UNIVERSITY OF SANTIAGO DE COMPOSTELA
FACULTY OF MEDICINE AND DENTESTRY

Department of Dermatology and Otolaryngology

DOCTORAL THESIS

"EPIDEMIOLOGICAL AND EVOLUTIONARY STUDY OF VESTIBULAR SCHWANNOMAS AFTER DIFFERENT TYPES OF TREATMENT"

Jamol ERGASHEV

Academic year 2013 / 2014

Directors: Prof. Dr. Sofía Santos Pérez

Prof. Dr. Andrés Soto Varela

Prof. Dr. Torcuato Labella Caballero

Dissertation Comittee:

SOFÍA SANTOS PÉREZ, Professor, Head of Dermatology and Otolaryngology Department, Staff Physician of Otolaryngology division of Santiago de Compostela University Hospital;

ANDRÉS SOTO VARELA, Professor of Otolaryngology and Staff Physician of Otolaryngology division of Santiago de Compostela University Hospital;

TORCUATO LABELLA CABALLERO, Honored Professor, Former Chairman of Otolaryngology division of Santiago de Compostela University Hospital;

CERTIFIES: That Jamol ERGASHEV has realized the work entitled*: "Epidemiological and Evolutionary study of Vestibular Schwannoma after different types of treatment"* under our direction for the degree of Doctor of Medicine fulfilling the requisites for "European Doctor" mention, and that mentioned work is ready to be presented from the present day.

Signed: Prof. Torcuato Labella   Prof. Sofía Santos   Prof. Andrés Soto

…………………………   ……………………   ……………………..

November 7th, 2013

Dedication

I dedicate this dissertation to my parents for their unconditional love and support.

I also dedicate it to the memory of my first school teacher Juraboy NISHONOV, who would have been happy to see my achievements.

Acknowledgement

Foremost, I offer my sincerest gratitude to my mentor and thesis supervisor, Prof. Sofía Santos Pérez, who supported me with her encouragement, patience, knowledge and endless advice throughout my courses for my PhD at the University of Santiago de Compostela. I attribute my PhD degree to her and am ever thankful for her encouragement, effort and friendly attitude. Without her guidance and persistent help, this thesis would not have been possible.

My sincere thanks also goes to Prof. Andrés Soto, a punctual person and a great scientist who was always at my disposal in spite of his having a tight schedule. Especially in my difficult moments, he spared no efforts to support me and always stood with me, shoulder to shoulder, helping me to bring my thesis to the light of day.

I have received generous support from Professor Torcuato Labella and appreciated the friendly countenance he often expressed towards me as I was in my home country hospital during his chairmanship at the Department Otolaryngology and Head & Neck surgery of the CHUS. Thanks to him, I did not have any difficulties in collecting primary source materials for my PhD thesis. Also, I have learned many things from the lectures of Prof. Labella and in the surgeries in which I assisted him. He is a great mentor.

In my daily work, I have been blessed with a friendly and cheerful group of otolaryngologists, residents, nurses and administrative personnel. I appreciate the feedback offered by Dr. María del Río, who helped me in refreshing patient data with new audiologic tests performed by her. Also to Dr. Crisanto Castro, who always motivated me and consistently asked how I was going with my papers in the last three years, I am ever grateful. Ana Burés and Begoña Rey helped me in obtaining primary source materials and in repeating the vestibular tests for VS patients.

I would like to thank Dr. Pilar Gayoso and university professor, Xosé Luis Otero, who is a great teacher, for their valuable support, in my most difficult times, as I worked on the statistical part of my thesis.

TABLE OF CONTENTS

List of Abbreviations

ABR: auditory brainstem response

ABI: auditory brainstem implantation

AN: acoustic neuroma

AR: asymmetry ratio

AVCN: anterior ventral cochlear nucleus

BSAEP: brain stem auditory evoked potential

CAP: compound action potential

CCG: craneocorpography

CDP: computerized dynamic posturography

CHUS: Santiago de Compostela University Hospital

CM: cochlear microphonic

CN: craneal nerve

CNS: central nervous system

CPA: cerebellopontine angle

CSF: cerebrospinal fluid

CT: computed tomography

DNA: deoxyribonucleic acid

DCN: dorsal cochlear nucleus

DP: directional preponderance

DPOAEs: distortion product otoacoustic emissions

EEG: electroencephalography

EP: endocochlear potential

ENG: electronystagmography

ENT: ear, nose and throat

ORL: otorhinolaryngology

FSE: fast spin-echo

GKRS: gamma knife radiosurgery

GTR: gross-total resection

HMD: head mounted audio displays

HVIN: hyperventilation induced nystagmus

IAA: internal auditory artery

IAC: internal acoustic canal

IT5: absolute latency of wave V

MCF: middle cranial fossa

MMN: mismatch negativity

MRI: magnetic resonance image

NF: neurofibromatosis

NF2: neurofibromatosis type II

OAE: otoacoustic emissions

OHC: outer hair cells

PET: positron emission tomography

PST: peristimulus

PTA: pure tone audiometry

PTT: pure tone threshold

PVCN: posterior ventral cochlear nucleus

RS: retrosigmoid

SCCs: semicircular canals

SCM: sternocleidomastoid muscle

SFOAEs: sustained-frequency otoacoustic emissions

SOAEs: spontaneous otoacoustic emissions

SOT: sensory organization test

SP: summating potential

SN: spontaneous nystagmus

SNHL: censorineural hearing loss

SPL: sound pressure level

SRS: stereotactic radiosurgery

SRT: speech reception threshold

SR: stapedial reflex

TOAEs: transient otoacoustic emissions

TOB: test of balance

TL: translabyrinthine

VEGF: vascular endothelial growth factor

VOR: vestibule-ocular reflex

VNG: videonystagmography

VS: vestibular schwannoma

WRT: word recognition test

WRS: word recognition score

2D: two-dimensional

3D: three-dimensional

QOL: quality of life

LIST OF FIGURES

14

LIST OF TABLES

Resumen

"Estudio epidemiológico y evolutivo de los schwanomas vestibulares tras distintos tipos de tratamiento"

1. Antecedentes

Los schwanomas vestibulares (SVs) son tumores intracraneales benignos que se originan en las células de Schwann del nervio cócleo-vestibular; suponen el 80-90% de las masas localizadas en el ángulo pontocerebeloso[1,3,8,12,20,22,32].

El estudio histopatológico de los SV determina la existencia de dos tipos celulares, Antoni "A" y Antoni "B". Rubinstein (1989) describió que los cambios mucinosos y microquísticos tienden a suceder en las células Antoni B[20].

A medida que el tumor crece, lo hace en la dirección de menor resistencia, medialmente en el APC o hacia el oído interno (formando un cordón en el CAI). Por ello, los SV pueden tener componente extracanalicular, intra-extracanalicular o exclusivamente intracanalicular. El SV bilateral es poco frecuente y se asocia generalmente con la Neurofibromatosis tipo 2 (NF2). La aparición de SVs esporádicos y NF2 parece estar asociado con una mutación de un gen supresor tumoral en el cromosoma 22q12. La base biológica que explique los diferentes patrones de crecimiento permanece desconocida.

La presentación clínica de un SV es muy variable; incluye hipoacusia neurosensorial unilateral en frecuencias agudas, acúfenos, desequilibrio, presión ótica, otalgia y vértigo. Todos son resultado de la presión ejercida por el tumor sobre las ramas coclear y vestibular del VIII par craneal. La hipoacusia es el hallazgo más frecuente; ocurre en más del 95% de los pacientes en el transcurso de la evolución.[35]

Según algunas publicaciones, la incidencia de los SVs está aumentando[52,53] mientras que el tamaño del tumor en el momento del diagnóstico es cada vez menor y la edad media al diagnóstico se mantiene estable[130,132]. Este incremento en la incidencia probablemente se deba a un uso generalizado de la RM en la práctica clínica.

Las modalidades de tratamiento incluyen vigilancia, radiocirugía (Gamma Knife or Cyber Knife) y cirugía convencional. La elección de una u otra alternativa depende de muchos factores: tamaño, edad del paciente y estado general, severidad de la hipoacusia, presencia de síntomas neurológicos y preferencia del paciente.

1.1 Planteamiento del problema.

La tasa de crecimiento de los SVs es variable y difícil de predecir. El tamaño del tumor puede permanecer estable, aumentar o disminuir. Cuando crece, habitualmente lo hace de forma lenta. Sin embargo, algunos SVs se comportan de un modo distinto y pueden causar signos neurológicos incluso mortales por compresión del tronco encefálico. Es necesario identificar los tumores que representen una amenaza frente a los que no.

