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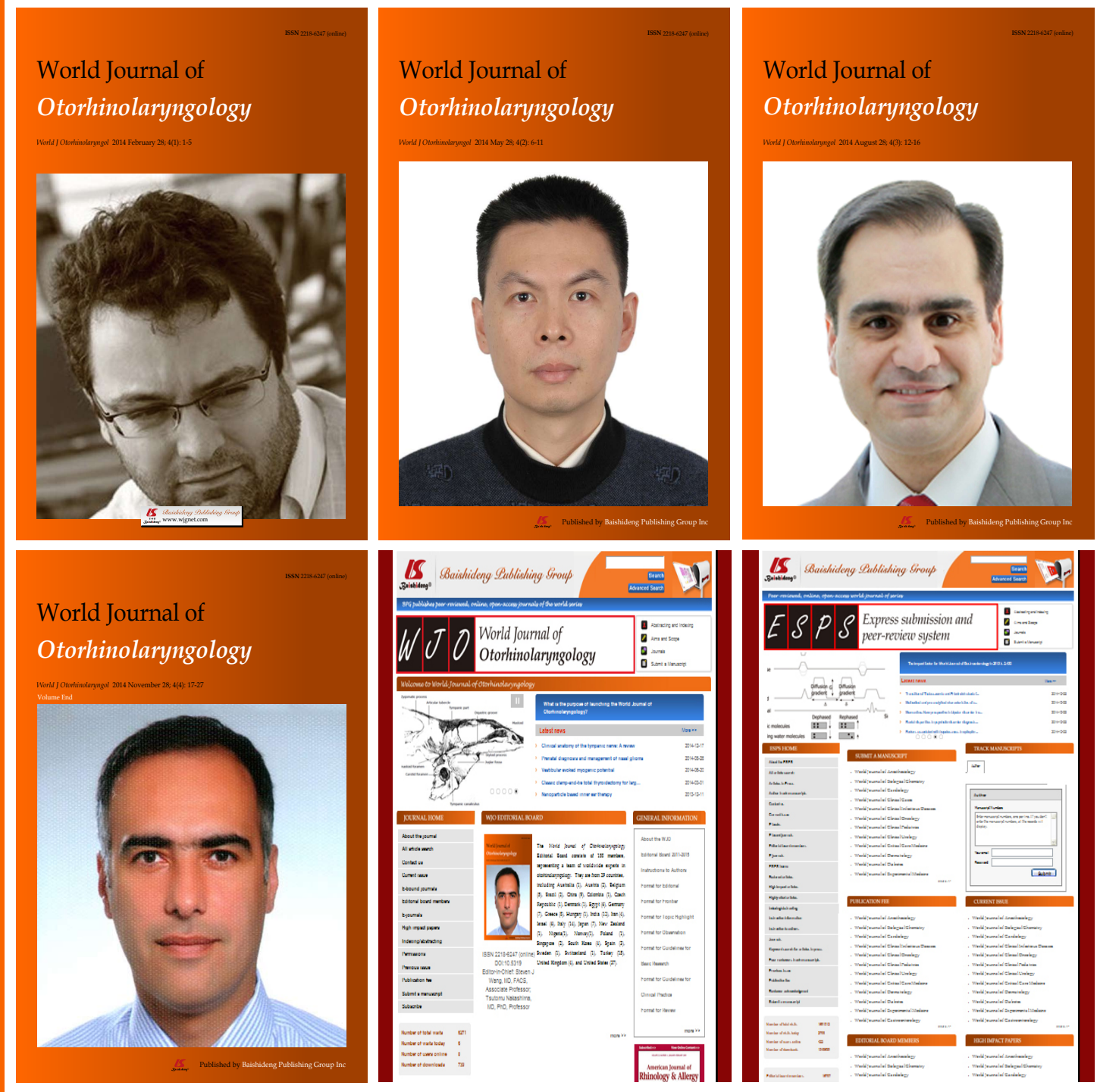

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World Journal of Otorhinolaryngology (*World J Otorhinolaryngol*, *WJO*, online ISSN 2218-6247, DOI: 10.5319) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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BRIEF ARTICLE

Classic clamp-and-tie total thyroidectomy for large goiters in the modern era: To drain or not to drain?

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Abstract

AIM: To evaluate the role of drains in clamp-and-tie total thyroidectomy (cTT) for large goiters.

METHODS: A hundred patients were randomized into group D (drains maintained for 24 h) and ND (no drains). We recorded epidemiological characteristics, thyroid pathology, hemostatic material, intraoperative events, operative time and difficulty, blood loss, biochemical and hematological data, postoperative vocal alteration and pain, discomfort, complications, blood in drains, and hospitalization.

RESULTS: The groups had comparable preoperative characteristics, pathology, intraoperative and postoperative data. Hemostatic material was used in all patients of group ND. Forty patients in group D and 9 in ND felt discomfort ($P < 0.001$).

CONCLUSION: Drains in cTT for large goiters give no advantage or disadvantage to the surgeon. The only "major disadvantage" is the discomfort for the patient. Inversely, drains probably influence surgeons' serenity, especially when cTT is performed in nonspecialized departments.

Key words: Total thyroidectomy; Drains; Postoperative complications; Postoperative hemorrhage; Discomfort

Core tip: The present aim is to elucidate the significance of drains in thyroid surgery for large goiters in the modern era. The authors conclude that there are two major parameters that influence the placement of drains: the surgeon's experience and the patient's discomfort.

Papavramidis TS, Pliakos I, Michalopoulos N, Mistriotis G, Panteli N, Gkoutzamanis G, Papavramidis S. Classic clamp-and-tie total thyroidectomy for large goiters in the modern era: to drain or not to drain? *World J Otorhinolaryngol* 2014; 4(1): 1-5 Available from: URL: http://www.wjgnet.com/2218-6247/full/v4/i1/1.htm DOI: http://dx.doi.org/10.5319/wjo.v4.i1.1

INTRODUCTION

Total thyroidectomy (TT) is nowadays considered a "routine" operation in specialized endocrine departments. This operation can be performed either by classic incisions (Kocher or Sofferman) or by minimal scar techniques. Conventional clamp-and-tie thyroidectomy consists of devascularization of the thyroid by double ligating and dividing the branches of the thyroid vessels, followed by excision of the gland. During thyroid surgery, adequate hemostasis and keeping the operative field dry and clean is of utmost importance. Suture ligations are time-consuming, carry the risk of knot slipping, and are not suitable for endoscopic surgery[1]. For that reason,

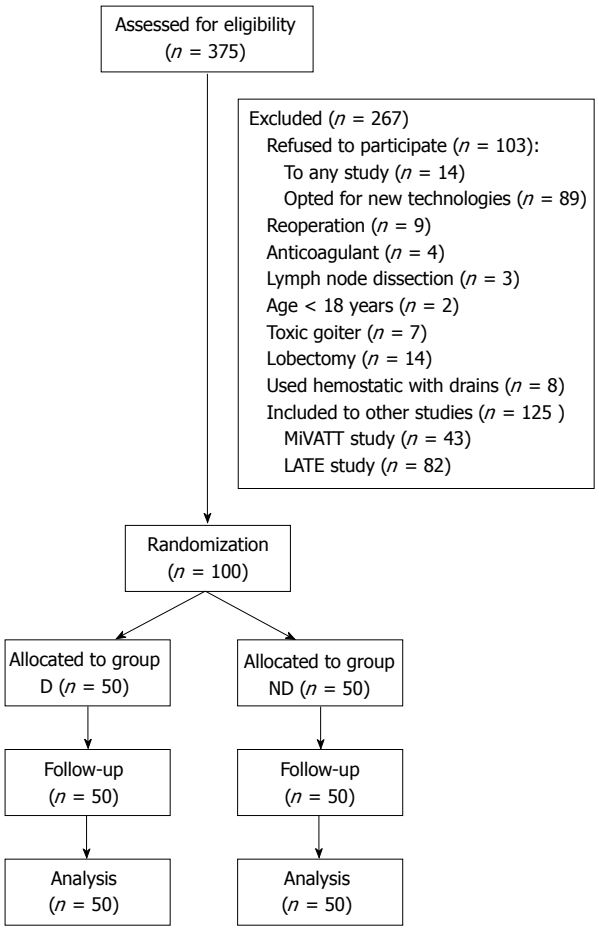

Figure 1 Flow diagram of the study.

new energy sources and methods of hemostasis have been used in the last years in thyroid surgery with great effectiveness. However, the classic clamp-and-tie thyroidectomy has not been abandoned and is frequently employed in general surgery departments, either due to the unavailability of new technologies or to a lack of training in other techniques. Whatever the method of hemostasis, when TT is performed, it is of prime importance to achieve accurate and efficient hemostasis in order to minimize complications.

Since meticulous hemostasis is of prime importance in every type of thyroid surgery, the use of draining tubes seems paradoxical. With small volume goiters, the above statement may be true; however, this is not the case in large goiters, especially those performed with the classic clamp-and-tie technique. From that perspective, the present prospective randomized trial was designed, aiming to evaluate the necessity of drains when a clamp-and-tie total thyroidectomy (cTT) is performed for a large goiter.

MATERIALS AND METHODS

The present prospective randomized trial was approved by the ethics committee of AHEPA University Hospital. It was registered to ClinicalTrials.gov (identifier: NCT00691990). The registration period for the study lasted from 1st July, 2008 to 31st December, 2010.

The inclusion criteria were: (1) acceptance to participate in the study (signed informed consent form); (2) age > 18 years; and (3) a scheduled cTT. The exclusion criteria were: (1) participation in another clinical trial which affects outcomes (small volume thyroids < 50 mL were included in other studies); (2) a previous thyroid operation; (3) a toxic condition; and (4) anticoagulation treatment. Figure 1 displays the flow diagram of the study. One hundred adult patients with benign or malignant thyroid disease scheduled for classic total thyroidectomy at the 3rd Department of Surgery of AHEPA University Hospital of Thessaloniki were randomized into 2 groups according to whether drains were going to be used (group D) or not (group ND). Randomization was performed by using computer-generated tables immediately after the assessment for eligibility.

Classic TT was performed with patients in the supine position with the head slightly hyperextended[2]. All procedures were performed by a team dedicated to endocrine surgery. Preoperative laryngoscopy was performed in all patients to assess vocal cord motility. A 4 cm cervicotomy was performed. Ligatures were done with resorbable 4-0 vicryl ligatures; in group D, a 14 French negative pressure drain was placed, whereas in group ND no drain was placed. Both groups received 2 doses of 40 mg parecoxib sodium, one at the end of the operation and one 12 h later. Anesthesia was standardized following the protocol proposed by Andrieu *et al*[3]. Patients were premedicated with hydroxyzine (1.5 mg/kg orally) 2 h before surgery. General anesthesia was induced using propofol (2-3 mg/kg) and sufentanil (0.3 mg/kg). Tracheal intubation was facilitated by the administration of atracurium (0.5 mg/kg). General anesthesia was maintained with sevoflurane (0.5%-1.8%) in an oxygen-nitrous oxide mixture (60/40%). The sevoflurane was adjusted to maintain a bispectral index (Aspect Medical Systems, Inc., Newton, MA) between 40 and 60. Additional doses of sufentanil (0.15 mg/kg) were administered for variations of systolic blood pressure and heart rate of > 20% when compared with the values measured before operation.

The following data were recorded: age, gender, body mass index, American Society of Anesthesiologists (ASA) status, medications, thyroid pathology and weight, use of hemostatic material, intraoperative events/complications, duration of the operation, intraoperative blood loss, operative difficulty, calcemia (preoperative, postoperative), preoperative and postoperative standard biochemical and hematological data (SGOT, SGPT, LDH, Glc, Ure, Cre, K^+, Na^+, Mg^{2+}, TP, ALB, fT3, fT4, TSH, PTH, PT, aPTT, INR, Ht, Hgb, WBC), preoperative and postoperative vocal motility, postoperative vocal alteration, postoperative pain, discomfort, complications, blood in the drains, and length of hospital stay.

