is treated by relatively simple physical maneuvers without the need for additional investigations or drug therapy. About 80% of patients with posterior canal idiopathic BPPV become free of symptoms and signs following a single maneuver [43-46]. The percentage of successful repositioning after the first CRM decreases in posttraumatic cases. Our hypothesis is that it may be due to the increased number of otoliths displaced as consequence of trauma.

Although the improvement of patients affected by BPPV is remarkable after treatment, if compared with cervicogenic vertigo patients as shown in our results, any difference emerged comparing DHI after treatment of idiopathic BPPV vs posttraumatic cases. This may be explicable considering that the pathophysiology of BPPV, even if posttraumatic, is related to the same mechanism of otolith movements into labyrinth.

It is widely believed that a whiplash injury may induce a disorder of neck proprioceptors caused by forces applied to the neck in the course of the accident. We concur with Fischer et al [47] in distinguishing either spontaneous or positional nystagmus arising in certain static head positions from the previously reported "cervical nystagmus" because static labyrinthine stimulation may exist. Several authors have failed to demonstrate a relationship between nystagmus and neck proprioceptors' stimulation [30,31,48].

5. Conclusions

A syndrome in which the dizziness is the main complaint often follows a whiplash trauma. With simple bedside examination of peripheral vestibular system, it is possible to find out the patients with true vertigo; and a treatment could be done in the same session. The diagnosis of posttraumatic BPPV is not different from the idiopathic form, but the treatment may require more CRMs to achieve satisfactory results. In addition, the complete neurotologic examination of vestibular system allows us to recognize maligners who complain of vertigo or dizziness with the aim of insurance claim.

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Analysis of visually guided eye movements in subjects after whiplash injury

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Abstract

Objective: The aims of present research were to analyze the visually guided eye movements of subjects suffering from the consequences of whiplash injury and the possibility to differentiate patients from feigning subject. We analyzed the role of video-nystagmography for clinical and forensic aspects.
Methods: It was a prospective case–control study. Detailed history was taken and patients were thoroughly investigated. Smooth pursuit and saccadic eye movements were assessed in 33 patients affected by imbalance following a whiplash injury. A control group of 20 subjects was also evaluated. All tests were executed in neutral neck position and after left and right trunk rotation.
Results: The *t*-test, applied to all parameters showed that difference of the parameter between the groups was not statistically significant.
Conclusion: The visually guided eye movement evaluation does not seem to offer a clinically relevant method to differentiate patients suffering from the effects of whiplash injury from normal subjects.

Keywords: Whiplash; Trauma; Vertigo; Saccadic; Optokinetic; Smooth-pursuit

1. Introduction

The evaluation of the vestibular system disease is always a challenge for the clinician. Symptoms of imbalance or true vertigo, complained by patients, may be present in numerous diseases and can be due to lesion at different levels in vestibular system. The quantification of vestibular damage is also difficult in case forensic tests are done. For these reasons it is mandatory to employ instrumental tests to verify without bias the symptoms reported after an injury and to detect patients who are feigning [1].

The equilibrium is the result of a perfect integration of input from the ocular, proprioceptive and vestibular systems. The whiplash injury is a traumatic lesion due to rapid flexion–extension movement of the cervical column. Such trauma to the neck causes an alteration of signals reaching from the cervical proprioceptive system to the central vestibular system and thus affects equilibrium. Balance problems are reported by 5–50% of patients of whiplash injury [1,2]. The whiplash injury is generally due to car collision and is the first cause of insurance claims. About 15–20% of cases develop the so-called late whiplash syndrome with persistent complaints including headache, vertigo, instability, nausea and tinnitus [2].

The cervical trauma may increase the discharge of muscles' proprioceptive receptors of the neck [3]. As described in literature the abnormal input coming from neck receptors interfere with normal activity of vestibular system and may result in alteration of vestibular–ocular reflexes [4,5].