La ventaja principal de la cirugía convencional es la posibilidad de conseguir una extirpación completa. Sin embargo, implica morbilidad potencial por complicaciones como fístula de LCR, meningitis, daño en el nervio facial y lesiones vasculares.[171,173,224]

El tratamiento con radioterapia es cada vez más preciso, al mejorar las técnicas de administración y disminuir las dosis de radiación. Aunque es generalmente bien tolerado, persisten los interrogantes sobre el control del tumor a largo plazo y la morbilidad potencial, incluyendo hipoacusia permanente, parálisis facial, hidrocefalia y daño del tronco cerebral; su incidencia es menor que con cirugía convencional.[139,190, 196,231.]

2. Objetivos

Nuestro estudio tiene como objetivo comparar la actitud vigilante frente a la radiocirugía, para ayudar en la toma de decisiones en el tratamiento conservador del SV. Planteamos los siguientes objetivos específicos:

1. Realizar un análisis epidemiológico de los pacientes con VS diagnosticados en nuestro Servicio.
2. Evaluar la utilidad de diferentes pruebas audiológicas y vestibulares en el diagnóstico del SV.
3. Analizar la historia natural del SV, tanto en aspectos morfológicos como funcionales.

4. Comparar la eficacia de dos estrategias terapéuticas diferentes (vigilancia y radiocirugía) en el manejo SVs pequeños.

5. Establecer un protocolo terapéutico para SVs pequeños.

3. Material y métodos

Desarrollamos un estudio retrospectivo observacional de 107 casos consecutivos de SV diagnosticados en el Servicio de Otorrinolaringología del Complexo Hospitalario Universitario de Santiago de Compostela, desde febrero de 1992 hasta febrero de 2013. La duración media del seguimiento fue de 56.52±10.79 (rango 25.02-71.74) meses. 57 pacientes (53.8%) eran mujeres y 50 (46.2%) varones; uno de los varones (0.9%) presentaba un SV bilateral por NF2.

Se empleraron los siguientes equipos diagnósticos:

- Audiómetro - "Audiotest 340"
- Craneocorpógrafo (CCG) - Eymasa CCG600SE®
- Posturógrafo dinámica computerizado (PD) - Neurocom®
- Videonistagmógrafos - Nicolet Instrumental®, "*Veonys*" from Biodigital® y VNG de "Intracoustics®".
- Otoemisiones acústicas (OEA) - TEOAE "*ILO 292*
- Potenciales evocados auditivos (PEA) - *"Nicolet Viking IV P System"* de Nicolet Biomedical, Inc.
- Potenciales evocados miogénicos vestibulares (VEMPs) - *"Intelligent Hearing Systems"*
- Resonancia magnética (MRI) - magnetom symphony maestro class, siemens.

4. Resultados

En nuestra serie, el número de mujeres fue ligeramente mayor al de varones. En la mayoría de los casos, 68 (64.1%), el síntoma principal fue hipoacusia, mientras que en 24 (22,1 %) fue un acúfeno. En 11 (16,1%) de los 68 que debutaron con hipoacusia, ésta fue el único síntoma en el momento del diagnóstico. Pero en 54 (59.0%) de los pacientes con hipoacusia, los acúfenos y los síntomas vestibulares estaban también presentes. Sólo en un caso (0.94%) de los 106 pacientes, el acúfeno fue el único síntoma al debut. Por el

contrario, en 23 (21.6%) casos, la hipoacusia o los síntomas vestibulares se asociaban al acúfeno. El vértigo y la inestabilidad no se presentaron nunca como único síntoma de debut. Sin embargo, en un enfermo (0,94%), el mareo fue el único síntoma inicial.

No se encontró una asociación entre el lado afecto y el sexo (*p*=0.87, test de Chi-cuadrado). Entre los pacientes con SV intracanalicular, había 27 (65.8%) mujeres y 14 (34.1%) varones. No encontramos correlación entre la localización del tumor y el sexo (p=0.09, Chi-cuadrado). Pero sí hallamos relación estadísticamente significativa entre los síntomas iniciales y la localización del SV (p=0.01, Pearson y Spearman).

En las pruebas audiométricas, 51 (53.1%) mujeres tenían un umbral auditivo medio (PTA) de 64.93 dB y 45 (46.8%) varones de 60.96 dB. Diez (8.4%) pacientes presentaban una audición normal. El PTA medio fue menor en pacientes menores de 40 años (49.94±32.69 (Rango 12.50-120)) que en los mayores de esa edad (60.54±28.07 (Rango 13-120)). La mayoría de los pacientes (63.5%) presentaban inicialmente una hipoacusia neurosensorial con caída de graves a agudos, mientras que el 5.0% mostraban una mejora de graves a agudos. Se observó hipoacusia pantonal en el 25 % de los casos. Otros patrones audiométricas se hallaron en el 6,3 % de los pacientes.

Los valores medios del PTA no difieren significativamente entre hombres y mujeres (p=0.47). Sin embargo, sí hubo diferencias significativas en función de la localización (p=0.014, ANOVA). Asimismo, hubo diferencias estadísticamente significativas entre las localizaciones intracanalicular e intra-extracanalicular (p=0.016, Bonferroni). Entre los grupos extracanalicular e intra-extracanalicular (p=0.750) y entre los intracanaliculares y extracanaliculares (p=0.200), no hubo diferencias significativas.

En los PEA, más del 80% de los pacientes presentaban alteraciones en las latencias I-V y I-III (83.7%); encontramos una fuerte correlación entre el tamaño del tumor y el IT5 (p < 0.001, Chi-cuadrado).

En las OEA, los siete pacientes (6.5%) en los que estaban ausentes tenían un SV mayor de 20 mm, con localización extracanalicular o intra-extracanalicular; su PTA media fue 70.22 ±28.66 (Rango 30-120) dB.

El tamaño medio de los SV con craneocorpografía tipo IV era mayor que el de los que tienen una craneocropografía tipo I (normal). No se encontró asociación significativa entre localización y tamaño del SV, y la CCG. Tampoco entre la CCG y las manifestaciones clínicas.

La PD era normal en 38 pacientes (63.3), siendo patológico el equilibrio medio en 22 (36.6%). Encontramos diferencia significativa entre hombres y mujeres en la condición 6 (p= 0.005) (t-Student).

En 67 pacientes (63.2%) se habían realizado pruebas calóricas. La mayoría de los que tenían pruebas anormales (78.3%) correspondían a SVs intracanaliculares o intra-extracanaliculares; su PTA media era 67,24±32.66 (Rango 12.50-120) dB. El tamaño medio era de 16.82±10.02 (Rango 4-50 mm). Los pacientes con pruebas calóricas normales tenían una PTA media de 49.13±21.78 (3.75-88.78) dB y un tamaño tumoral significativamente menor (13.77 ±7.96 (2-32.50)). En cuatro casos (5.9%), las pruebas calóricas mostraron arreflexia vestibular.

En 12/21 (57.14%) pacientes, los VEMPs estaban presentes en el lado afecto y en nueve (42.8%) ausentes. No encontramos asociación entre VEMPs y localización del SV.
En cuanto a la RM, el tamaño medio del tumor es algo mayor en los varones (17.37 mm (±9.05)) que en las mujeres (14.96 (±10.16)). Esta diferencia fue más pronunciada en pacientes ≤ 40 años (21,7 ±12.21 (6-50 mm)). Las pruebas estadísticas (t-Student) no mostraron diferencia significativa en el tamaño entre los dos sexos.

4.1. Grupos de tratamiento.

En 67 pacientes (63.2%) se realizó vigilancia del SV. 36 (53.2%) eran mujeres y 31 (46.3%) varones. La edad media era 59.21±14.35 (Rango 24-85) y el tamaño medio 12.68 ±6.76 (Rango 2-35). El valor medio de la PTA era 57,30 ±28,53. 35 (52.2%) eran intracanaliculares, 10 (14.9%) extracanaliculares y 22 (32.8) intra-extracanaliculares.
De los 27 (25.5%) pacientes sometidos a radiocirugía, 15 (55.67%) eran mujeres y 12 (44.4%) varones. El PTA promedio era 59.80±26,86; el tamaño medio, 16,13±7,56. La edad media fue 56.82±14.30. El tamaño fue levemente mayor en las mujeres (14,86±8,06) que en los varones (17,7±6,88) (p=0.064). La localización del SV en este grupo fue: 7

intracanaliculares (25.9%), 9 extracanaliculares (33.3%) y 11 (40.74%) intra-extracanaliculares.