Operative difficulty was assessed by a rating scale ranging from 1 (very easy) to 5 (very difficult). Postoperative voice alteration was assessed by a VAS, ranging from 1 (no voice alteration) to 10 (worst imaginable alteration). Postoperative pain was assessed by a visual analogue scale

Table 1 Epidemiological characteristics of both groups (mean ± SD)

	Group D (n = 50)	Group ND (n = 50)
Sex (male/female)	4/46	6/44
Age (yr)	47.0 ± 5.6	51.4 ± 10.5
Body mass index (kg/m^2)	27.35 ± 5.15	28.08 ± 6.06
ASA score	1.64 ± 0.71	1.42 ± 0.67
Pathology		
Benign	43	45
Malignant	7	5
Thyroid weight (g)	51.8 ± 34.5	49.4 ± 34.4
Use of hemostatic material	No	Yes
Duration of operation (min)	98.5 ± 14.1	94.6 ± 13.9
Intraoperative blood loss (mL)	26.7 ± 18.9	24.8 ± 21.3
Blood in the drains (mL)	76.3 ± 44.4	-
Operative difficulty	1.90 ± 0.54	1.96 ± 0.53
Pain VAS score	1.58 ± 1.60	1.68 ± 1.59
Discomfort	40	9
Complications (no of patients)		
Transitory RLN palsy	1	1
Transitory hypoparathyroidism	7	5
Bruising	1	4

Group D: Drains maintained for 24 h; Group ND: No drains. ASA: American Society of Anesthesiologists; RLN: Recurrent laryngeal nerve.

(VAS), ranging from 1 (no pain) to 10 (worst imaginable pain). Pain and voice alterations were evaluated by the patient, whereas operative difficulty was assessed by an observing surgeon. The observing surgeon was the same for all operations. Discomfort was evaluated using a yes or no question.

Calcemia was determined every postoperative day until hospital discharge. Clinical hypocalcemia was defined as total calcium < 8.2 mg/dL, associated with a positive Chvostek or Trousseau sign or a patient complaint of paresthesia.

RESULTS

A total of 375 patients were assessed for eligibility but only 100 were included in this trial (Figure 1). The volunteers were divided into two groups. The epidemiological characteristics of both groups are presented in Table 1. Both groups were comparable preoperatively concerning age, male/female ratio, body mass index and ASA score.

The pathology evaluation revealed benign disease in 88 patients (43 in group D and 45 in group ND) and malignant disease in 12 patients. Intraoperative blood loss, duration of the operation and operative difficulty were comparable for both groups. Hemostatic material was used in all of the patients in group ND. The suction drain was maintained for 24 h in all group D patients regardless of the content of the drains.

There was no postoperative hemorrhage with compromised airway in any patient. Thus, surgical evacuation of the hematoma was not required. From this perspective, 4 patients in group ND and 1 patient in group D presented with bruising in the area of operation. The levels of postoperative pain (measured in the VAS scale) were comparable between the two groups. Permanent unilateral recurrent laryngeal nerve (RLN) injury was not observed; however, transient RLN palsy was noticed in 1 patient in each group. Permanent hypoparathyroidism was not observed in any patient; however, transient hypoparathyroidism occurred in 12 patients (7 in group D and 5 in group ND). Those patients were treated as preplanned (see section material and methods). Finally, 40 patients from group D and 9 patients from group ND felt discomfort ($P < 0.001$).

DISCUSSION

Drains or no drains after thyroid surgery? This seems to be an obsolete question for specialized units in thyroid surgery. New technologies and hyperspecialization make the answer appear obvious: no drains. However, the above mentioned two conditions are not fulfilled for the majority of patients and the majority of departments. Most patients around the globe are operated on in general surgery departments that perform the classic clamp-and-tie technique with no advanced hemostatic devices. By performing this clinical trial, we aim to evaluate the effect that drains have when executing a classic clamp-and-tie thyroidectomy for large goiters (more than 50 mL).

When designing the present study, we included only patients scheduled for cTT in order to establish a homogenous population. In this way, the effects of new hemostatic technologies and the effect of partial thyroidectomies were eliminated. No patients with a previous operation of the thyroid gland were included to avoid possible alteration of the regional anatomy. Additionally, patients participating in other clinical trials that could potentially affect this study's outcomes were also excluded (*e.g.*, patients with preoperative thyroid volumes less than 50 mL). Patients receiving anticoagulation treatment for other medical conditions were excluded in order to minimize the probability of bleeding due to anticoagulation treatment. For the same reason, we excluded the 7 patients screened that were not in euthyroid condition (toxic). What is noteworthy is that we expected a higher percentage of acceptances to participate in the study. Surprisingly, 89 patients (24.25%) refused to participate in the study because they opted for the use of new technologies. Happily, this seemed to have no impact on the studied population characteristics. This was further confirmed by the fact that the epidemiological characteristics of the present study are comparable to our previous studies[2,4-6]. We should, however, notice that patients exhibit a clear preference towards total thyroidectomies performed using new technologies rather than the classic clamp-and-tie technique, even when assured that complication rates and hospitalization are comparable[2,4].

Complications associated with thyroid surgery occur regardless of the technique employed. Nowadays, there are two major complications related to total thyroidectomies: iatrogenic hypoparathyroidism and RLN palsy[7]. One of the primary aims of this study was to examine

whether drains altered the occurrence of these two major complications in any way. As mentioned in the results section, the present study supports the fact that the incidence of major complications is not altered in any way by the usage of drains. This data is in accordance with previous clinical trials[8-17]. On the other hand, among the rare complications following thyroidectomy, but without doubt the most serious, is postoperative hemorrhage with the potential for tracheal compression, airway involvement and death. Immediate or early hemorrhage occurs in a small percentage[18]. Additionally, postoperative hematoma remains a more or less unknown and unpredictable event with a possibility of subsequent respiratory distress[19]. The rate of postoperative bleeding with formation of a hematoma has been reported to be 0.1%-4.3%, with the rate for symptomatic hematomas being 0.1%-1.0%[20,21]. The present study indicates a 5% rate of asymptomatic hematomas without any symptomatic ones. This marginally increased incidence is probably due to the increased volume and weight of the thyroids excised in this study (see inclusion criteria). What is noteworthy, however, is that there is no statistical difference between the two groups concerning hematomas (bruising). So, from this point of view, the presence or not of a drain has no influence on hematoma formation occurrence.

The time frame for observation after total thyroidectomy is changing[18]. Schwartz *et al*[22] described a critical period of time in which bleeding occurs most commonly (in all cases, the potential for airway compromise was identified within 4 h of surgery). Accordingly, Burkey *et al*[23] found that 43% of hematoma presentations were within 6 h, 38% between 7 and 12 h, and 8% after 24 h or more. Many studies agree that late hematomas are uncommon and the large majority of hematomas occur in the earlier period[18,23-25]. It has been shown that late hematomas (> 24 h) occurred only in patients with resection of substernal goiters and who had cardiac comorbidity that required anti-coagulation/anti-platelet therapy[7]. Postoperative drains allow withdrawal of postoperative hemorrhage. However, they cannot be considered a substitute for meticulous surgical dissection and hemostasis and may predispose to postoperative infection. Under these perspectives, it seems very logical that the use of drains does not alter the duration of hospitalization, as proved in this study. Most surgeons remove the drains after 24 h and send the patient home.

From all of the above, we can actually see no disadvantage or advantage in the use of drains in thyroid surgery. Why then do we observe surgeons with similar experiences following different strategies? Two parameters have to be taken into consideration when thinking around this subject: patients' discomfort and surgeons' serenity. We found no study to date that correlates patients' discomfort and the presence of drains in any way. We observed that drains were positively correlated with discomfort. On the other hand, surgeons' serenity has to be taken into account. We believe that the above two factors pull the two ends of the rope in the tug of war of the decision between drains or no drains. Since surgeons' serenity seems to be largely influenced by the number of thyroidectomies performed, this is probably the reason why no drains are used in high volume specialized centers. However, as thyroidectomies are largely performed by general surgeons or otorinolaryngologists in general departments, this is the reason why drains are placed in a large proportion of thyroidectomised patients.

The results of this study confirm that the usage of drains when performing total thyroidectomy for a large goiter gives no advantage or disadvantage to the surgeon. Postoperative course and complication rates are comparable in both groups. The only "major" disadvantage that drains have is that they induce discomfort in the patient. On the other hand, they probably play an important role in the surgeons' serenity, especially when the operation is performed in nonspecialized departments.

COMMENTS

Background

New energy sources and methods of hemostasis have been used in thyroid surgery with great effectiveness over the last years. However, the classic clamp-and-tie thyroidectomy has not been abandoned and is frequently employed in general surgery departments, either due to the unavailability of new technologies or a lack of training in other techniques.

Research frontiers

The present study supports the fact that the incidence of major complications is not altered in any way by the usage of drains.

Innovations and breakthroughs

The results of this study confirm that the usage of drains when performing total thyroidectomy for a large goiter gives no advantage or disadvantage to the surgeon.

Applications

Drains in clamp-and-tie total thyroidectomy for large goiters give no advantage or disadvantage to the surgeon.

Peer review

The authors have studied the potential benefits of drainage after total thyroidectomy in cases where no advanced hemostatic instruments were used.

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15 Morse SS. Factors in the emergence of infectious diseases.

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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FRONTIER

Vestibular evoked myogenic potential

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Abstract

Vestibular evoked myogenic potential (VEMP), is an electromyographic response of vestibular origin evoked by sound, vibration or electrical stimulation. VEMP is widely used as a clinical test of the otolith organs. Nowadays, two kinds of VEMP, cervical VEMP (cVEMP) and ocular VEMP (oVEMP) are clinically used. cVEMP is a test of sacculo-collic reflex while oVEMP is a test of utriculo-ocular reflex. Absence of responses, large interaural asymmetry of amplitudes, prolonged peak latencies, and abnormal thresholds of responses are regarded as abnormal responses. Clinical application to various diseases of the vestibular system was performed. Using VEMP, a new type of vestibular neuritis, inferior vestibular neuritis was established. A prominent feature of VEMP in Meniere's disease is a shift of a preferred frequency in cVEMP. The whole aspects of VEMP findings in patients with benign paroxysmal positional vertigo are not clarified yet. Sensitivity of cVEMP to vestibular schwannoma was 80.0%, while specificity was 52.7%. Concerning diagnosis of superior canal dehiscence syndrome (SCDS), oVEMP to air-conducted sound is the most helpful. Augmentation of oVEMP responses is a prominent feature in SCDS. I also presented "idiopathic otolithic vertigo", which I proposed as a new clinical entity based on VEMP findings. Some patients complained of lateral tilting sensation in the roll plane, or tilting or translational sensation in the pitch plane without rotatory vertigo. Majority of patients with these symptoms had absent or decreased responses of oVEMP and/or cVEMP. I proposed that these patients could be diagnosed as having "idiopathic otolithic vertigo".

Key words: Vestibular evoked myogenic potential; Otolith; Saccule; Utricle; Otolithic vertigo

Core tip: This is a review of Vestibular evoked myogenic potential (VEMP). In this review I presented fundamentals concerning VEMP. Also I showed various types of clinical application of VEMP. Finally I introduced a new clinical entity, idiopathic otolithic vertigo which I poroposed. Idiopathic otolithic vertigo cannot be diagnosed without application of VEMP.

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INTRODUCTION

Vestibular evoked myogenic potential (VEMP) is an electromyographic response derived from the vestibular labyrinth evoked by sound, vibration, or electrical stimulation[1]. VEMP is a clinical test of the otolith organs, sensors of linear acceleration. The otolith organs in human are consisted of the saccule and the utricle. VEMP was first reported by Colebatch and Halmagyi in 1992[2]. Since 1992 many papers concerning VEMP have been published all over the world. At first, VEMP, which was recorded on the sternocleidomastoid muscle (SCM), was performed as a test of otolith-collic reflex[3]. Later, another method, recording around the eyes, has been also adopted as a test of otolith-ocular reflex[4,5]. The former is called cVEMP (cervical VEMP), and the latter is called oVEMP (ocular VEMP). These tests provide different

information concerning the vestibular labyrinth from a caloric test and a head-impulse test (HIT)[6], which are tests of the semicircular canals. In this review I will present fundamentals concerning VEMP.