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A whiplash injury can induce an elongation of the cervical column that may reach 5 cm and, as consequence, a stretching of the medulla, brainstem and also cerebellum as reported in literature. Some clinicians noted also alteration of saccadic and smooth pursuit movements [6–9].

The neural pathways of both system saccadic and smooth pursuit extend from cerebral cortex to oculomotor nuclei trough the cerebellum. The alterations of ocular movements may represent a sensitive markers of central nervous system damage. For such reason the attentions of clinicians were focused on eye movements to find some justification of dizziness after a whiplash injury. Furthermore Hinoki et al. founded an increased activity of cervical proprioceptors and a concomitant dysfunction of central nervous system after a traumatic distortion of cervical tract [10].

Our work's aim was to evaluate the visually guided eye movements in patients of whiplash injury, by the analysis of the saccadic eye movements and smooth pursuit movements matching the data of whiplash patients with a control group, to make an attempt to clarify such argument.

2. Materials and methods

A case–control clinical evaluation was done on two groups in the year 2008. The first group included patients of whiplash injury that were referred to our department. The exclusion criteria for the first group were: history of vertigo before the whiplash injury, ear disease or hearing loss, and of central nervous system pathology. The control group consisted of normal subjects without vestibular symptoms or general disease, negative history for head and neck disease or trauma. The first group was subdivided in 3 subgroups, depending upon the interval of time between trauma and evaluation: Group A (1–2 months), Group B (2 to 6 months) and Group C (7–12 months). This further subdivision was done to find a relation between symptoms persistence and time of injury.

The evaluation included: complete head and neck examination, clinical vestibular tests, pure tone audiometry and video-oculography/video-nystagmography with infrared system. All the tests were performed in an isolated room with dim light. During the tests the patients were seated at 42 cm from the display. The smooth-pursuit movement was evaluated by following an oscillating illuminated target on a 29-in. screen; the target velocity was regular (18°/s) and the oscillating movements were from center to right, back to the center and then center to left. Each trial was of 20 cycles of 57 s. The saccadic test was performed by asking the patient to watch the target on a horizontal plane; the frequency was 0.4 Hz and the amplitude was ±20°. The tests were done in normal position (central) and repeated after left and right 30-° trunk rotation with hand-fixed head by operator for at least 60 s. The same operator performed all tests. The presence of spontaneous nystagmus in the various positions was recorded. The parameters analyzed in saccadic movement evaluation were: latency, velocity and accuracy. Our cut-off parameters to consider the results as pathological were: value more than 200 ms for latency, a score under 77% for accuracy and a highest velocity under 530°/s. The smooth-pursuit movement analysis was evaluated measuring the gain (eye velocity/target velocity) and the parameter of normality was a value of 0.88 ± 0.2.

The values of the data evaluated were averaged to compare all the groups and subgroups. A parametric test (*t*-test) was done to demonstrate any significant difference between analyzed parameters.

All patients and normal subjects enrolled in the study were informed and they signed the informed consent. Our Institutional Review Board approved the study.

3. Results

The first group included 37 patients, of which 23 were males. The mean age was 36.5 years (range 21–53 years). All patients had a history of whiplash injury (without loss of consciousness) of 12 months duration. All patients in the first group complained of persistent imbalance after the trauma. Four patients were excluded from the evaluation: 3 patients with post-traumatic benign paroxysmal positional vertigo (BPPV) and 1 patient with asymptomatic bilateral hearing loss in 4–8 kHz (PTA 45 dB). The audiological examination did not show any hearing loss in the remaining patients. The first group was subdivided 3 subgroups based on interval of trauma to evaluation as mentioned before. The group A comprised of 11 patients with mean age of 34.1 years. The group B included 11 patients with mean age of 37.6 years and the group C consisted of 11 patients with mean age of 37.6 years.

The control group had 23 asymptomatic subjects, of which 12 were male. The mean age of the control group was 30.4 years (range 19–49 years). All subject of the control group matched the inclusion/exclusion criteria. The audiological examination was normal in all cases but 3 (2 males and 1 female) were excluded from the study.