El grupo de 12 (11.32%) pacientes sometido inicialmente a cirugía convencional, incluía 6 (50.0%) mujeres y 6 (50.0%) varones. La edad media era 43.78 ±9.28 (Rango 29.16–57.85) años. La PTA promedio fue 66.40±35.84 y el tamaño medio 30.04±11.37. Cinco (41.6%) pacientes presentaban SVs extracanaliculares y 7 (58.3%) intra-extracanaliculares.

4.2. Asociación entre grupos de tratamiento

Entre los grupos de vigilancia y radiocirugía, encontramos una diferencia estadísticamente significativa en el tamaño tumoral ($p=0.002$), pero no en la PTA ($p=0,33$). Comparados globalmente, las diferencias entre grupos fueron significativas ($p<0.001$, ANOVA). El tamaño medio en el grupo de vigilancia (12.68±6.76) fue menor que en el de radiocirugía (16.13±7.56) ($p= 0.014$). El tamaño medio del grupo de cirugía convencional (30.04 ±11.37) fue significativamente mayor que el de los otros dos ($p<0.001$, Bonferroni).

4.2.1. Complicaciones del tratamiento.

Las complicaciones tras cirugía convencional son evidentes; por ello, hemos analizado exclusivamente las complicaciones de la radiocirugía. Basándonos en los datos de anamnesis y exploración en la primera revisión (un mes tras la radiocirugía), el 61.90% (26/42) no presentaron ninguna complicación. Sin embargo, el 38.1% (16/42) sí. Entre éstos, el 11.09% (5/42) sufrieron paresia facial, el 2.3% (1/42) parálisis facial, el 6.9% (3/42) cofosis, el 2.3% (1/42) hipoacusia significativa (>10dB) y el 4.76% (2/42) vértigo (que no presentaban previamente). El 4.76% (2/42) referían incremento del acúfeno. Un enfermo (2.3%) aquejó de cefalea holocraneal continua una semana tras la radiocirugía, presentando posteriormente atrofia del hemisferio cerebeloso.

4.3. Seguimiento

La primera consulta de seguimiento tras el diagnóstico se realizó a los seis meses; las siguientes, al año, tres años y cinco años. El seguimiento medio fue de 56,52±10,79 meses (vigilancia: 55,30±11,92; radiocirugía: 58,60±9,22; cirugía convencional: 58,70±5,7).

En doce casos fue necesario cambiar la opción terapéutica a lo largo del seguimiento, por aumento del tamaño tumoral o empeoramiento clínico. Concretamente, cinco pacientes pasaron del grupo de vigilancia al de cirugía convencional y ocho del grupo de vigilancia al de radiocirugía; cinco de ellos lo hicieron por empeoramiento de la clínica, aún sin incremento en el tamaño. En tres casos, el cambio de opción de tratamiento se debió al deseo del paciente, pese a mantenerse estable la situación clínica y el tamaño tumoral.

4.3.1. Resultados de la exploración en el paciente con NF2.

Los síntomas iniciales fueron hipoacusia, acúfenos, inestabilidad y cefalea holocraneal. La audiometría mostró hipoacusia neurosensorial derecha (PTA: 51,25dB) y cofosis izquierda (PTA: 120dB). LA RM detectó múltiples meningiomas intracraneales y SVs extranaliculares puros bilaterales (tamaño máximo: 11mm en el lado derecho y 20mm en el izquierdo). En febrero de 2006, recibió radiocirugía bilateral con una dosis única de 12Gy, permaneciendo estable el tamaño tumoral en los siguientes controles. Sin embargo, en junio de 2010 el paciente refería acúfeno, empeoramiento de los síntomas vestibulares y parálisis facial izquierda. La RM mostró un crecimiento del SV hacia el CAI, por lo que fue remitido al Servicio de Neurocirugía. En marzo de 2013, fue intervenido con un abordaje retrosigmoideo. En el control postoperatorio en Otorrinolaringología, presentaba atrofia de la hemilengua izquierda y parálisis del hipogloso izquierdo, con parálisis del tensor del velo del paladar.

5. Discusión
5.1. Población y características clínicas.

En nuestra serie, hay una ligera diferencia en cuanto al sexo, con 57 (53.8%) mujeres frente a 49 (46.2%) varones. Otros estudios con mayor tamaño muestral sugieren una ligera predilección por el sexo femenino. En una serie de 1000 SV intervenidos, Samii (1997) describe una distribución de 54.0% de mujeres y 46.0% de hombres.

La edad media al diagnóstico fue 57.0 años (rango 24-86). A pesar de que es infrecuente el diagnóstico en la tercera década,[236-240] hay estudios que comunican que los SVs se diagnostican entre los 30 y los 68 años.[246] En nuestra serie, sólo 4 (3.0%) pacientes se

diagnosticaron en la tercera década de la vida; la mayoría estaban distribuidos entre la 5ª y la 6ª décadas.

El síntoma otológico más frecuente es la hipoacusia.[243-246] En nuestra serie, éste era el síntoma inicial en 68 (64.1%) pacientes. La mayoría de los trabajos revisados coinciden en que el acúfeno como síntoma de debut es el segundo más frecuente.[240-246] En nuestros pacientes, 24 (22.6%) lo presentaron como síntoma inicial y 43 (40.5%) asociado con otros síntomas otológicos o vestibulares.

El SV era derecho en 55 (51.9%) enfermos e izquierdo en 51 (48.1%). No encontramos correlación estadística en términos de frecuencia entre la afectación de un oído u otro. En la serie de Edwards y cols., con 160 pacientes, la afectación del derecha era más frecuente (59%) que la izquierda (41%).[250] Otros autores (Christensen y cols., 2004; Takebayashi y cols., 2006) no encuentran diferencias significativas entre los dos lados.[251-252]

En nuestra serie, el SV era intracanalicular en 41 (38.7%) pacientes, intra-extracanalicular en 40 (37.7%) y extracanalicular en 25 (23.6). En la literatura, pocos artículos describen la distribución de los SVs según su localización. Kwan y cols. (2004) analizaron 54 pacientes: 22 (40.0%) eran SVs intracanaliculares puros y 32 (59.2%) intra-extracanaliculares.

En cuanto a la PTA, en el momento del diagnóstico, 96 (90,5%) pacientes presentaban hipoacusia, con un PTA promedio de 58,8dB. No encontramos asociación entre la PTA y el sexo. Hajioff y cols. (2007) presentaron 72 casos de SVs con diez años de evolución; el promedio del PTA al diagnóstico era 43.8±17.5; no hacen referencia a la prevalencia por edad o sexo, pero sí por la localización.[257] Woodson y cols (2010) estudiaron la PTA pre y post-tratamiento de 156 SVs; en su serie, la PTA media pre-tratamiento fue 29±13 dB[259]. Un 63.5% de los pacientes mostraban hipoacusia neurosensorial con caída en agudos.

Suzuki y cols. (2010), desarrollaron un estudio retrospectivo de 500 pacientes con hipoacusia neurosensorial asimétrica; el 2,6% tenían un SV.[261] Postularon que una neuropatía por compresión o un bloqueo en la conducción del nervio coclear producían una hipoacusia en frecuencias graves.[262]

En los PEA, en siete 7 (16.2%) de 43 pacientes fueron normales, pese a presentar hipoacusia. En nuestra serie, el intervalo IA5 es el más sensible para diagnosticar SVs. Hay bastante controversia en la literatura sobre el valor de los PEA en el diagnóstico de los SVs; algunos autores consideran que no hay lugar para ellos en el manejo moderno de los SVs[263-264]. Sin embargo, otros estudios defienden todavía su utilidad.

Gómez y cols. (2000) estudiaron la craneocorpografía en 21 pacientes con SV; pero eran pacientes ya operados, por lo que no tiene valor diagnóstico.[269] Claussen y cols (1989) también analizaron 20 pacientes con SV tras cirugía[270]. Concluyeron que, como otras pruebas vestibulares, la craneocorpografía no abarca todo el rango de patologías vestibulares[270-271].

Gouveris y cols. (2007) estudiaron la PD en 216 pacientes con SV, con una edad media de 54 años. Encontraron diferencias significativas en las condiciones 5 y 6 entre pacientes con y sin síntomas vestibulares[272]. En nuestro caso, no encontramos una correlación clara entre los resultados de la PD y el hecho de presentar o no síntomas vestibulares. No obstante, hemos encontrado una diferencia significativa en la condición 6 entre varones y mujeres. Así, aunque los pacientes con síntomas vestibulares tienen puntuaciones menores en las condiciones 5 y 6 que los pacientes sin estos síntomas, las diferencias no permiten discriminar a los pacientes entre estos grupos[272].