RESPONSIBILITY TO SOUND OF THE MAMMALIAN VESTIBULAR LABYRINTH

For understanding VEMP, responsiveness to sound of the mammalian vestibular labyrinth must be addressed. In 1977 Young *et al*[7] reported responses of the vestibular labyrinth to air-conducted sound (ACS) and bone-conducted vibration (BCV) using squirrel monkeys. They showed vestibular afferents could respond to ACS and BCV. Concerning ACS, saccular afferents showed lower thresholds than other end-organs. Didier *et al*[8] showed that the inferior branch of the vestibular nerve (the inferior vestibular nerve) could respond to sound stimulation using guinea pigs which had destroyed cochlea but preserved vestibular labyrinth by amikacin injection. In 1990s, McCue *et al*[9,10] using cats and Murofushi *et al*[11-13] using guinea pigs showed sound-sensitivity of the mammalian otolith organs using single-unit recording technique. McCue *et al*[10] reported that saccular afferents responded to sound stimulation and that best frequencies of responses were between 500 and 1000 Hz. Murofushi *et al*[12] showed that sound-sensitive otolith afferents could be also tilt-sensitive and were in the caudal part of the superior vestibular nerve as well as the inferior vestibular nerve. Both groups reported that irregularly firing units, which are from type I hair cells, responded to sound well. Their studies confirmed that hair cells in the saccular macula, especially type I cells could respond to sound. McCue *et al*[10] also suggested that preferred frequencies of the saccule were between 500 and 1000 Hz while Murofushi *et al*[13] suggested that the utricle might be also respond to sound. Curthoys *et al*[14] studied responsibilities to BCV. Their study showed that irregularly firing otolith afferents also responded to BCV well.

RECORDING METHODS AND NORMAL RESPONSES OF VEMP

cVEMP

Surface electrodes are used for recording. Active electrodes are placed on the belly of the sternocleidomastoid muscle (SCM) with reference electrodes on the lateral end of the upper sternum. The ground electrode is placed on the nasion. Nowadays 500 Hz short tone bursts (STB) (rise/fall time = 1 ms, plateau time = 2 ms, 125-130 dBSPL, ACS) are usually used as stimuli. Clicks are also applicable. The repetition rate of stimulation presentation is 5 Hz, and the time window for analysis is -20-80 ms. Signals are bandpass-filtered (20-2000 Hz) and 100 responses are averaged. BCV can be also used. Subjects must be instructed to keep contracting their SCM during recording. As methods for contraction, rotation of the neck or raising the head from the pillow is recommended.

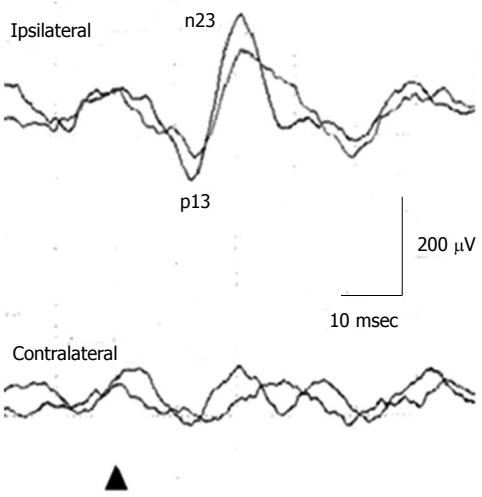

Figure 1 Cervical vestibular evoked myogenic potential waveforms in a healthy subject.

In a healthy subject, to 125 dBSPL 500 Hz ACS STB, the first positive deflection, of which the peak is around 15 ms is recorded in the ipsilateral SCM to the stimulated ear, followed by the negative deflection, of which the peak is around 23 ms (Figure 1). Conventionally, the first positive peak and the following negative peak are called p13 and n23 respectively. Absence of responses, large interaural asymmetry of p13-n23 amplitudes, prolonged peak latencies, and abnormal thresholds of responses are regarded as abnormal responses[1]. Concerning cVEMP, a published guideline should be referenced[5].

For assessment of amplitudes, correction of amplitudes using background muscle activities is desirable. For assessment of interaural asymmetry of amplitudes, percent cVEMP asymmetry has been used[15,16]. Percent cVEMP asymmetry = 100 (CAcu - CAca)/(CAcu + CAca)CAcu(a) = corrected amplitude of p13-n23 on the unaffected (affected) side. The upper limit of percent cVEMP asymmetry in our laboratory is 41.6. The above-mentioned guideline indicated 50.0 as a strict standard of the upper limit of percent cVEMP asymmetry[15]. As latencies can be affected by recording conditions, each laboratory should set their own normal range. The upper limit of p13 latency in our laboratory is 17.7 msec (125 dBSPL 500 Hz STB ACS)[16]. Thresholds lower than 95 dBSPL (500 Hz STB ACS) are definitely abnormal.

It should be taken into consideration that subjects with conduction problems in the middle ear would show absence of responses even though they had normal vestibular function. Air-bone gap more than 15dB makes recording of cVEMP to ACS useless.

oVEMP

Surface electrodes are used for recording. Active electrodes are placed just beneath the lower eye lids with reference electrodes 2 cm below active electrodes[16]. The ground electrode is placed on the nasion. STB of 500 Hz (rise/fall time = 1 ms, plateau time = 2 ms, 125-130 dBSPL, ACS) are standard stimuli. Clicks are not used because healthy subjects frequently show absence of re-

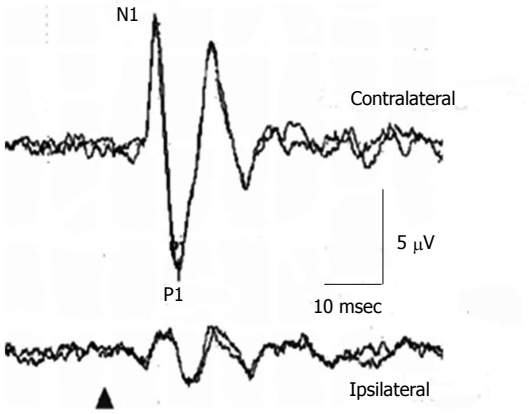

Figure 2 Ocular vestibular evoked myogenic potential waveforms in a healthy subject.

sponses[5]. Instead, BCV are used more frequently for recording oVEMP than cVEMP[17]. The repetition rate of stimulation is 5 Hz, and the time window for analysis is -20-80 ms. Signals are bandpass-filtered (20-2000 Hz) and 100 responses are averaged. Other ranges of bandpass-filter may be used (*e.g.*, 5-500 Hz)[17]. Subjects must be instructed to keep upward gaze during recording (approx. 20 deg).

In a healthy subject, to 125 dBSPL 500 Hz ACS STB, the first negative deflection, of which the peak is around 11 msec, is recorded beneath the contralateral eye to the stimulated ear, followed by the positive deflection, of which the peak is around 15 ms (Figure 2)[16]. Conventionally, the first negative peak and the following positive peak are called N1 and P1. Absence of responses, large interaural asymmetry of N1-P1 amplitudes, prolonged peak latencies, and abnormal thresholds of responses are regarded as abnormal responses. For assessment of interaural asymmetry of amplitudes, percent oVEMP asymmetry has been used[16]. The formula is basically the same as percent cVEMP asymmetry. The upper limit of percent oVEMP asymmetry in our laboratory is 44.3. The upper limit of N1 latency in our laboratory is 13.6 msec (125 dBSPL 500 Hz STB ACS)[16]. As latencies can be affected by recording conditions, each laboratory should set their own normal range. Thresholds lower than 105 dBSPL (500 Hz STB ACS) are abnormal.

Pathways of VEMP

Main pathways related to VEMP are considered as follow (Figure 3). The main neural pathway of cVEMP is uncrossed in the brainstem. cVEMP mainly reflects sacculo-collic reflexes to sound stimulation. Saccular afferents project to the vestibular nucleus through the inferior vestibular nerve. Neurons in the vestibular nucleus (inhibitory) project to the motoneurons in the ipsilateral accessory nerve nucleus through the ipsilateral medial vestibulo-spinal tract[1,18].

The main neural pathway of oVEMP is crossed in the brainstem[5]. oVEMP mainly reflects utriculo-ocular reflexes to sound stimulation[16,19]. Utricular afferents

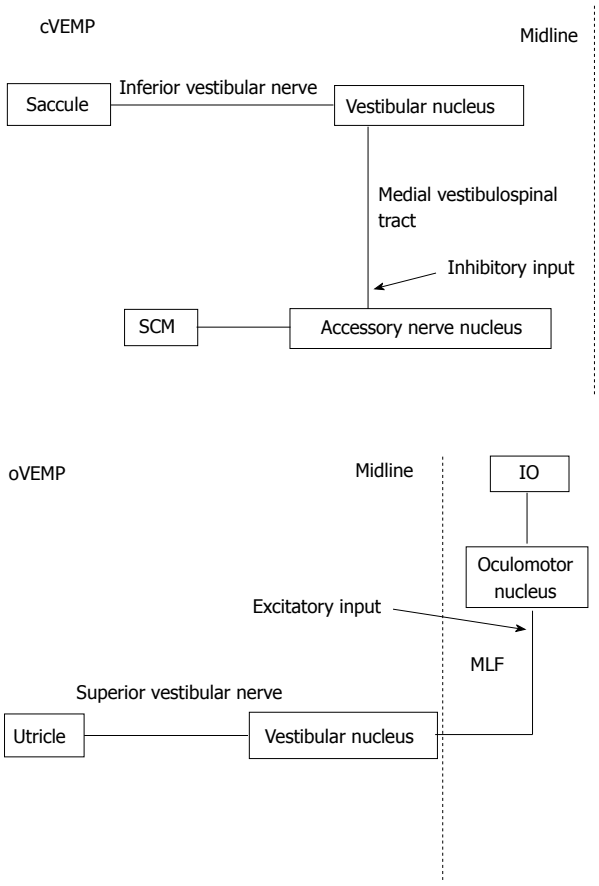

Figure 3 Supposed neural pathway of Cervical vestibular evoked myogenic potential and ocular vestibular evoked myogenic potential. cVEMP : Cervical vestibular evoked myogenic potential; oVEMP: Ocular vestibular evoked myogenic potential; SCM: Sternocleidomastoid muscle; IO: Inferior oblique muscle; MLF: Medial longitudinal fasciculus.

project to the vestibular nucleus through the superior vestibular nerve. Neurons in the vestibular nucleus (excitatory) project to the contralateral oculomotor nucleus through the contralateral medial longitudinal fasciculus (MLF)[20]. oVEMP responses are mainly from the inferior oblique muscle[21]. However, the pathway of oVEMP is still somewhat controversial.

Clinical application of VEMP

VEMP has been clinically applied to various diseases or conditions which might have abnormal findings in the vestibular system.

Vestibular neuritis

Conventional diagnostic criteria of Vestibular neuritis (VN) were as follow: (1) a single attack of acute spontaneous vertigo lasting at least several hours without accompanying auditory symptoms; (2) absence of other cranial nerve or central nervous system symptoms or signs; and (3) severe canal paresis (CP) on caloric testing (CP more than 50%)[22]. These criteria are good for detection of acute deafferentation of the superior vestibular nerve, but they cannot detect deafferentation of the inferior vestibular nerve. In VN patients diagnosed accord-

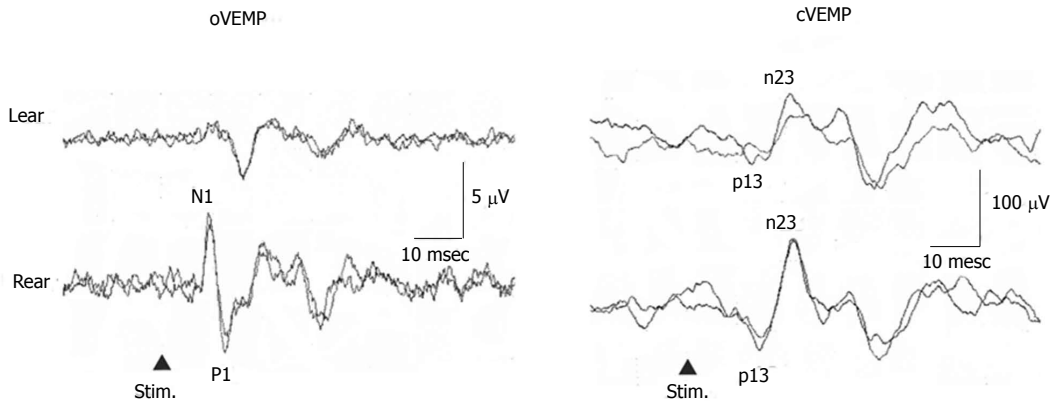

Figure 4 Vestibular evoked myogenic potential responses of a 57-year-old man with episodic lateral tilt sensation diagnosed as having idiopathic otolithic vertigo. He showed absent oVEMP to the left ear stimulation. cVEMP : Cervical vestibular evoked myogenic potential; oVEMP: Ocular vestibular evoked myogenic potential.

ing to these conventional diagnostic criteria, cVEMPs were absent or decreased in amplitudes in one third to half of patients[1,22], while oVEMPs were abnormal in most patients[16]. Patients with absent or highly decreased caloric responses and abnormal cVEMP responses can be regarded as superior and inferior (total) VN, while patients with absent or highly decreased caloric responses but normal cVEMP responses can be regarded as superior VN with spared inferior vestibular nerve functions. This classification lead to a new clinical entity, inferior VN with spared superior vestibular nerve functions[23]. According to retrospective study by Chihara *et al*[23], at the period when 24 patients were diagnosed as total VN and 34 patients were diagnosed as superior VN, 13 patients were regarded as inferior VN. Patients with inferior VN showed tendency of milder and shorter symptoms than patients with total or superior VN. Clinical application of cVEMP enabled us to diagnose patients as having inferior VN. These patients, otherwise, would be left as undiagnosed.