The results of the analysis are summarized in Tables 1 and 2, where the mean and the standard deviation of all parameters tested of both groups are reported. No statistically significant differences ($p > 0.05$) were noted between the groups and between positions of the head as respect to the trunk. No spontaneous nystagmus related to the neck rotation was recorded. The sex and the age were not related with results of the tests.

4. Discussion

The effects of trauma on cervical column were first described by Crowe in 1928 and by Gray and Abbott in 1953 [11,12]. Significant injuries can occur even at low speed collision but simulated accidents have shown that a 5-miles an hour rear-end car crash can result in a positive

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Table 1
Mean and standard deviation (SD) of parameters tested in neutral position.

	Control Group	Group A	Group B	Group C
Smooth-pursuit gain (SD)	0.87 (±0.04)	0.85 (±0.03)	0.87 (±0.04)	0.87 (±0.03)
Saccadic velocity in degree/sec (SD)	573.05 (±25.25)	574 (±31.05)	564.9 (±28.67)	574.7 (±33.39)
Saccadic latency in degree/sec (SD)	161.63 (±15.67)	154.6 (±10.36)	155.2 (±14.25)	156.1 (±11.68)
Saccadic accuracy in % (SD)	0.84 (±0.05)	0.81 (±0.06)	0.84 (±0.07)	0.82 (±0.06)

Table 2
Mean and standard deviation (SD) of parameters tested in neutral position and after rotation in the patients group.

	Neutral position	30° left rotation	30° right rotation
Smooth-pursuit average value of gain (SD)	0.87 (±0.04)	0.86 (±0.03)	0.87 (±0.04)
Saccadic average value of velocity in degree/sec (SD)	571 (±34.1)	572.05 (±24.35)	565.9 (±27.47)
Saccadic average value of latency in degree/sec (SD)	155.3 (±13)	161.73 (±13.07)	155.4 (±14.35)
Saccadic average value of accuracy in % (SD)	0.83 (±0.06)	0.83 (±0.06)	0.84 (±0.06)

acceleration of 8.2 G of the head [13]. The increasing numbers of car collisions have resulted in an increased number of hospital admissions due to the whiplash injury. Consequently, the insurance claims and the need for forensic evaluation of the damages have increased which spurred us to conduct the present study.

The whiplash injury produces a distortion of the cervical column causing lesions of several cervical sites: muscles, ligaments, vertebral joints, vessels and nerves. The more serious injury could be the stretching of the cervical spine during the flexion–extension of the head. Such sudden and violent movement may result in an elongation of the medulla oblongata or a distention of the cerebellum. Pathophisiologically it is possible to note a central nervous system weakness following a whiplash injury. With respect to inner ear, the exact nature of the lesion is not known but some possible explanation may be: transient ischemia by vertebral artery compression, hemorrhage into labyrinth, direct labyrinthine concussion and noise of the collision.

The typical acute symptoms after whiplash includes: neck pain, headache, paraesthesia of upper cervical dermatomes, dizziness or imbalance and tinnitus. The majority of patients show spontaneous recovery after few months of symptomatic treatment. In some patients the symptoms may persist.

The imbalance is the most incapacitating symptom after whiplash injury [14,15]. The cervicogenic dizziness may occur after trauma of the cervical column however cervical vertigo remains a highly controversial entity [7,15,16].

A neurotological evaluation should be performed in an attempt to find a possible cause and to find out if treatment is possible. The examination includes the assessment of peripheral labyrinth and vestibulo–ocular reflex system by clinical vestibular tests and caloric test. The tests include the evaluation of visually guided eye movements by video-oculography/video-nystagmography.

Previous studies have scarcely demonstrated any relationship between peripheral dysfunction and trauma. Some studies present in literature have shown positional nystagmus and unilateral hyporeflexia in patients of whiplash injury [9,17–22]. Ettlin et al. reported peripheral vestibular deficits in only two cases among 18 after whiplash injury [23]. However all these reports have not used a standard value as benchmark or any proper control group.