En las pruebas calóricas, la proporción de normal vs patológico fue de 44.8:55.2. Diallo y cols. (2006) analizaron el valor diagnóstico de las pruebas calóricas en 100 pacientes con SV. El 61.0% eran normales y el 11% anormales. En el 28% de los pacientes, no pudieron analizar la respuesta calórica.[274] Algunos autores consideran que las pruebas calóricas son los más frecuentemente alterados (77%) de los tests vestibulares, mostrando hiporreflexia o arreflexia[273].

Iwasaki y cols. (2005) estudiaron 811 pacientes con alteraciones del equilibro; 40 de ellos (5%) tenían VEMPs anormales con pruebas calóricas normales. Ocho de estos pacientes tenían SVs[275]. En nuestra serie, el valor medio de la amplitud de los 12 VEMPs normales fue 33.94±24.0% (Rango 87-6.2%). Ushio y cols. (2009) desarrollaron un estudio comparativo de los VEMPs y las pruebas calóricas en 78 pacientes con SVs. Los VEMPs (con clicks) fueron anormales en 46 (59%) enfermos. En ocho (10.3%), las respuestas

fueron normales bilateralmente y en los 24 restantes (30.8%) no se detectaron VEMPs en ningún oído[277]. En su serie, la especificidad de los VEMPs fue del 52.7%, mientras que en nuestro caso fue un poco menor (42.8%). Esta especificidad relativamente baja de VEMPs y pruebas calóricas se debe a que no son pruebas selectivas para lesiones retrococleares[277-278].

En cuanto a la RM, los varones tenían SVs de un tamaño medio ligeramente mayor (17.37±9.05) que las mujeres (14.96±10.16). Esta diferencia era mayor en los menores de 40 años. No obstante, las diferencias nos fueron significativas. Esto coincide con los datos de otros trabajos con series más amplias. Por ejemplo, Harun y cols. (2012)[279] desarrollaron un estudio retrospectivo en 1296 pacientes diagnosticados de SV unilateral; los varones tenían tumores significativamente mayores que las mujeres (18.23 versus 16.81mm, p=0.031); curiosamente, en sus casos, esta diferencia también era más pronunciada en los menores de 40 años.

Con respecto a la edad, encontramos que el aumento de edad se correlacionó negativamente con el tamaño del tumor y positivamente con la hipoacusia, pero no predijo la presencia de mareo. La PTA promedio en SVs intracanaliculares fue (48.87±25.47), diferente a la de las otras dos localizaciones. Por el contrario, Massick y cols. (2000) estudiaron la influencia del tamaño y localización del SV en la audición, en 21 pacientes; no encontraron relación significativa entre la audiometría y las características tumorales[281].

5.2. Seguimiento

Nos centramos en la comparación entre los grupos de vigilancia y radiocirugía. El seguimiento medio del grupo de vigilancia fue de 55.30±11.92 (rango 25.02-71.21) meses; el de radiocirugía, 58.80±9.22 (36.16-71.74).

La mayoría de las publicaciones revisadas[255,257-258,281,287-289] describen un seguimiento medio, en los pacientes bajo vigilancia, de 52,68±13,82 (Rango 43,2-80) meses; el número medio de pacientes seguidos era de 79,28±87,64 (Rango 21-273). La mayoría de estos autores deben enfrentarse al problema de los casos perdidos[255, 257-258,281, 288].

6. Conclusiones

El SV afecta por igual a ambos sexos y en todas las edades, aunque su incidencia es máxima en la sexta década de la vida. En nuestros pacientes, el porcentaje de afectación intra y extracanalicular es similar.

El síntoma más común en el momento del diagnóstico es la hipoacusia; el patrón audiométrico más frecuente es la hipoacusia neurosensorial con caída en frecuencias agudas. En nuestra serie, la hipoacusia era mayor en los casos intracanaliculares que en los extracanaliculares.

Las pruebas instrumentales para evaluar la función vestibular tienden a estar alteradas en pacientes que refieren síntomas vestibulares en el momento del diagnóstico y tienden a ser normales en los que no los refieren. En el caso de SVs pequeños, las dos actitudes comparadas (vigilancia y radiocirugía) son efectivas para controlar el crecimiento tumoral.

En los pacientes sometidos a radiocirugía, el deterioro auditivo observado durante el seguimiento es mayor que en el grupo sometido a vigilancia. Sin embargo, la reducción del tamaño tumoral es mayor en los pacientes sometidos a radiocirugía que en el grupo de seguimiento.

En los pacientes con SVs pequeños, el protocolo de vigilancia es un enfoque terapéutico correcto, que no empeora el pronóstico a medio plazo. Consideramos que esta actitud es una herramienta adecuada para el manejo de los SVs en las primeras fases tras el diagnóstico.

Palabras clave: Schwannoma vestibular, neurinoma del acústico, vigilancia del neurinoma del acústico, Gamma Knife, Radiocirugía.

Introduction

1 Introduction

1.1 Anatomy of Vestibulocochlear nerve (CN VIII)

The vestibulocochlear nerve or acoustic nerve is the eighth of twelve cranial nerves, and is responsible for transmitting sound and equilibrium (balance) information from the inner ear to the brain. It consists of the cochlear and the vestibular nerves which relay sensory input regarding hearing and balance, respectively.[1-3]

The cochlear and the vestibular nerves courses together until they reach their respective nuclei in the brain stem. Their entire pathway is discussed from peripheral to central.[3]
The vestibular apparatus contains two sack-like structures, the utricle and saccule, and three semicircular canals: superior, lateral, and posterior that are joined together in the same fluid environment.[4]

The special sensory receptors are the hair cells. Signals from hair cells in the macula of the utricle and from hair cells on the cristae of the superior and lateral semicircular canals travel first to the superior vestibular ganglion. Impulses from hair cells of the macula of the saccule and hair cells on the cristae of the posterior semicircular canal travel to the inferior vestibular ganglion. The superior and inferior vestibular ganglia (Scarpa's) is located in the vestibule.[1, 3]

Postganglionic fibers from Scarpa's ganglia become the superior and inferior vestibular nerves that traverse the internal acoustic canal (IAC) in the posterosuperior and posteroinferior compartments, respectively. Cadaveric investigations show that the superior vestibular nerve is usually larger than the inferior vestibular nerve.[2,4] The cochlear nerve usually represents the most inferior part of the vestibulocochlear nerve near the brain stem.[2] In some occasions, even the superior vestibular nerve lies completely separated from the remaining portion of the vestibulocochlear nerve.[1,4]

At the porus acousticus, the medial IAC, the superior and inferior vestibular nerves and cochlear nerves are more fused are sometimes seen as a crescent shape.[1,3-4] The cochlear and vestibular nerves are usually separated about 3 to 4 mm from the lateral end of the internal auditory canal (e.g. see fig 1).[3] The relationship between the cochlear and vestibular nerves

changes from the lateral end of the IAC to the cerebellopontine angle (CPA); the two nerves rotate 90° from the labyrinth to the brainstem. [3-4] Most of the rotation occurs within the IAC. [4] Some histological researches show that if there is complete separation between the two nerves, the cochlear nerve contains the variable number of vestibular fibers that are characterized by a larger diameter.[4] They course through the CPA cistern as two distinct nerves surrounded by cerebrospinal fluid and enter its root entry zone in the brainstem at a slight angle.[1-4.] The cochlear division is separated from the vestibular division by the cerebellar peduncle.[4]
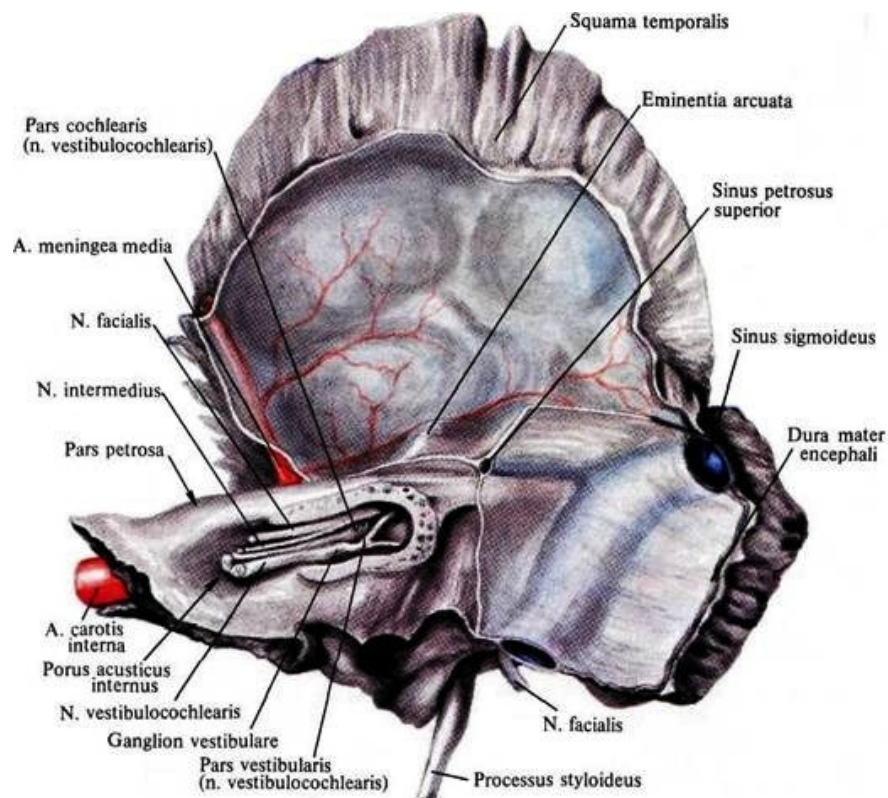
Figure 1. Internal aspect of temporal bone and contents of IAC
Source: http://www.studmed.ru/4/129.htm (11.11.2013)