Meniere's disease

One of distinct features of VEMP in Meniere's disease (MD) patients is a shift of a preferred frequency in cVEMP[24,25]. Healthy subjects show the largest amplitudes and the lowest thresholds in ACS cVEMP to stimulation of STB around 500 Hz. On the other hand, MD patients frequently showed a shift of a preferred frequency to 1000 Hz. Node *et al*[26] found that the preferred frequency shift was normalized by dehydration using furosemide. Probably, the frequency shift was caused by endolymphatic hydrops in the saccule. Endolymphatic hydrops in the saccule can be also detected by glycerol-VEMP test. Murofushi *et al*[27] found that 50% of MD patients with abnormal cVEMP prior to glycerol administration showed significant improvement of VEMP responses in 3 h after oral administration of glycerol (1.3 mg/kg body weight) on the affected side.

Benign paroxysmal positional vertigo

The whole aspects of VEMP findings in patients with Benign paroxysmal positional vertigo (BPPV) are not clarified yet. Some investigators reported unilaterally abnormal oVEMP in patients with posterior canal BPPV[28]. Abnormal oVEMPs could be decrease or augmentation of responses. Seo *et al*[28] assumed that reduced responses on the affected side might be from partial degeneration of the utricular hair cells and that augmented responses might be from hypermobility of stereocilia due to detachment of otoconia. On the other hand, Nakahara *et al*[29] reported bilaterally abnormal oVEMP in patients with posterior canal BPPV. They assumed that bilaterally abnormal (= absent) oVEMP might reflect utricular degeneration as a background of BPPV. Further study is required concerning VEMP in BPPV.

Vestibular schwannoma

Majority of patients with Vestibular schwannoma (VS) showed absent or decreased responses on the affected side, while some had prolonged latencies[30,31]. According to Ushio *et al*[31], sensitivity of cVEMP was 80.0%, while specificity was 52.7%. Although it is expected that combined application of cVEMP with caloric tests might be useful for prediction of the nerve origin of VS, Ushio *et al*[32] did not find correlation of results of these tests to the nerve origin. However, Murofushi *et al*[33] reported that a patient with very small VS from the inferior vestibular nerve showed abnormal cVEMP to clicks with normal cVEMP to 500 Hz ACS STB, normal caloric responses, and normal auditory brainstem responses (ABR). Study concerning prediction of the nerve origin of VS using physiological tests should be focused on cases with very small mass. Kinoshita *et al*[34] and Murofushi *et al*[35] reported that oVEMP might be also useful for diagnosis of VS. However, diagnostic values of oVEMP are remained to be clarified.

Superior canal dehiscence syndrome

Dehiscence of the bone overlying the superior (anterior) semicircular canal was first described in 1998 by Minor *et al*[36]. It has been reported that this condition (SCDS) manifests as various vestibular and/or auditory symptoms[36-38]. While detection of dehiscence with computed tomography scans is essential for definite diagnosis, it

has been also reported that augmentation of VEMP responses, especially oVEMP to ACS is marked[37,39,40]. ACS oVEMP might be useful for screening of SCDS in dizzy patients. Zuniga *et al*[40] reported that an n10 (N1 in this paper) amplitude of greater than 9.3 μV and a peak-to-peak amplitude (N1-P1 in this study) of greater than 17.1 μV exhibited 100% sensitivity and specificity for SCDS.

Idiopathic otolithic vertigo

Murofushi *et al*[41,42] reported that some patients complained of lateral tilting sensation in the roll plane, or tilting or translational sensation in the pitch plane without rotatory vertigo. Majority of patients with these symptoms had absent or decreased responses of oVEMP and/or cVEMP (Figure 4). Patients with tilting sensation in the roll plane had tendency to show abnormal oVEMP, while patients with tilting or translational sensation in the pitch plane had tendency to show abnormal cVEMP. Murofushi *et al*[41,42] proposed "idiopathic otolithic vertigo" as a new clinical entity, because the otolith organs are sensors of linear acceleration and dysfunction of them could result in illusion of linear movement[43]. Abnormal VEMP findings may be essential for diagnosis of otolithic vertigo. As a next step, pathophysiology of idiopathic otolithic vertigo should be clarified.

Sensorineural hearing loss

Sensorineural hearing loss itself does not affect cVEMP or oVEMP. Patients with total hearing loss showed normal responses[1,3,44,45].

VEMP is a still developing technique and new discovery is expected. I hope that many clinicians and researchers may be interested in it.

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World Journal of Otorhinolaryngology (*World J Otorhinolaryngol*, *WJO*, online ISSN 2218-6247, DOI: 10.5319) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJO covers topics concerning endoscopy, rhinology, pharyngology, laryngology, tracheo-esophagology, otology, tracheology, cancer, nasal symptomatology, congenital nasal diseases, inflammatory diseases of the external nose, rhinitis, allergic rhinitis, nasal polyps, nasal septal diseases, nasal bleeding, nasal or sinus foreign bodies, sinusitis, rhinogenic complications, diagnostic imaging, evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of otorhinolaryngologic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Prenatal diagnosis and management of nasal glioma

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Abstract

Advances in foetal imaging have increased our detection rate of craniofacial abnormalities in utero. Nasal glioma is a rare, benign, congenital facial defect. Once detected, further imaging is required to assess for intracranial communication, the presence of additional defects, determine the patency of the aerodigestive tract and decide on timing of delivery. The authors review the current literature on diagnosis and management of nasal glioma in this rapidly advancing field of craniofacial anomalies detected in utero. Literature search of EMBASE and MEDLINE databases yielded 594 articles, which were screened by 2 independent reviewers. A total of 7 papers were selected after exclusion. There have been seven cases of prenatally diagnosed nasal glioma. The earliest of these was detected at 20 wk gestation. The majority were investigated with foetal magnetic resonance imaging (MRI) to establish any intracranial communication or bony defects. Ultrasound monitoring, doppler waveform and 3D rendered images were utilised to delineate the lesion, monitor growth and differentiate potential diagnosis. Postnatal MRI is favoured by most to re-evaluate the lesion and aid surgical planning. Surgical resection was performed within the first few months of life. Diagnostic uncertainty was seen in all cases, until formal histology was obtained, emphasising the challenges, and need for early appropriate specialist input. Whilst the prenatal detection of craniofacial abnormalities increases, there remain diagnostic challenges in differentiating prenatal congenital midfacial defects in utero. These defects are best investigated and monitored using prenatal ultrasound and MRI, to narrow the differential diagnosis, guide timing of delivery and allow for appropriate surgical planning. Prenatally detected nasal glioma, may only be confirmed on histology and families must be counselled appropriately to prepare them for the possible alternative diagnoses. Early surgical resection was undertaken to achieve more favourable aesthetic outcomes, reduce complications of ocular development and provide definitive histological diagnosis.

Key words: Nasal glioma; Prenatal; Craniofacial; Imaging

Core tip: Advances in foetal imaging have increased our detection rate of craniofacial abnormalities in utero. This enables early surgical input providing differential diagnosis, surgical planning, timing of delivery and counselling for families. Seven cases of prenatally diagnosed nasal glioma have been reported. The authors advocate ultrasound and foetal magnetic resonance imaging (MRI) to delineate the lesion, exclude intracranial involvement and monitor size. Foetal MRI also provides accurate delineation of the upper aerodigestive tract, allowing clinicians to anticipate airway compromise, in this otherwise benign condition. Early surgical resection is advised, for better aesthetic outcomes and to ensure normal ocular development.

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INTRODUCTION

Advances in foetal imaging have improved our detection rate of craniofacial abnormalities in utero. These improvements allow for earlier diagnosis, which can be made as early as the 11th week of gestation[1]. As such, the Head and neck surgeon is thrust into a new role in foetal management as part of the multidisciplinary team, providing differential diagnosis, advising on timing of birth and postnatal surgical planning.

While craniofacial abnormalities are uncommon, the most frequently occurring include; encephaloceles, nasal gliomas and nasal dermal sinus cysts. The differential detectable on prenatal ultrasound also includes haemangiomas, dacryocystocele, teratoma and retinoblastoma[2]. These pathologies are of interest to maxillofacial, head and neck, ophthalmology and neurosurgeons alike and their role is integral in the psychosocial counselling of the parents, preparing them for delivery and discussion of treatment options and their timing. The authors' review the reported cases of prenatal diagnosis and management of nasal glioma and review the literature on this rapidly advancing field of craniofacial anomalies detected in utero.

NASAL GLIOMA

Nasal Glioma is a rare, benign, congenital facial lesion occurring in 1:20000-40000 live births[3]. They are comprised of heterotopic neuroglial tissue, arising in the midline and are most commonly extranasal (60%)[4] (Figure 1) but may be intranasal (30%) or display both extra and intranasal components (10%)[2]. It is important to differentiate nasal glioma from an anterior encephalocele, which involves a herniation of meninges through an incompletely closed fontanel, retaining intracranial communication, requiring neurosurgical assessment[5].

Prenatal ultrasound is typically used to confirm gestational age, foetal number, monitor foetal well being and detect gross abnormalities[6]. Modern ultrasound technology provides accurate multiplanar views of the foetal face *via* surface rendered images of 3D ultrasound, maintaining its prominent role in antenatal care[7,8]. Such advances have increased the detection rate of craniofacial abnormalities that once would not have been appreciated.

Complications of nasal glioma depend on its location and include nasal deformity, amblyopia, impaired visual field and nasal obstruction. As neonates are obligate nasal breathers this poses a threat to the foetal airway, requiring accurate delineation of the lesion and involvement of the appropriate specialists within the multidisciplinary team (MDT) that can address parental questions and anxiety and facilitate pre and postnatal planning.

Foetal magnetic resonance imaging (MRI) is favoured by most, to provide more accurate soft tissue imaging, confirm equivocal findings and identify intracranial involvement in utero[9]. It avoids unnecessary irradiation of mother and foetus and is favoured over computed tomography (CT). Is also provides synchronous identification of abnormalities of the upper aerodigestive tract, delineation of the foetal airway and ensures a well rehearsed MDT is prepared for definitive intra or postpartum airway interventions, should they be required[10]. Foetal MRI is not however considered an appropriate alternative to ultrasound, which can also provide doppler characteristics, and MRI should not be performed in isolation for foetal screening[6].

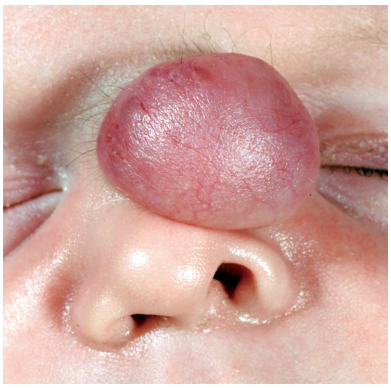

Figure 1 Clinical image of Nasal glioma in a neonate (original image with permission)[13].

Should foetal MRI raise concerns of foetal airway compromise, intrapartum procedures can be performed to treat predicted complications of postpartum airway obstruction. The Ex-Utero Intrapartum Procedure utilises the utero-placental circulation, providing foetal oxygenation for up to 30-60 min[11]. Life saving airway interventions can be made on the partially delivered foetus whilst the mother is under general anaethesia. Management using this procedure requires detailed planning and a highly specialised, well-rehearsed MDT[11].

SEARCH CRITERIA

The literature search was conducted on two electronic databases, MEDLINE and EMBASE with titles including "Glioma", "Prenatal", "In Utero" and "Craniofacial" published from 1980 to present. Two independent reviewers screened 594 articles, and articles with repetition/duplication of original data, animal studies and studies written in non-english language were exclude. We were guided by the PRISMA checklist and flow diagram for article selection (Figure 2). A total of 7 papers were selected.

To date, very little has been published on prenatal management of nasal gliomas. There are seven cases reporting prenatally detected nasal glioma in the literature, summarised in Table 1. Five of these were successfully managed with good outcomes, one lead to termination of pregnancy and one resulted in death secondary to post-operative neonatal infection.