The most common type of true vertigo following whiplash injury is BPPV [24]. Following the trauma the otoliths are detached from utricle and displaced within the labyrinth. The diagnosis is confirmed by positional tests. Such patients that present with a true inner ear disease should be separated from those subjects with imbalance due to neck trauma, as we have done in our series to find a true cervical nystagmus, in other words the true presence of nystagmus or eye movement disturbance related to the neck proprioception abnormality (cervical nystagmus).

It is widely considered that a whiplash injury may induce a disorder of neck proprioception caused by forces applied to the neck in the course of the read-end accident. A clinical sign of such disturbance is the so-called ‘‘cervical nystagmus’’, a nystagmus arising from neck rotation with no labyrinthine stimulation. We agree with Fischer et al. in distinguishing either spontaneous or positional nystagmus arising in certain static head positions from the previously reported ‘‘cervical nystagmus’’, because static labyrinthine stimulation may exist [25]. Several Authors failed to demonstrate a relationship between nystagmus and neck proprioceptors’ stimulation [18,19,26]. Also in our series any spontaneous and/or ‘‘cervical nystagmus’’ was noted neither in neutral position nor after 30° left/right rotation. We preferred a 30° rotation to avoid any restriction of the rotation due to the trauma because of testing the patients.

The infrared video-oculography/video-nystagmography allowed us to detect even slight alterations of saccadic and smooth-pursuit movements. This would have been to our

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advantage in revealing a feigning subjects if the damage of neck proprioceptors had produced a recognizable nystagmus or some abnormality of cervico–ocular reflex.

As mentioned before, the neural pathways of ocular movement systems extend from cerebral cortex to oculomotor nuclei trough the cerebellum and the interruption of such ways induces an alteration of ocular movements. Excluding those patients with a known lesion of central nervous system (i.e.: spine, brainstem) after the trauma of the head and focusing the attention only to subjects that had a cervical column disturbance, the prevalence of ocular movements alteration may be very low or totally absent as our series showed, probably because an interruption of the central ways is improbably for a common whiplash trauma.

The functional performance of voluntary oculomotor systems depends upon attentional processing and in patients that had a whiplash injury was demonstrated a reduction of the attention and of information processing velocity [27]. We believe that most of the alterations (increased latency or decreased gain) of saccadic and smooth-pursuit movements, reported elsewhere in whiplash patients, may be due only to a diminishing of attention processing. As Mosimann et al. demonstrated, only intentional saccades are impaired in whiplash patients, while reflexive eye movements are normal [28]. In fact also the searching of nystagmus after cervical torsion in both sides was not significant. Our results showed a normality of all parameters tested in patients of whiplash injury; consequently we can exclude in whiplash patients a correlation between cervical column distortion and alteration of systems that control the saccadic and smooth-pursuit movements. The data recorded in this study is not in accordance with those reported by some authors that noted alterations of optokinetic reflexes and saccadic in theirs cases [7,10,29–31]. Our findings agree with those reported by Fischer et al. [18,19] and Kongsted et al. [32,33].

The absence of differences between normal subjects and patients of whiplash injury underscores the futility of the ocular movements analysis in patients complaining cervical column trauma without central nervous system damages in case of litigation following car collision.

5. Conclusions

Caution is required in interpreting the abnormalities of eye movements in cases of whiplash injury as robust data is not available to support the presence of abnormalities in eye movements. Attention to methods of evaluation should be kept in mind to avoid mixing up a nystagmus arising from labyrinth stimulation with ‘‘cervical nystagmus’’. Furthermore, the reproducibility of the alteration found should be verified to exclude any deliberate alteration by feigning subjects or by decreasing of concentration. The study of ocular movements does not offer a valid tool to differentiate a true patient from a feigning subject after whiplash injury.

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