In the brain stem, the vestibular nerves course medially to the root of the inferior cerebellar peduncle located at the pontomedullary junction along the lateral floor of the fourth ventricle. Just medial to the cerebellar peduncle, the vestibular nerve branches and terminates in one of the four vestibular nuclei that make up the "vestibular nuclear complex" or the flocculonodular lobe of the cerebellum. Axons from there nuclei travel in the following ways: via the vestibulocerebellar tract to aid in coordination, via the vestibulospinal tracts along the length of the spinal cord to modulate muscle tone, to the

reticular formation to regulate consciousness, and via the medial longitudinal fasciculus in the brain stem and upper cervical cord to the paired nuclei of cranial nerves III, IV, and VI, thus, controlling the extraocular muscles.[1]

The nerve fibers originated from hair cells of the organ of Corti of the cochlea composed to the cochlear nerve the central portion of which forms at the cochlear apex. From the apex to the base of the cochlea, outer fibers converge centrally and complete the formation of the nerve. Nerve fibers course toward the medial IAC where the cochlear and vestibular portions of the vestibulocochlear nerve occupy anteroinferior and posterosuperior portions of the canal, respectively and unite with the superior and inferior vestibular nerves and become the vestibulocochlear nerve bundle. In the Magnetic Resonance Image (MRI) image the nerve complex in this part is seen as a crescent shape.[1, 4.]

The cochlear nerve traverses the CPA cistern heading toward the brain stem at a slightly oblique angle. The nerve enters the anterolateral brain stem at the pontomedullary junction. Here the primary sensory neurons bifurcate and terminate in secondary cochlear neurons, the dorsal and ventral cochlear nuclei. They lie superficially on the dorsal surface of the upper medulla immediately lateral to the restiform body.[2] From this point, the ascending hearing pathway becomes complicated because there are multiple decussations at all levels. Most nerve fibers from the ventral cochlear nucleus cross the midline and form the trapezoid body, the major acoustic pathway decussation, located in the pontine tegmentum. Neurons from the trapezoid body synapse with the contralateral superior olivary nucleus (lateral pons) and lateral lemniscus. Most neurons from the dorsal cochlear nucleus tend to extend directly to the contralateral lateral lemniscus. A few auditory fibers ascend in the ipsilateral lateral lemniscus.[4]

Neurons from the dorsal cochlear nucleus tend to extend directly to the contralateral lateral lemniscus. From the lateral lemniscus, neurons ascend into the tectal plate to the inferior colliculus in the lower midbrain.[7]

 At the inferior colliculus, some fibers cross back to the original side but the majority continue upward to the medial geniculate body, located posterolaterally at the level of the superior colliculus immediately lateral to the ambient cisterns. From the medial geniculate body, the acoustic radiations ascend through the thalamus and sublenticular internal

capsule and terminate in the transverse temporal gyry of Heschl of the superior temporal gyrus (Brodmans area 41 and 42), the primary auditory cortex, and central processing area where the conscious perception of sound occurs. Associative areas (Brodmans area 22) are located nearby in the posterior transverse and superior temporal gyri.[1]

A small number of neurons from the superior olivary complex extend to the facial nucleus, which provide for reflex contraction of the stapedius muscle.

1.2 Anatomic relationship of CN VIII

The vestibulocochlear nerve travels from the brainstem towards the inner ear and passes through CPA and IAC and makes up the vicinity with the important anatomic structures like brain tissue, nerves and vessels. Therefore the anatomic considerations are divided into sections dealing with the topographic relationships (e.g. see fig. 2, and 3). In general, in the IAC, the facial nerve has a close relationship with the three components of the vestibulocochlear nerve as the facial and vestibulocochlear nerves always run together from the brain stem to the internal auditory canal.

.
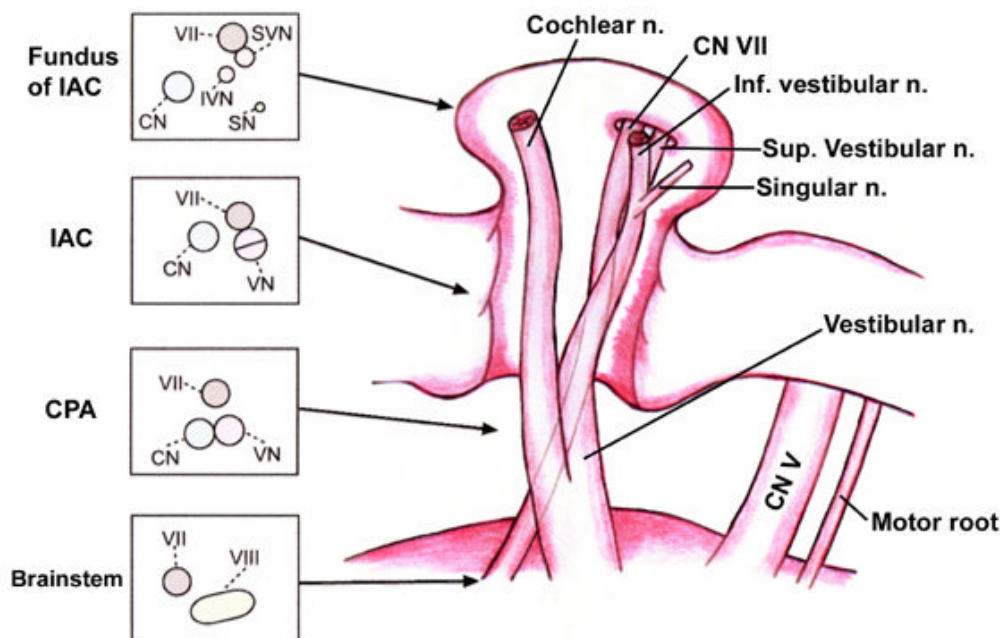
Figure 2. Spatial anatomical relationship between the nerves traveling through the internal auditory canal is shown. Source: http://emedicine.medscape.com/article/835286-overview#showall (11.11.2013)

In general in the IAC, the facial nerve has a close relationship with the three components of the vestibulocochlear nerve as the facial and vestibulocochlear nerves always run together from the brain stem to the internal auditory canal.

The average number of fibres forming vestibular, cochlear, and facial nerves was not constant during their courses within the IAC. The superior and the inferior vestibular nerves showed an increase in the number of nerve fibres from the inner ear end towards the brainstem end of the IAC, whereas the facial and the cochlear nerves show reduction in the number of fibres (e.g. see fig. 3).
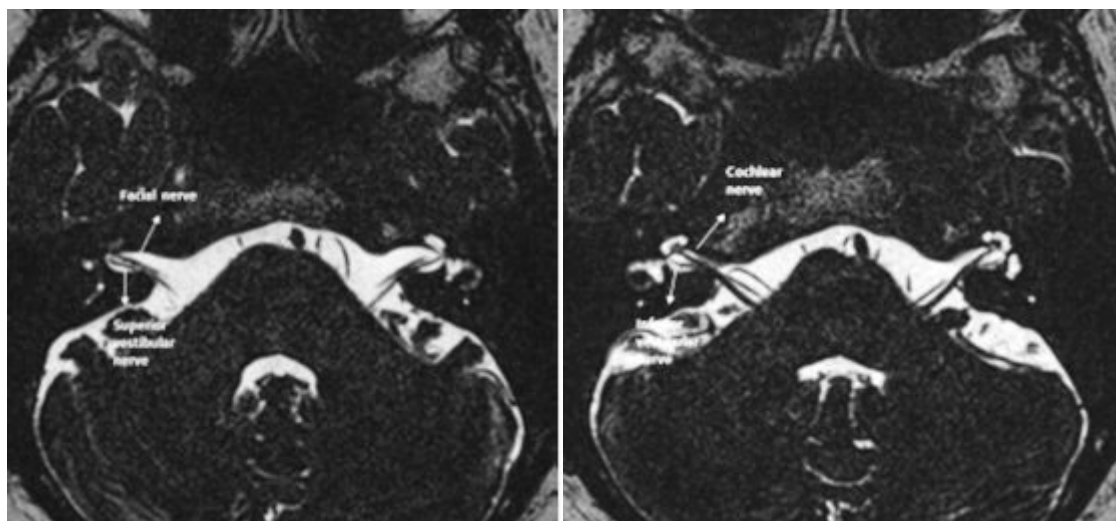
Figure 3. MRI views of Facial and vestibulocochlear nerves within the IAC
Source: Bhuta S, Hsu Ch, Kwan G. The Course of the Facial & Vestibulo-Cochlear Nerves through the Temporal Maze: A Gazeinto Embryology, Anatomy& Common Pathology 2011; Power point presentation.