CASE REVIEW

Chmait *et al*[12] (2002) were the first to report a prenatal diagnosis of nasal glioma in the literature. At 31 wk of

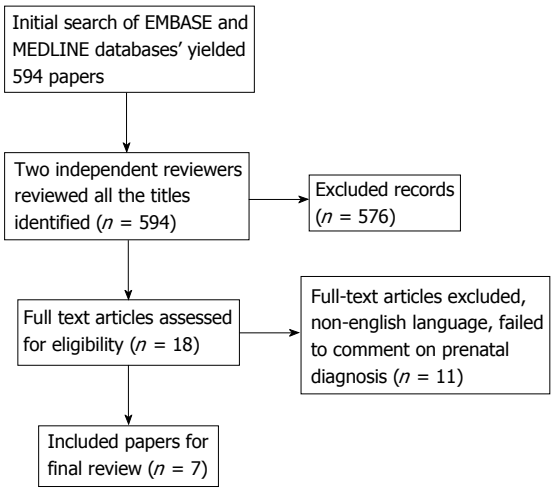

Figure 2 PRISMA flow diagram for inclusion/exclusion.

gestation they identified a 19 mm × 15 mm left paraorbital cystic mass on 2D ultrasound scan. 3D ultrasound was performed and generated a surface rendered image of the foetal face, leading to a preliminary diagnosis of a dacryocystocele. No Doppler flow was present within the mass and no further prenatal imaging was undertaken.

The baby was delivered at term *via* uncomplicated spontaneous vaginal delivery, with a 20 mm firm, extranasal lesion in the left nasoglabellar region. The diagnosis was still inconclusive and postnatal MRI was performed, showing a distinct mass with no intercranial communication. The lesion was excised at 3 mo of age, using a forehead flap, and histological analysis confirmed a diagnosis of nasal glioma.

Beegun *et al*[13] (2012) reported the earliest prenatal detection of nasal glioma, at 20 wk gestation. A 10 mm × 10 mm × 9 mm left paraorbital soft tissue mass was reported on repeat ultrasound scan at 23 wk gestation. It demonstrated a single vessel supply but its origin and communication with the foetal brain could not be determined. Foetal MRI and repeat ultrasound were undertaken at 24 wk and showed the lesion had grown to 13 mm × 11 mm × 12 mm. The foetal brain appeared normal and was not in communication with the lesion. Repeat ultrasound scans were performed every two weeks to monitor the lesions size, which remained stable until 28 wk, where it increased to 16 mm × 12 mm. Repeat MRI at 28 wk and 36 wk did not show any associated bony erosion or deep extension. At this time the diagnosis was still in question.

The baby was delivered at 38 wk *via* uncomplicated spontaneous vaginal delivery, with a 20 mm × 15 mm soft cystic mass in the left nasoglabellar region, suspected to be a haemangioma. The lesion grew to 30 mm × 40 mm by 2 mo of age. A postnatal MRI excluded bony involvement however there were concerns that the lesion may obstruct the baby's binocular vision and surgical excision with primary closure was undertaken at 2 mo of age and histology confirmed a diagnosis of nasal glioma.

Both De Biasio *et al*[2] (2006) and Grzegorczyk *et al*[9] (2010) report prenatal diagnosis of nasal glioma at 22 wk gestation. Basio detected a 7 mm lesion, with no doppler blood flow and undertook a foetal MRI that excluded intracranial communication and bone involvement, but no specific diagnosis could be made. Ultrasound monitoring showed the lesion increased in size to 20 mm at 32 wk gestation. The baby was delivered at 38 wk gestation *via* uncomplicated spontaneous vaginal delivery, with a 20 mm pink non-compressible mass medial to the left internal canthus. Postnatal MRI suggested a diagnosis of nasal glioma with partial intranasal extension. The lesion was excised at 4 mo of age and histology confirmed the diagnosis. Similarly, Grzegorczyk *et al*[9] identified a vascular hypoechoic mass on the left nasal bone on ultrasound scan. This was also investigated with foetal MRI that excluded intracranial communication and bony erosion. Following delivery, the lesion appeared as a reddish mass, suspected to be a haemangioma. Postnatal imaging further established low velocity flow consistent with a nasal glioma that was removed at 5 mo of age and the diagnosis was confirmed with histology.

Okumura *et al*[14] (2012) described a recent case of a craniofacial anomolie detected in the third trimester. A facial mass protruding from the left nostril with no doppler flow was identified at 33 wk gestation. No additional prenatal imaging was undertaken and the baby was delivered at 35 wk gestation *via* spontaneous vaginal delivery and immediately intubated. Postnatal CT scan was undertaken on day 8, and suggested an osseous defect the ethmoid bone with herniation of intracranial contents into the nasal cavity. A preliminary diagnosis of transethmoidal encephalocele was made. This was revised following postnatal MRI that demonstrated no intracranial involvement or bony defect, utilising better soft tissue delineation. An intranasal glioma was suspected and excised *via* endoscopic intranasal and oral routes, and the diagnosis was confirmed on histology. This case was complicated by the development of a lower respiratory tract infection and subsequent neonatal death.

Ajose-Popoola *et al*[5] (2011) described the management of a nasal glioma in a 3 mo old child, who had a 25 mm × 25 mm non-pulsatile solid nasoglabellar mass detected on prenatal ultrasound. It was subsequently investigated with foetal MRI that showed the mass was separated from brain parenchymal by a distinct cerebrospinal fluid plane. The baby was delivered without complication and postnatal MRI revealed a 28 mm × 18 mm × 18 mm mass in the midline, with possible intracranial communication through an anterior bony defect. Postnatal CT was undertaken at 3 mo of age, and showed the lesion had grown to a 28 mm × 20 mm × 20 mm mass that appeared to have intracranial connection *via* a 8 mm × 6 mm bony defect of the glabella and metopic suture. The lesion was excised *via* a midline nasal incision and no communication with the intracranial vault was seen. Histology confirmed a diagnosis of nasal glioma.

Tonni *et al*[4] (2011) described a second trimester detection of a midline craniofacial anomolie. Further ex-

Table 1 Summarising the management of prenatal nasal glioma

Ref.	Gestational age at detection	Prenatal Ix	Postnatal Ix	Age at surgery	Outcome
Chmait *et al*[12], 2002	31 wk	Ultrasound + 3D image	MRI	3 mo	Complete excision-forehead flap
Di Biasio *et al*[2], 2006	22 wk	Ultrasound (inc. Doppler) and MRI	MRI	4 mo	Complete excision
Grzegorczyk *et al*[9], 2010	22 wk	Ultrasound (inc. Doppler) and MRI	MRI	5 mo	Complete excision
Ajose-Popoola *et al*[5], 2011	Second trimester	Ultrasound (inc. Doppler) and MRI	CT and MRI	3 mo	Complete excision
Tonni *et al*[4], 2011	Second trimester	Ultrasound (inc. Doppler) and Amniocentesis	N/A	N/A	Termination of pregnancy: elevated α-FP
Okumura *et al*[14], 2012	33 wk	Ultrasound (inc. Doppler)	CT and MRI	8 d	Nasal and extranasal excision Neonatal death secondary to LRTI
Beegun *et al*[13], 2012	20 wk	Ultrasound (inc. Doppler) and MRI	MRI	2 mo	Complete excision

MRI: Magnetic resonance imaging; CT: Computed tomography; N/A: Not applicable.

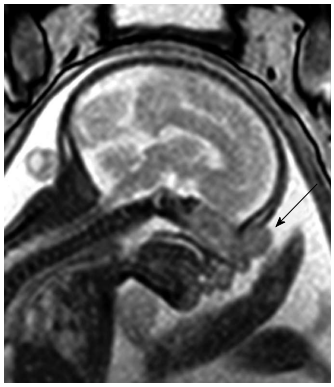

Figure 3 Sagittal foetal magnetic resonance imaging in utero, identifying nasal lesion (arrow). Original image with permission[13].

amination *via* amniocentesis showed a 46,xx Karyotype with elevated α-FP levels. The parents declined further antenatal investigation and opted for legal termination of pregnancy in view of the severe psychophysical disturbances associated with the detection of the abnormality with life threatening risks to the mother. Tissue obtained by necropsy confirmed the diagnosis of nasal glioma.

DISCUSSION

Nasal glioma is a rare benign congenital midline facial defect that is being detected in the prenatal period with increasing frequency[2]. Advances in foetal imaging provide more accurate delineation of the foetal face. Ultrasound scanning is still the dominant antenatal imaging modality in modern obstetrics. The use of 3D rendered images along with doppler waveforms show characteristics that allows specialists to narrow their differential diagnosis[12].

An anterior encephalocele, appears as a midline cystic or solid mass emanating from a calvarial defect and may be accompanied by ventriculomegaly[2]. Haemangioma demonstrates a typical doppler blood flow pattern, high during arterial diastole, within a septate or solid mass protruding from the skull[2]. Nasal glioma are firm and nonpulsatile masses, most commonly originating from the nasoglabellar region, with low flow on doppler signal. Retinoblastoma appear as a heterogeneous mass arising directly from the orbit, with an irregular echogenic structure and covering membrane[2].

Beegun *et al*[13] emphasised the value of ultrasound in monitoring lesion size, using two-weekly ultrasound with repeated prenatal MRI to exclude bony erosion associated with lesion growth, in order to guide prenatal plans and timing of birth (Figure 3). Chmait *et al*[12], supports the use of 3D rendered ultrasound images but underscored the difficulty in achieving an accurate prenatal diagnosis. These cases all shared diagnostic uncertainty and each had an alternative working diagnosis, with diagnostic confirmation only being confirmed as nasal glioma with histological analysis.

Antenatal MRI is the modality of choice to investigate craniofacial abnormalities in utero and was performed in all except two cases; one was declined by parents who opted for termination of pregnancy, the other when the anomaly was detected late, in the third trimester. T1-weighted MRI demonstrates nasal glioma to be isointense to grey matter, with moderate contrast enhancement[4]. T2 weighted imaging will show hypointense mass similar to a congenital haemangioma, with low resistance arterial flow on doppler imaging[4]. It is important to identify any intracranial communication and exclude the presence of an anterior encephalocele. This distinction was unclear in two cases where a suggestion of intracranial communication was present even after postnatal imaging. Okumura *et al*[14] opted for initial postnatal CT to delineate the lesion. This suggested a small anterior calvarial bony defect; leading to a preliminary diagnosis of transethmoidal encephalocele that was revised once postnatal MRI was repeated. This emphasises the diagnostic difficulties inherent with these lesions. MRI is generally favoured over CT as it is at least as accurate as CT in detecting intracranial extension and avoids radiation to the head, neck and radiosensitive lens[15].

Grzegorczyk *et al*[9] recommends that pre and postnatal MRI should be performed, where available, in all cases where a craniofacial defect is detected on ultrasound. This can exclude intracranial extension, identify additional abnormalities, allow accurate planning of surgical

approach, and reduce risks of incomplete resection.

CONCLUSION

Prenatal diagnosis of nasal glioma may be suggested as early as the second trimester, but diagnostic certainty is rarely achievable until postnatal imaging or histological examination. Investigations may suggest or exclude certain diagnosis but families must be counselled accordingly to ensure they are fully prepared for all possible diagnostic eventualities.

Doppler ultrasound provides important detection and monitoring facilities to guide pre and postnatal planning and direct the working diagnosis, differentiating glioma from haemangioma.

Prenatal MRI improves the diagnostic accuracy of ultrasound but should not be employed as an independent screening tool. Foetal MRI can identify associated intracranial communication, additional lesions, cerebral defects and delineate the upper aerodigestive tract of the neonate, predicting airway complications and allowing appropriate planning. Postnatal MRI imaging is essential to accurately identify the lesion, and is as good if not superior to CT in identifying intracranial extension, with the added benefit of avoiding neonatal exposure to ionising radiation[15]. It is also important to identify the glioma stalk, as full excision is required to reduce risk of recurrence, cerebrospinal fluid leak and meningitis.

When radiological investigations are combined with chorionic villous and or amniocentesis, the clinicians are provided with valuable diagnostic and prognostic information that may be used to empower families and inform a multidisciplinary discussion regarding genetic counselling, timing of delivery, postnatal treatment options and surgical planning[13]. The importance of this aspect of prenatal care cannot be underestimated, as the psychosocial impact of detecting these prenatal anomalies can be great.

Early surgical intervention is recommended, and is believed to correlate with more favourable aesthetic outcomes, reduce complications of ocular development and provide definitive histological diagnosis. Once a diagnosis of nasal glioma is confirmed, the overall prognosis is favourable, with low recurrence rate following complete excision.

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REVIEW

Clinical anatomy of the tympanic nerve: A review

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Abstract

The tympanic (Jacobson's) nerve is a useful anatomical structure in the middle ear with both practical and physiological functions extending beyond its origin. The paper reviews its clinical anatomy in adults and its surgical significance. English language articles from 5 major databases and Google scholar search engine were used to identify papers outlining the anatomy of the tympanic nerve, associated pathology and surgical relevance. In the majority of cases the tympanic nerve arises from the inferior ganglion of the glossopharyngeal nerve traversing through the tympanic canaliculus into the middle ear. On the promontory it coalesces with sympathetic fibres from the carotid chain forming the tympanic plexus which has individual variability. Functionally, as well as giving off parasympathetic fibres to the parotid gland *via* the lesser petrosal nerve, it is a useful anatomical landmark for cochlear implantation. The surgical importance of the tympanic nerve is not only restricted to middle ear surgery; it also extends to salivary gland disorders. The tympanic nerve remains clinically relevant to the modern otolaryngologist and as such a detailed understanding of its anatomy is crucial.

Key words: Tympanic nerve; Canaliculus; Glossopharyngeal nerve; Promontory

Core tip: The tympanic nerve is the first branch arising from the inferior ganglion of the glossopharyngeal nerve. Despite its modest size it has a multitude of functions which are not only limited to the middle ear. In this review we detail the clinical anatomy of the tympanic nerve and its surgical applications in Otolaryngology as they have evolved over the years. We also provide a brief summary of the life and achievements of the indefatigable Ludwig Levin Jacobson, an anatomist and military surgeon, who is credited with the discovery of the tympanic nerve.

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INTRODUCTION

This review describes the present evidence outlining the anatomy, function and surgical significance of the tympanic nerve.

The tympanic nerve arises from the inferior ganglion of the glossopharyngeal nerve traversing through the tympanic canaliculus into the middle ear. On the promontory it coalesces with sympathetic fibres from the carotid chain forming the tympanic plexus. Functionally, it provides somatic fibres to the middle ear as well as parasympathetic fibres to the parotid gland *via* the lesser petrosal nerve.

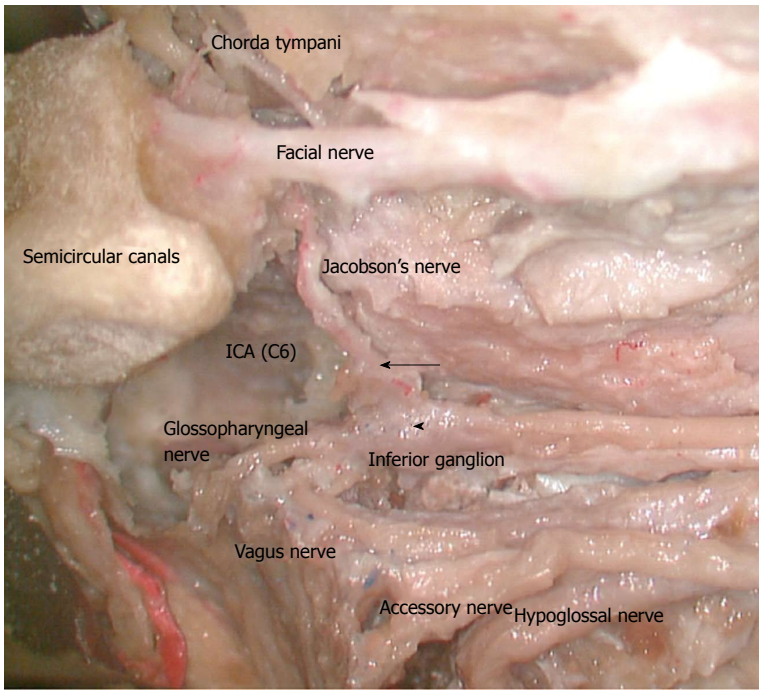

Figure 1 Image demonstrating the path of the glossopharyngeal nerve and the origin of the tympanic/Jacobson's nerve (arrow) at the inferior ganglion (arrowhead). (Used with permission from Dr. Takanori Fukushima, Professor of Neurosurgery, Duke University Medical Centre and Duke Raleigh Hospital). ICA: Internal Carotid artery.

We have summarised the anatomy from its origin and traced its course through the relevant anatomical segments namely extra tympanic; hypotympanic; and intratympanic. We also elucidate its role in middle ear innervation and secretomotor supply to the parotid. The surgical relevance of the tympanic nerve and the relevant pathological processes are also covered in detail. Further, we have detailed, a historical perspective on the intriguing life of Ludwig Levin Jacobson who is credited with the discovery of the tympanic nerve. For clarity we will use the term tympanic nerve throughout the article although the term "Jacobson's nerve" is used synonymously throughout the literature.

SEARCH STRATEGY

We conducted a systematic review using Pubmed, Medline, Embase, Google Scholar, Web of Science and the Cochrane library in January 2014. Databases were searched using the term "Jacobson's/tympanic nerve" before exploring the relevant subheadings. Results were limited to articles published in English. The abstracts were reviewed and most relevant selected for inclusion. Citation links were hand searched to identify further articles of relevance.

DISCOVERY OF THE TYMPANIC NERVE: ROLE OF LUDWIG LEVIN JACOBSON

Ludwig Levin Jacobson was born in Copenhagen on 10th January 1783 to a family of jewellers[1]. After attending a German school in Stockholm he returned to surgical training in Copenhagen[1,2]. His interests included human anatomy, zoology, chemistry and teaching. He is credited with various anatomical discoveries in animals and most importantly in humans[1,2]. As early as 1809 he discovered a previously undetected vomeronasal organ found in the nasal cavities of mammals only fully understood over a hundred years after his death[2]. In 1813 he would first describe the tympanic nerve outlining its anatomical relations and physiological function[1,2]. Later he also detailed the anatomy and function of Jacobson's canaliculus (tympanic canaliculus) and "Jacobson anastomosis" plexus (tympanic plexus)[1]. By the time of his death in 1843 he had become a Professor and the King's personal physician[1].

ORIGINS AND EXTRA-TYMPANIC SEGMENT

The tympanic nerve is the first branch arising from the inferior ganglion (petrous ganglion) of the glossopharyngeal nerve as it exits the jugular foramen[3-5] (Figure 1). Anatomical variations of its origin are rarely reported. Historically Arnold, cited by Donaldson, noted that the tympanic nerve may occasionally arise at a higher point than the inferior ganglion of the glossopharyngeal nerve and Cuvellier, also cited by Donaldson, suggested that it could arise from contributions from both cranial nerves IX and X[6]. These findings have not been supported by more recent studies.

The anatomical study of the tympanic nerve by Tekdemir *et al*[7] using ninety-six cadaveric temporal bones states that it arises from the inferior ganglion which is located at a mean distance of 11.3 mm from the genu (knee like bend). It invariably angulates at 90 degrees inferior to the genu en route to the tympanic canaliculus[7].

The tympanic nerve and the inferior tympanic artery enter the inferior tympanic canaliculus, a bony septum that lies between the internal carotid foramen medially and the internal jugular foramen laterally[8] (Figure 2). The tympanic canaliculus is located medial to the styloid

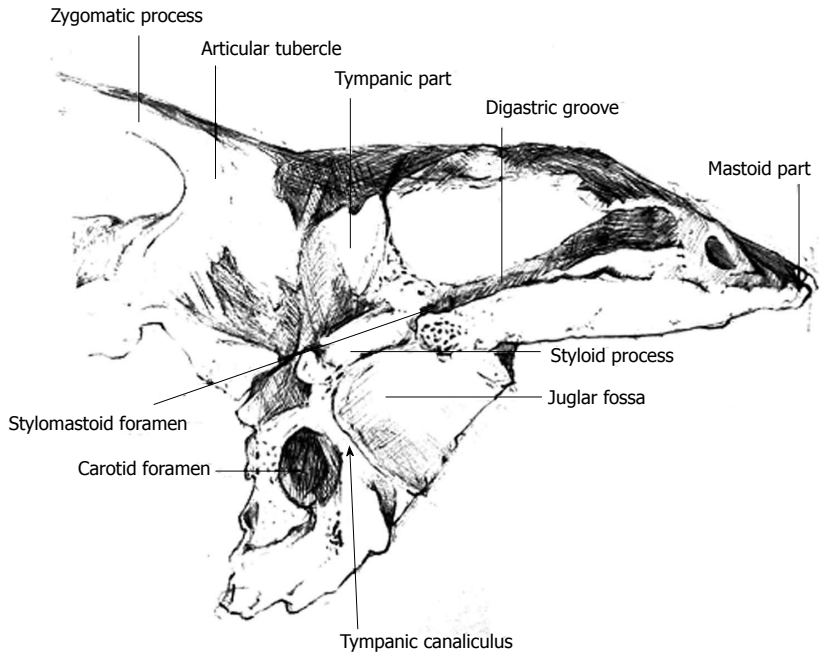

Figure 2 Illustration of the temporal bone demonstrating the relationship between the tympanic canaliculus, the carotid foramen and the jugular fossa.

process and the stylomastoid foramen[9]. In the tympanic canaliculus, the tympanic nerve traverses superiorly on the medial wall of the middle ear onto the cochlea promontory[6]. The auricular branch of the superior ganglion of the vagus nerve (Arnold's nerve) courses 1-2 mm lateral to the tympanic nerve[9,10].

The mean length of the tympanic canaliculus is 9.5 mm and the inferior 2/3 of the tympanic canaliculus follows a vertical course whilst the superior 1/3 courses anteromedially at an angle between 160 and 170 degrees[7]. In the study by Tekdemir *et al*[7], the external opening of the tympanic canaliculus was located inside the petrosal fossula, the depression on the inferior surface of the petrous portion of the temporal bone between the jugular fossa and the carotid canal opening in 80% of cases. In the 20% of the cases where the fossula was not identifiable, the opening was found on the anterolateral aspect of the jugular bulb[7].

Porto *et al*[3] (20 specimens) and Tekdemir *et al*[7] (96 specimens) both reported findings of the tympanic nerve being covered in bone in its entire course in 5% and 20% of their specimens respectively. Donaldson, in a study of 50 temporal bones, observed that in 6% of the specimens the tympanic nerve ran part or its entire middle ear course deep to the bone of the middle ear and that in these cases there was no hypotympanic branch[6].

An aberrant course of the tympanic nerve where it coursed anteromedially within the bony septum before entering the middle ear anteriorly accompanied by the sympathetic branch from the internal carotid sympathetic plexus was reported in one of the specimens in the same study[6]. Another unusual finding was a unilateral duplication of the tympanic nerve[6].

INTRATYMPANIC AND HYPOTYMPANIC COURSE

The tympanic nerve emerges on the promontory of the middle ear, on its medial wall and anterior to the round window[3]. It exits through the internal aperture of the tympanic canaliculus which lies anterior to the inferior half of the round window[7]. The nerve divides on the promontory forming an anterior branch which courses up towards the Eustachian tube and a posterior branch that skirts the rim of the round window[11,12]. The two divisions of the tympanic nerve are often found running parallel to each other on the promontory[13]. On average the distance between Jacobson's nerve and the lip of round window niche is 2.1 mm with a range of zero to 3.2 mm[14]. A study of 82 temporal bones demonstrated that if the main trunk of the tympanic nerve is visible on the promontory it can be concluded with 95 per cent certainty that it is within 3.3 mm of the lip of the round window niche[14].

Hypotympanic branches are common and therefore an important consideration in surgery of the tympanic nerve. One of the earliest observations on the anatomy of the tympanic nerve suggested that in 40% of cases a hypotympanic branch arises from the main trunk and runs anteriorly and below the promontory to connect to the pharyngotympanic tube recess[15]. Later studies suggests a slightly higher preponderance of a hypotympanic branch of the tympanic nerve, *i.e.*, 50% and 48%, albeit with a variable distribution[3,6]. The hypotympanic branch can have occasional single or double divisions[3,6]. It is reportedly narrower in diameter coursing anterosuperiorly in approximately 45% of cases and posteriorly in 5%[3]. The presence of a hypotympanic branch correlates strongly with the main trunk of the tympanic nerve being covered by promontory bone for the majority of its course, only surfacing on the promontory for 1-2 mm[3]. Interestingly, two canaliculi with nerves passing over the promontory have been reported[6].