At the IAC in most of cases the facial nerve occupies the superior and anterior position to the vestibulocochlear nerve or its branches and maintains its tubular shape throughout its course in the canal.[1, 5] Close to the transverse crest the facial and cochlear nerves moves are farther anterosuperiorly and anteroinferiorly, respectively.[3]
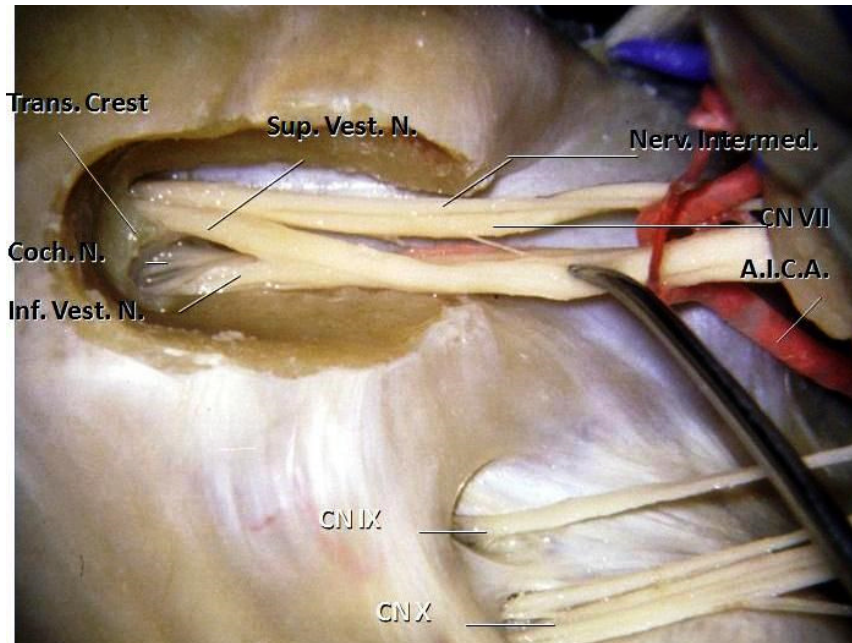
Figure 4. Posterior view to CN VIII, IX and X. Internal acoustic meatus drilled and dura mater removed. Source: Seker Askin, Kilic Turker. Atlas of anatomical dissections: The Cerebellopontine angle. Marmara University, Turkey, http://nsa.marmara.edu.tr/anatomy/6/Serebellopontin-Aci (11.11.2013).

Accordingly, in the lateral part of the IAC there are facial, cochlear and the inferior and superior vestibular nerves. The position of the nerves is most constant in the lateral portion of the canal, which is divided into a superior and an inferior portion by a horizontal ridge, called either the transverse crest or the falciform crest.[4] The facial and the superior vestibular nerves are superior to the crest. The facial nerve is anterior to the superior vestibular nerve and is separated from it at the lateral end of the canal by a vertical ridge of bone, called the vertical crest. The vertical crest is also called Bill's bar in recognition of William House's role in focusing on the importance of this crest in identifying the facial nerve in the lateral end of the canal.[3] The cochlear and inferior vestibular nerves run below the transverse crest, with the cochlear nerve being located anteriorly. Thus, the lateral meatus can be considered to be divided into four portions, with the facial nerve being anterior superior, the cochlear nerve anterior inferior, the superior vestibular nerve being posterior superior, and the inferior vestibular nerve being posterior inferior.

In the CPA, the filaments of the nervus intermedius are also stretched around the fibers of the vestibulocochlear nerve (e.g. see fig. 4). The nervus intermedius is divisible into three parts: a proximal segment that adheres closely to the vestibulocochlear nerve, an intermediate segment that lies free between the eighth nerve and the motor root of the facial nerve, and a distal segment that joins the motor root to form the facial nerve.[7]

Some nerves adhere to the eighth nerve throughout in the posterior cranial fossa and can be found as a separate structure only after opening the internal acoustic meatus. In most instances, the nerve is a single trunk, but in some cases, it is composed of two to four rootlets.[3] The nerve most frequently arises at the brain stem anterior to the superior vestibular nerve as a single large root and in the meatus, lies anterior to the superior vestibular nerve. When multiple rootlets are present, they may arise along the whole anterior surface of the eighth nerve; however, they usually converge immediately proximal to the junction with the facial motor root to form a single bundle that lies anterior to the superior vestibular nerve.[4]

The vestibulocochlear nerve in the level of brainstem makes up the vicinity with the consistent set of neural, arterial and venous vessels which facilitate identification of the nerves on the medial side of the tumour. In the medial side the pons, medulla, and cerebellum are also closely related to the vestibulocochlear nerve. These structures are helpful in guiding the junction of the facial nerve with the brain stem are the pontomedullary sulcus; the junction of the glossopharyngeal, vagus and accessory nerves with the medulla, the foramen of Luschka and its choroid plexus and the flocculus.[6]
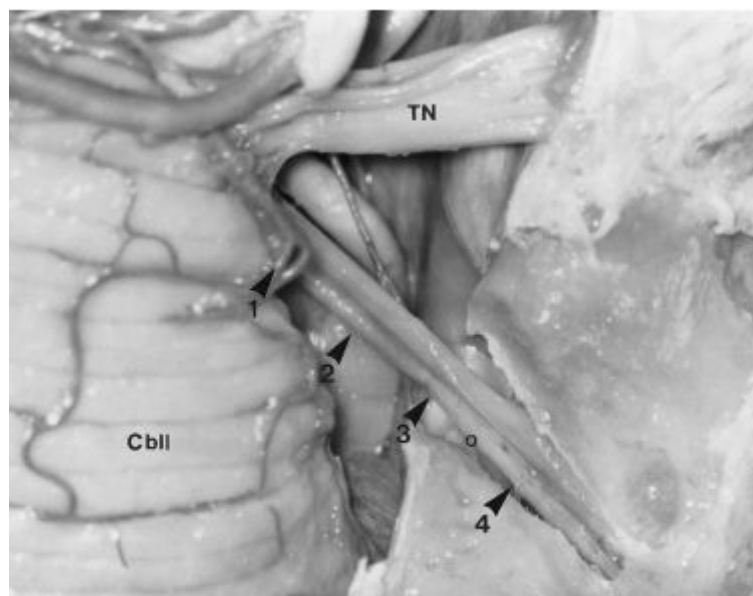
Figure 5. Topographical relationship of the facial and vestibulocochlear nerves at four levels.
1. Near the brainstem; 2. At the CPA; 3. At the IAC; 4. At the midportion of the IAC.
TN- trigeminal nerve; Cbll - cerebellum.
Source: Kim Hyun-Sook, Kim Dong-Ik, Chung In-Hyuk, Lee Won-Sang, Kim Kyo. Topographic relationship of the Facial and Vestibulocochlear Nerves in the Suparachnoid Space and Internal Auditory Canal. Am J Neuroradiol 1998; 19:1155-1161

Introduction

The facial nerve arises from the brain stem near the lateral end of the pontomedullary sulcus. This sulcus extends along the junction of the pons and the medulla, and ends immediately in front of the foramen of Luschka and the lateral recess of the fourth ventricle. The facial nerve arises in the pontomedullary sulcus 1 to 2 mm anterior to the point at which the vestibulocochlear nerve joins the brain stem at the lateral end of the sulcus. The interval between the vestibulocochlear and facial nerves is greatest at the level of the pontomedullary sulcus and decreases as these nerves approach the meatus.[2-3] Mean distances between the exits of the VIIth and VIIIth are 4.7 ± 0.9 mm (e.g. see fig. 6), between the VIIth and IXth 6.2 ± 1.2 mm and between the VIIIth and IXth 5.5 ± 1.0 mm. [10]
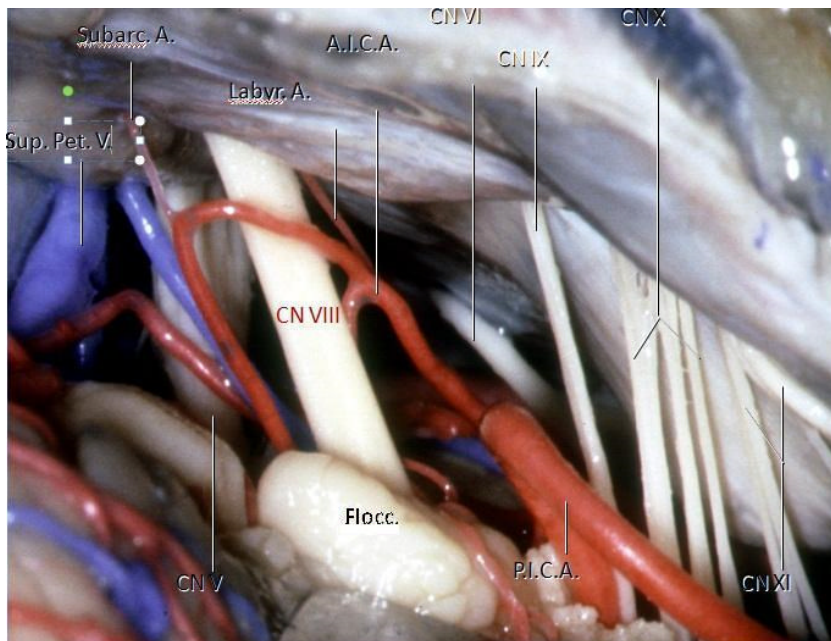
Figure 6. The neighboring structures of a CN VIII at CPA
Source: Seker Askin, Kilic Turker. Atlas of anatomical dissections: The Cerebellopontine angle. Marmara University, Turkey, http://nsa.marmara.edu.tr/anatomy/6/Serebellopontin-Aci (11.11.2013).

The structures related to the lateral recess of the fourth ventricle which have a consistent relationship to the facial and vestibulocochlear nerves are the foramen of Luschka and its choroid plexus and the flocculus. The foramen of Luschka is situated at the lateral margin of the pontomedullary sulcus, just dorsal to the junction of the glossopharyngeal nerve with the brain stem, and immediately posteroinferior to the junction of the facial and vestibulocochlear nerves with the brain stem. The foramen of Luschka is infrequently well visualized.[7,10] However, there is a consistently identifiable tuft of choroid plexus which hangs out of the foramen of Luschka and sits on the posterior surface of the

glossopharyngeal and vagus nerves just inferior to the junction of the facial and vestibulocochlear nerves with the brain stem. [11]

Another structure related to the lateral recess is the flocculus. It is a fan-shaped cerebellar lobule that projects from the margin of the lateral recess into the CPA. The flocculus, together with the nodule of the vermis, forms the primitive flocculonodular lobe of the cerebellum.[10,11] The flocculus is attached to the rostral margin of the lateral recess and foramen of Luschka. It continues medially with the inferior medullary velum, a butterfly-shaped sheet of neural tissue which forms on the surface of the nodule and sweeps laterally above the tonsil to form part of the inferior half of the roof of the fourth ventricle. The lateral part of the inferior medullary velum narrows to a smaller bundle, the peduncle of the flocculus, which fuses to the rostral margin of the lateral recess and foramen of Luschka.[11-12] The flocculus projects from the peduncle of the flocculus into the cerebellopontine angle just posterior to the site at which the facial and vestibulocochlear nerves join the pontomedullary sulcus.

At the CPA, among the other structures, the blood vessels are closely related to facial-vestibulocochlear complex [5]. The arteries crossing the cerebellopontine angle, especially the anterior inferior cerebellar artery, have a consistent relationship with the facial and vestibulocochlear nerves, foramen of Luschka and the flocculus. After coursing near, and sending branches to the nerves entering the acoustic meatus and the choroid plexus protruding from the foramen of Luschka, the anterior inferior cerebellar artery passes around the flocculus to reach the surface of the middle cerebellar peduncle and terminates by supplying the lips of the cerebellopontine fissure and the petrosal surface of the cerebellum.[5, 6]

The anterior inferior cerebellar artery usually bifurcates near the facial and vestibulocochlear nerves to form a rostral trunk and a caudal trunk. The rostral trunk courses along the middle cerebellar peduncle to supply the upper part of the petrosal surface, and the caudal trunk passes near the lateral recess and supplies the lower part of the petrosal surface [6].

Introduction

The trunk of the anterior inferior cerebellar artery is divided into three segments based on its relationship to the nerves and the meatus: the premeatal, meatal and postmeatal segments. [5]

The premeatal segment begins at the basilar artery and courses around the brain stem to reach the region of the meatus. The meatal segment is located in the vicinity of the internal acoustic meatus. [3, 6] The postmeatal segment begins distal to the nerves and courses medially to supply the brain stem and cerebellum. The meatal segment often forms a laterally convex loop, the meatal loop directed toward or into the meatus. [1,3,6]

In most cases, the anterior inferior cerebellar artery passes below the facial and vestibulocochlear nerves as it encircles the brain stem, but it may also pass above or between these nerves in its course around the brain stem. In some occasions it could be displaced by tumours arising in this area. If the artery courses between the facial and vestibulocochlear nerves, a tumour arising in the latter nerve will displace the artery forward.

In the internal auditory canal, the IAA supplies the ganglion cells, nerves, dura and arachnoid membranes. It then divides into two main branches, the common cochlear artery and the anterior vestibular artery (e.g. see fig. 6 and 7). The common cochlear artery further divides into the main cochlear artery and the vestibulocochlear artery, the latter forming the posterior vestibular artery and the cochlear ramus. The main cochlear artery supplies the apical three fourths of the cochlea, whereas the cochlear ramus irrigates the basal one fourth.[1,3] The anterior vestibular artery supplies the utricle, superior part of the saccule, and ampullae of the anterior and horizontal semicircular canals. The posterior vestibular artery is the source of blood supply to the inferior part of the saccule and the ampulla of the posterior semicircular canal. The intraosseous branches or collaterals of the vestibulocochlear artery and its vestibular branch are more abundant than those of the anterior vestibular artery.[1]
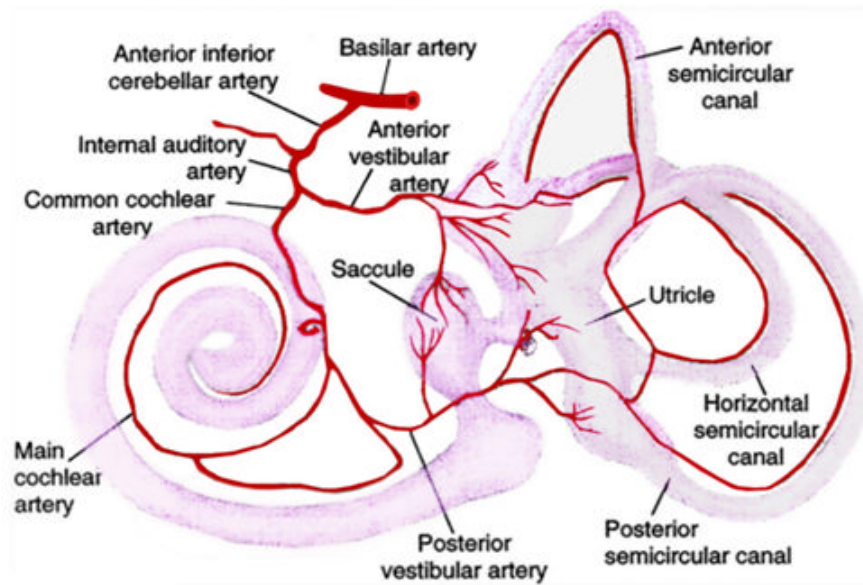
Figure 7. The branches of the anterior inferior cerebellar artery that arise near the facial and vestibulocochlear nerves are the IAA arteries, which supply the facial and vestibulocochlear nerves. Source: dizziness.webs.com/vestibularneuronitis.htm (11.11.2013)