On the promontory, the tympanic nerve coalesces with the superior and inferior caroticotympanic nerves

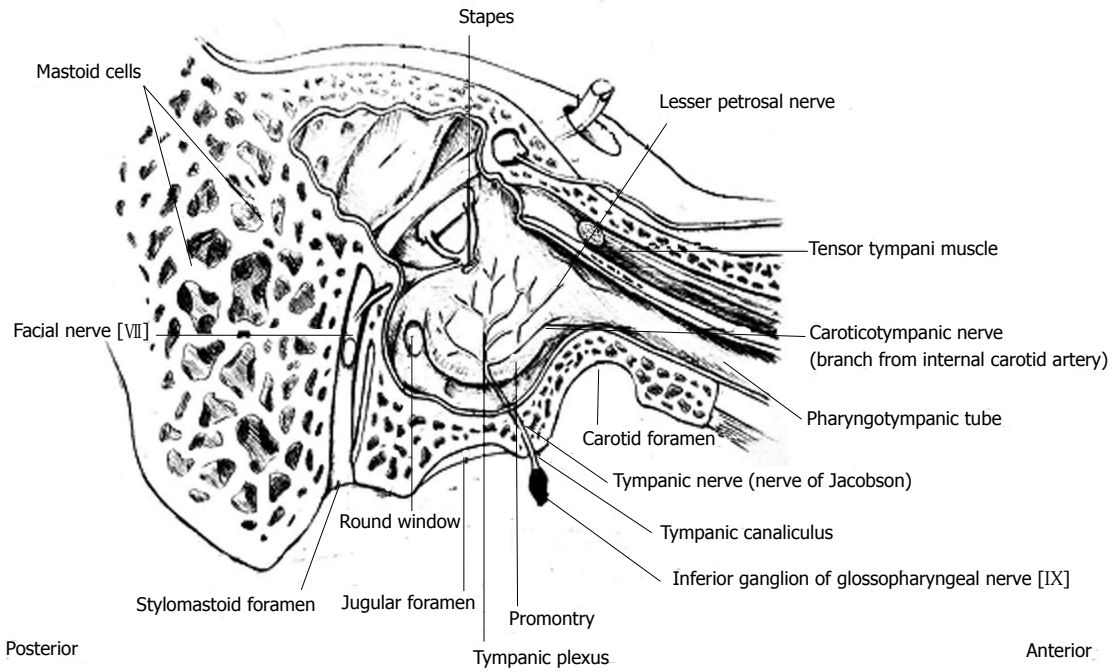

Figure 3 Schematic illustration of demonstrating the tympanic nerve from its origin (shaded in black), its course and its anatomical relations within the right middle ear.

which branch from the carotid plexus to form the tympanic plexus[16-18] (Figure 3).

Even though the tympanic nerve and plexus can be found in open grooves (submucosally) on the promontory, in approximately 20% of cases its branches are hidden in bony canals of varying depth making it difficult to locate[18]. Additionally, the nerve and plexus exhibit a multitude of variations as to course, branching and anastomoses. In fact there is no bilateral symmetry; each plexus is unique[18].

The tympanic nerve has a close anatomical relationship with the cochlea; it extends superiorly directly underneath the cochleariform process[19]. Furthermore, it acts as a useful marker in identifying the anterior and posterior parts of the basal segment of the scala tympani of particular relevance in cochlear implantation[8,14,20]. Both segments are in close relation to the hypotympanic cells, infralabyrinthine cell tracts and the jugular bulb[8,14]. The preganglionic parasympathetic fibres reconstitute posteriorly to the cochleariform process, eventually lying medial to it coursing superiorly across the promontory towards the geniculate ganglion of the facial nerve[8].

The tympanic nerve exits the middle ear through its own canal below the tensor tympani muscle or through the canal for the tensor tympani muscle as the lesser superficial petrosal nerve[20]. From the anterior surface of the temporal bone the lesser superficial petrosal nerve exits the middle cranial fossa *via* foramen ovale or the emissary sphenoidal foramen (canal of Vesalius) en route to the otic ganglion conveying presynaptic parasympathetic fibres[21]. The post ganglionic fibres travel with the auriculotemporal nerve, a sensory branch of the mandibular division of the trigeminal nerve to provide the parasympathetic innervation of the parotid gland[11] (Figure 4).

FUNCTION

In addition to conveying parasympathetic fibres to the parotid, the tympanic nerve provides somatic fibres to the tympanic cavity: the medial wall of the tympanic membrane, mastoid air cells and the Eustachian tube[8,22]. Animal studies suggest that the tympanic nerve plays an important role in the regulation of middle ear pressure[23,24]. Eden *et al*[23,24] demonstrated the existence of a neural pathway between the tympanic plexus and the pons and the presence of efferent fibres connecting the pons and the Eustachian tube. The deduction from these studies was that the glomus bodies located along the tympanic nerve, in concert with other structures, sense changes in middle ear pressure[24]. These changes are in turn conducted to the pons *via* the tympanic nerve resulting in a feedback loop thereby regulating middle ear pressure[23,24]. Songu *et al*[25] in an attempt to replicate these findings in humans demonstrated, albeit inconclusively, that the tympanic plexus might play a more significant role in the regulation of middle ear pressure *via* the Eustachian tube than had been previously thought. Such findings are encouraging and more studies of this nature are required given that Eustachian tube dysfunction and its sequelae remains a difficult condition to manage within otolaryngology.

PATHOLOGY

The tympanic nerve is covered in bone for most of its course and is unlikely to be damaged in trauma; injury would indicate severe force[26]. The nerve can be involved in non-traumatic pathological processes along its course, particularly within the foramen[9]. Glomus jugulare tu-

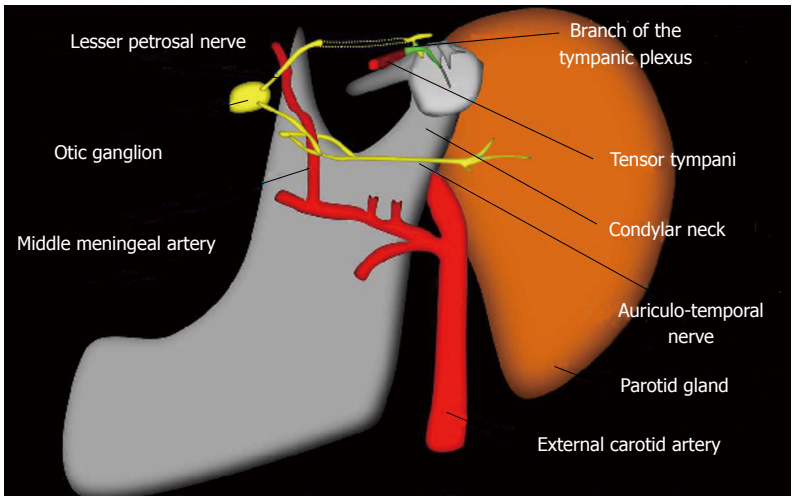

Figure 4 Illustration depicting the link between the tympanic plexus (formed by the tympanic nerve) and the parasympathetic supply to the parotid via the lesser petrosal nerve and the otic ganglion. (Used with permission from Dr. José M. García Santos, MD, PhD, Head of the Radiology Department, University Hospital Morales Meseguer, Murcia, Spain).

mours, which tend to be slow growing in nature, are the commonest tumour found in the jugular foramen[9]. They have a preponderance to form along the tympanic and Arnold's nerves as well as in the adventitia of the internal jugular vein[9,27]. In advanced stages they tend to be multidirectional in growth and owing to the narrowness of the jugular foramen may expand and erode to into cranial nerves IX to XII[9].

Tympanic nerve schwannomas have been reported but are still rare[9,27]. They are Schwann cell derived tumours which arise intracranially and then extend inferiorly along the jugular foramen[27]. Pressure erosion is common in patients with jugular foramen schwannomas but rare in glomus jugulare tumours where bony erosion is common[9].

Post-surgical traumatic neuromas of Jacobson's nerve have been reported, usually occurring in the context of previous middle ear surgery where the tympanic nerve is damaged or severed (intentionally or otherwise) leading to formation of neuromas from nerve growth around the amputated stump, leading to recurrent otalgia[28].

SURGICAL RELEVANCE IN OTOLARYNGOLOGY

Lempert first described tympanic plexus ablation for the relief of tinnitus in 1946, referring to it as tympanosympathectomy[29]. Clinical use of the procedure faltered owing to unsatisfactory results. Hemenway later suggested interruption of the efferent neuronal pathway at the level of the middle ear by sectioning the tympanic nerve as a theoretical approach to the management of Frey's syndrome[30]. However, the procedure was later popularised by Golding-Wood who used it for the successful treatment of Frey's syndrome coining the term tympanic neurectomy to describe it[31]. In addition to the management of Frey's syndrome, Golding-Wood postulated other indications for the procedure notably, paradoxical gustatory lacrimal reflex "crocodile tearing" and chronic secretory otitis media although these have no indication in modern clinical practise[21]. Tympanic neurectomy has been considered useful in the management of otalgia with the proviso that other important causes of otalgia have been excluded[22].

Later Friedman added other important indications for tympanic neurectomy including parotid duct stenosis, salivary duct dilation (sialectasis) and parotid salivary fistula[21].

Owing to the potential serious complications of parotidectomy, duct ligation or radiotherapy as alternative forms of treatment for these conditions, tympanic neurectomy can be undertaken with little morbidity or operative discomfort[17]. A case series of ten patients for parotid sialectasis managed with tympanic neurectomy in the United Kingdom by Daud *et al*[17] demonstrated symptom alleviation in seven patients and as such is advocated by the authors as a first-line surgical procedure for such symptoms with parotidectomy in reserve.

To perform the procedure a tympanomeatal flap is raised to expose the promontory and hypotympanum[32]. Success of tympanic neurectomy lies in complete division of the tympanic nerve below its lowest intratympanic branch with the corollary that promontory branches are less significant to the success of the procedure[33]. As such adequate exposure may require drilling of the bony annulus inferiorly until the floor is flush with the hypotympanium[33]. Drilling is required medially below the basal turn of the cochlea to sever all nerve filaments[19]. A comprehensive understanding of the different anatomical segments, variations and most importantly the potential of the tympanic nerve being partially covered in bone as highlighted above is therefore crucial in the success of this procedure.

ANATOMICAL SIGNPOST FOR COCHLEAR IMPLANTATION

In more recent years the tympanic nerve has gained favour as a useful anatomical landmark in cochlear implantation where the classical approach to the scala tympani through the round window niche by way of facial recess is impossible[8,14]. Successful intubation of the scala tym-

pani in such instances utilises the anatomical proximity of the tympanic nerve to the round window and the cochlea as has already been highlighted[8,14].

CONCLUSION

The tympanic nerve remains an anatomical area of complexity that is easy to overlook yet functionally its relevance to the modern clinician is ever more pertinent. It is increasingly regarded as an important operative marker in cochlear implantation due to its anatomical relations and continues to retain an important role in the management of salivary disorders. In appreciating its anatomical path, we gain an improved understanding of the arrangement of the middle ear and its dual relevance to both anatomists and surgeons.

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MINIREVIEWS

Experimental models of cholesteatoma: A review

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Abstract

Cholesteatoma describes the keratinized, stratified squamous epithelium in the middle ear and mastoid, which has osteoclastic activity and is capable of bone resorption. Its origin is unknown and remains a topic of current investigation. In addition, ongoing studies are investigating new molecules for treatment. This review summarizes the various experimental models of cholesteatoma.

Key words: Animal; Cholesteatoma; Chronic otitis media; Experimental; Murine

Core tip: Cholesteatoma is the keratinized, stratified squamous epithelium in the middle ear and mastoid, which has osteoclastic activity and is capable of bone resorption. The mechanism of formation remains unknown, though different theories involving various models of formation have been proposed. This review summarizes the various experimental models of cholesteatoma.

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INTRODUCTION

Cholesteatoma describes the keratinized, stratified squamous epithelium in the middle ear and mastoid, which has osteoclastic activity and is capable of bone resorption. It involves subepithelial connective tissue, called the perimatrix, and is characterized by chronic inflammatory reaction. Resorption of bone occurs in the area neighboring the perimatrix, mediated by osteoclasts, and can lead to hearing loss, vestibular dysfunction, facial paralysis and even lethal intracranial complications[1]. The diagnosis for cholesteatoma is based on otoscopic examination, audiologic findings and radiolgic examination. The only immediate treatment is surgery, which requires follow-up due to the risk of recurrence (up to 15%)[2].

The pathogenesis of cholesteatoma is unknown, but there are four different theories regarding its genesis[3]: (1) metaplasia theory, metaplasia of middle ear epithelium into stratified squamous epithelium; (2) immigration theory, squamous epithelium of the external ear canal migrates to the middle ear through a perforation in the tympanic membrane; (3) hyperplasia theory, basal cell hyperplasia of keratinized epithelium in Shrapnell's membrane due to inflammation; and (4) retraction pocket theory, retraction in the Shrapnell's membrane due to chronic Eustachian dysfunction. Various animal models have been developed over the years to examine the pathogenesis and treatment of cholesteatoma, each indicating a different way of formation. In this review, we summarize and discuss these experimental models and the molecules for prevent or treatment.

ANIMALS USED IN EXPERIMENTAL MODELS

Chinchillas, guinea pigs, Mongolian gerbils (Meriones unguiculatus) and rats have all been used in experimental models of cholesteatoma. The auditory apparatus of the

Table 1 Canal ligation technique cholesteatoma formation articles

Ref.	Year	Result
Park *et al*[4]	2005	Control of inflammation with ofloxacin and maintenance of normal clearance mechanisms can manage early stage cholesteatomas
Choufani *et al*[2]	2007	Animal model cholesteatomas can differ from human cholesteatoma regarding growth regulatory markers
Park *et al*[6]	2001	Phospholipase C-γ1 may play a role in signaling pathways on genesis of cholesteatoma
Park *et al*[7]	2001	Cholesteatoma proliferates at a higher rate than retroauricular and deep meatal skin
Yamamoto-Fukuda *et al*[8]	2010	Tympanic membrane epithelium is the probable source of cholesteatoma epithelium

Chinchilla is similar to humans, and guinea pigs have a similar mastoid and epithelial and subepithelial lining ultrastructure of the middle ear. The osteoclastic and bone resorption characteristics of cholesteatoma in gerbils is similar to humans[3]. In the Mongolian gerbils and fat sand rat Psommomys obesus, cholesteatoma can form spontaneously, and these species have therefore been widely used in experimental cholesteatoma models[1]. Moreover, the incidence and severity of cholesteatoma increases with age in gerbils[3].

METHODS USED FOR DEVELOPMENT OF CHOLESTEATOMA

Ligation of external auditory canal

McGinn first popularized the method of retroauricular skin incision and ligation near the bony external auditory canal with 4.0 silk sutures in 1982[4]. This method of cholesteatoma formation is very effective and occurs in 100% of ligated Mongolian gerbils. The disadvantage of this method involves the high cost of the animals[3,5]. After formation of cholesteatoma, development of cholesteatoma can be staged into five groups: (1) accumulation of keratin debris on the outer surface of tympanic membrane; (2) medial displacement of tympanic membrane without contact with the bulla; (3) cholesteatoma is in contact with the prominence of the cochlea; (4) cholesteatoma fills the bulla; and (5) intracranial extension[3].

By using the external canal ligation method, Park *et al*[4] studied the reversibility of cholesteatoma with ofloxacin ear drops and saline irrigation[4]. They concluded that cholesteatomas can be managed with conservative mechanisms, such as control of inflammation and maintenance of normal clearance mechanisms at an early stage. Choufani *et al*[2] compared levels of differentiation and growth regulatory markers, including retinoic acid receptors, galectins, and macrophage migration inhibitory factors, in ligated gerbils with cholesteatomas in humans. Their immunohistochemical analyses showed that only macrophage migration inhibitory factors were similar, thus they concluded that animal models differ from the clinical presentation. Another study using the canal ligation technique by Park *et al*[6] in 2001 indicated that phospholipase C-γ1 plays a role in the formation of cholesteatoma. Further work from this group evaluating proliferative activity markers, including cytokeratin 13/16, proliferating cell nuclear antigen, epidermal growth factor receptor and thrombomodulin, demonstrated that cholesteatoma proliferates at a higher rate than retroauricular and deep meatal skin[7].

In 2010, Yamamoto-Fukuda *et al*[8] combined ligation of the ear canal with a new hybridization approach to find the origin of cells in the cholesteatoma. After making a perforation in the tympanic membrane of male gerbils, they performed myringoplasty using female gerbils' tympanic membranes as grafts; they ligated the external auditory canal to form cholesteatoma. After using *in situ* polymerase chain reaction, they found epithelium in the cholesteatoma of female origin in the male gerbil and concluded that tympanic membrane epithelium is the probable source for cholesteatoma[8] (Table 1).

Eustachian tube blocking model with ligation or electrocauterization

Dysfunction of Eustachian tube leads to pars flaccida retraction pocket and subsequent cholesteatoma. This method was popularized by Chloe and Wolfmann in 1986. With this technique, cholesteatoma formation occurred in three quarters of animals[3,5]. Eustachian tube blockage can be achieved surgically *via* trans-neck or trans-oral approaches. In the trans-neck approach, the Eustachian tube can be seen below the facial nerve and digastric muscle. In the trans-oral approach, the Eustachian tube orifice is found 5 mm posterior to the junction of hard and soft palates[5].

In 2001, Kim *et al*[9] investigated cytokeratins in the cholesteatoma using unilateral electrocauterization of the Eustachian tube and formation of retraction pocket cholesteatoma, which was staged as follows: stage 1: mild retraction of tympanic membrane with or without middle ear effusion; stage 2: retraction pocket surrounds ossicular chain; stage 3: deep retraction pocket with bone erosion and keratin formation; stage 4: total adhesion of the tympanic membrane. The expression of cytokeratin 13/16 with advancing stage of cholesteatoma suggested that the epithelium of retraction pocket cholesteatoma increasingly proliferates with stage. Wilmoth *et al*[10] used bilateral Eustachian tube obstruction to study matrix metalloproteinases and tumor necrosis factor alpha in the atelectatic tympanic membranes. Elevation of these markers with progression of retraction pocket stage indicated the possible role in cholesteatoma formation.

In 2009, von Unge *et al*[11] used repeated pressure loads to the tympanic membrane and Eustachian tube of gerbils with simulated habitual sniffing to form retraction pocket cholesteatoma similar to the Eustachian tube

Table 2 Articles using eustachian tube blocking model for cholesteatoma formation

Ref.	Year	Result
Kim *et al*[9]	2001	Cytokeratin expression increases with advancing stage of retraction pocket cholesteatoma
Wilmoth *et al*[10]	2003	Matrix metalloproteinases and tumor necrosis factor alpha may have a role in retraction pocket cholesteatoma
Tinling *et al*[12] (with combination of canal ligation)	2006	Basal cell keratinocytes' cell division rate is much more in cholesteatoma

Table 3 Articles using chemical reagant injection technique for cholesteatoma formation

Ref.	Year	Result
White *et al*[14]	1995	Hyaluronic acid doesn't inhibit cholesteatoma formation in experimental model
Kayhan *et al*[16]	2006	Prednisolone may inhibit cholesteatoma formation
Antunes *et al*[17]	2008	Trans-retinoic acid may inhibit cholesteatoma formation
Melo *et al*[18]	2013	Mitomycin-C may inhibit cholesteatoma formation
Massuda *et al*[13]	2005	Latex biomembrane is as effective as propylene glycol injection in cholesteatoma formation in experimental model
Kim *et al*[19] (With combination of canal ligation and Eustachian tube blocking)	2002	Expression of different types of cytokeratins increases according to cholesteatoma formation way

blocking model. To simulate sniffing, a vacuum was used to produce negative pressure in the chamber. They found that with a Moire interferogram, the gerbil tympanic membrane retains its stiffness after 7 to 12 d of repeated pressure loading, resulting in retraction pocket formation, but no cholesteatoma formation[11].

A combination of ear canal ligation and Eustachian tube obstruction can be used to form cholesteatoma. Tinling *et al*[12] compared gerbils after ear canal ligation, Eustachian tube obstruction or both and found that the rate of cell division of basal cell keratinocytes in the tympanic membrane and external auditory canal of gerbils with cholesteatomas was seven times higher than controls. However, there were no differences among the methods used for cholesteatoma formation (Table 2).

Chemical reagent injection

Chemical substance injection to the middle ear or bulla of animals is another widely used method for cholesteatoma formation. Materials that can induce cholesteatoma formation are talcum powder, dimethylbenzanthracene, latex, and propylene glycol[5,13-17], which is most widely used. Experimental usage of propylene glycol to induce cholesteatoma began after it was observed that the application of topical eye drops containing propylene glycol (Cortisporin) to the middle ear of chinchillas resulted in epithelial migration and formation of cholesteatomatous chronic otitis media. Cholesteatoma formation percentage increases to 100% with an increase in the application dose to 90% concentration of propylene glycol[3]. Application of propylene glycol can be with intratympanic injection or by the trans mastoid way through a small hole in the bulla[14-18]. With this method, different chemicals are used to inhibit the formation of cholesteatomas. 5-fluorouracyl, trans-retinoic acid, mitomycin-c and systemic prednisolone inhibit cholesteatoma in experimental models, whereas hyaluronic acid and cyclophosphamide have no significant effect[3,14,16-18].

In 2005, Massuda *et al*[13] reported on a different application of propylene glycol in rats. After forming a posterosuperior perforation in the tympanic membrane, they used a latex biomembrane with 50% propylene glycol or introduced a naturel latex biomembrane into the orifice of the tympanic membrane with one end in the middle ear and the other in the external auditory canal. Cholesteatoma occurred in 80% of ears with the propylene glycol, and 90% of ears using the latter method. They concluded that both methods are effective in experimental cholesteatoma formation[13]. Application of propylene glycol can also be combined with canal ligation and Eustachian blockage technique. Kim *et al*[19] studied proliferation and migration states of experimental cholesteatomas using canal ligation, Eustachian blockage (retraction pocket) or propylene glycol in Mongolian gerbils. Expression of cytokeratin 13/16 was mostly persistent in the group receiving the retraction pocket, whereas cytokeratins 5/6 and 1/10 were mostly expressed in the group with canal ligation. They stated that there was a complex alteration in the epidermal maturation pathway in the pathogenesis of cholesteatoma. Studies using chemical substance injection for cholesteatoma formation are summarized in Table 3.

Skin graft transfer to middle ear of animal

Another method used to form cholesteatoma is full thickness skin graft transfer. After skin graft implantation with superimposed infection, cholesteatoma formed with 89.3% success, but bone resorption was not observed[3]. However, Si *et al*[20] formed cholesteatoma by autologous skin graft implantation and pseudomonas injection to the middle ears of mice with 92% success. All cholesteatoma-forming mice had hearing loss measured by auditory-evoked brainstem responses and there was bone resorption demonstrated by computed tomography.

Dermal implant transfer to non-temporal bone

To form cholesteatoma and show the bone resorption pattern, dermal implants in mice can be transferred to

the calvarium or femoral bone. Sudhoff *et al*[1] transferred dermal implants consisting of skin and underlying cartilage to calvaria that resulted in localized inflammation and bone resorption. The authors therefore concluded that this method of cholesteatoma bone resorption would be a useful device in a genetically well-defined animals, such as mice. Chole *et al*[21] implanted keratin (from human volunteer fingernail filings, and mouse hair and nails) and polymethylmethacrylate to mice calvaria to form a bone resorption model similar to cholesteatoma. They showed a chronic inflammatory response with angiogenesis, mononuclear cell recruitment and osteoclastic bone resorption in calvaria that was similar to cholesteatoma. A similar model was used by Jung *et al*[22] who studied nitric oxide synthase levels after implantation of keratin to calvaria of rats. They found that levels of nitric oxide synthase, especially type II, were upregulated in response to keratin. In 2005, Magalhaes *et al*[23] formed cholesteatoma after implantation of full thickness skin graft to femoral bones of rat, concluding that a trapped keratinized epithelium (skin) causes epithelial cyst formation to expel the foreign tissue.

Bone marrow samples of mice for osteoclastogenic activity and cell cultures

Bone marrow samples are not used for forming cholesteatoma, but for determining bone resorption pathways. Nason *et al*[24] collected osteoclastic cell precursors from bone marrow of mice that showed transformation to bone-resorbing osteoclasts with lipopolysaccharide from *Pseudomonas aeruginosa*[24]. As the most cultured organism in infected cholesteatomas, *P. aeruginosa* may thus have a role in osteoclastic activity of cholesteatomas.

CONCLUSION

Experimental animal models are crucial for understanding the pathogenesis of cholesteatoma and for identifying new molecules for prevention or treatment. The use of differing models will ensure that all aspects of cholesteatoma formation are explored.

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