The veins on the side of the brain stem that have a predictable relationship to the facial and vestibulocochlear nerves are those draining the petrosal surface of the cerebellum, the pons and medulla, and the cerebellopontine and cerebellomedullary fissures.[3] The veins on the medial side of the CPA are the vein of the pontomedullary sulcus, which courses transversely in the pontomedullary sulcus; the lateral medullary vein, which courses longitudinally along the line of origin of the rootlets of the glossopharyngeal, vagus, and accessory nerves; the vein of the cerebellomedullary fissure, which passes dorsal or ventral to the flocculus before joining the other veins in the cerebellopontine angle; the vein of the middle cerebellar peduncle, which is formed by the union of the lateral medullary vein and the vein of the pontomedullary sulcus and ascends on the middle cerebellar peduncle to join the vein of the cerebellopontine fissure; and the vein of the cerebellopontine fissure, which is formed by the union of the veins that arise on the petrosal surface of the cerebellum and converge on the apex of the cerebellopontine fissure.[6]

All of these veins course near the lateral recess and the junction of the facial and vestibulocochlear nerves with the brain stem. [1,3]

1.3   Physiology of CN VIII

1.3.1   Physiology of the cochlear nerve

The cochlear nerve as a sensory nerve conducts auditory information from the inner ear to the brain.[1,3,7,11]

The cochlea of the inner ear is the system that converts the mechanical energy of the stapes motion into electrochemical impulses that can be transmitted by the central auditory nervous system to the auditory centers of the brain. [13]

The first stage in this process is the conversion of the stapes motion into the motion of the fluids of the cochlea and the subsequent creation of a traveling wave moving along the basilar membrane. The induced movement of the basilar membrane affects the motion of the stereocilia of the outer and inner hair cells. [1, 13]

The outer hair cells provide an amplification function, increasing the amplitude of the incoming sound wave, while the inner hair cells are sensory receptor cells, changing the mechanical motion of the stereocilia into the release of a neurotransmitter chemical that communicates with the auditory portion of the vestibulocochlear nerve. Therefore, the sound reception process in the inner ear is an active process which dissipates some of its energy in the form of otoacoustic emissions. [12, 14] The complex process by which the cochlea breaks down the mechanical motion of the basilar membrane and translates it into a series of nerve impulses that can be transmitted, reassembled, and interpreted has been theorized for over a century but is still under investigation. [1, 12-14]

The oval and round windows of the cochlea are both covered with elastic membranes that can bulge in and out of the cochlea. An inward motion of the stapes into the scala vestibuli causes movement of the incompressible perilymph from the scala vestibuli into the scala tympani. After the fluid passes through the helicotrema at the apex of the cochlea, the round window membrane bulges out to accommodate the increased amount of fluid in the scala tympani.[12] A motion of the stapes away from the scala vestibuli causes perilymph to move from the scala tympani into the scala vestibule and the membrane of the round window to consequently bulge inwards. The motion of the inner ear fluid caused by the

inward and outward motions of the stapes creates a traveling wave motion along the basilar membrane.[12] The basilar membrane responds differently to sound stimuli of different frequencies, making the location where it reaches its maximum displacement depend on the frequency of the sound wave. There is a systematic shift in the point of maximal vibration from the apex toward the base as the frequency increases. Thus, the basilar membrane is said to be tonotopically organized.[10,12]

The traveling wave was first described by Békésy (1953- 1955), who worked with cadaver ears and ear models. [13] He found that the point at which the displacement of the basilar membrane was the greatest was dependent on the frequency of the sound wave and considered the traveling wave mechanism to be responsible for the sound analysis done by the cochlea. The theory of hearing, or of sound perception, based on this concept is called the traveling wave theory.[13,14]

There is however another competing theory of hearing, called the *resonance theory*, that views the basilar membrane as an array of sequentially tuned tiny resonators distributed along the membrane. This theory was originally proposed by Helmholtz (1885) and states that the tiny resonators of the basilar membrane are set directly into motion by sound pressure changes in the perilymph without needing the traveling wave to set them off. [14] Both of these theories belong to a larger group of theories of hearing, called the *place theories*, which support the tonotopic organization of the basilar membrane (e.g. see fig. 8).
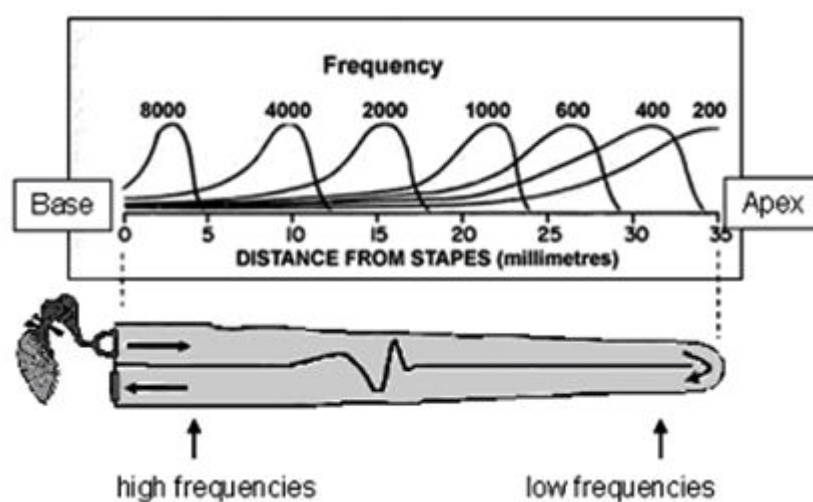
Figure 8. View of uncoiled cochlea and the traveling wave
Source: Bear M.F, Connors B.W, Paradiso M.A. Neuroscience 2001. Exploring the Brain. Baltimore: Lippincott, Williams and Wilkins. pp354-358.

Introduction

There are a number of experimental studies which support either the travelling wave or the resonance theory of hearing, but there is still a lack of complete agreement in the literature as to whether the traveling wave is directly responsible for the basilar membrane motion or whether it is a secondary effect caused by the direct stimulation of basilar membrane's resonators by sound pressure propagating through the perilymph (Bell, 2004; Bell and Fletcher, 2004). [14]

Regardless of the theory behind the true manner in which the cochlea analyzes sound, the basilar membrane is the element responsible for sound analysis, and its tonotopic organization is mirrored within the auditory nervous system. [1, 4, 12, 13]

Sound waves and mechanical vibrations acting on the surface of the human head are absorbed by the soft tissue and bones *(Bone Conduction)* of the head and propagate through the head's structures. They also induce complex physical vibrations of the skull that can be transmitted to the brain and sensory organs of the head. Both these mechanisms together can affect the hearing system and evoke auditory responses analogous to those caused by sound waves arriving at the outer ear of the hearing system. [12-14]

All important head resonances have frequencies below the transmission range of bone conducted stimuli to protect supporting them mechanisms from potential harmful effects of body vibrations and acoustic stimulation. [14] They include, but are not limited to, eyeball resonance, jaw resonance, neck resonance, and head and shoulder vibrations For the human communication purposes only bone vibrations created by directly applied physical vibrations (via a mechanical vibrator) have sufficient energy to be used as a carrier of information. Sound waves arriving to the surface of the head are either captured by the outer ear and delivered through the hearing system to the organ of Corti or are mostly reflected back into the environment due to the impedance mismatch between the impedance of the skull and the impedance of surrounding air. [10]

Sound waves can only be heard through bone conduction when the arriving sound has very high intensity and the person's ears are occluded by hearing protectors or head mounted audio displays (audio HMD). [13, 14]

However in such cases, perceived sound often constitutes the harmful noise which leaked to the hearing system by bone conduction pathways rather than a communication signal. The first modern theory of bone conduction hearing was proposed by Herzog and Krainz in 1926. [14] According to this theory the bone conduction hearing is a combination of the following two phenomena:

    1. Relative motion of the middle ear bones caused by head vibrations

    2. Compression waves in the cochlea resulting from the transmission of vibrations through the skull.

The two landmark publications on bone conduction by Békésy (1932) and Barany (1938) provided further evidence for and expanded this theory. Bekesy and Barany also provided clear evidence that air conduction and bone conduction mechanisms were two different hearing mechanisms resulting in the same excitation of the basilar membrane. [13, 14]

The current theory of bone conduction hearing is mostly based on the comprehensive studies by Tonndorf who expanded Herzog and Krainz's work and identified seven potential mechanisms which can contribute to human hearing. [14,15]

The four main mechanisms proposed by Tonndorf are the following:

1. Inertial Mechanisms

    a. A middle ear inertial mechanism involving relative and delayed movement of the ossicular chain in reference to the surrounding temporal bone (cochlear promontory).

    b. An inner ear inertial mechanism involving transmission of temporal bone vibrations on the inner ear fluids.

2. Compression Mechanisms

    a. An outer ear compression mechanism involving radiation of bone-conducted energy from the osseous walls of the ear canal back to the ear canal.

    b. An inner ear compression mechanism involving compression and decompression of the inner ear fluids by compression vibrations of the bony cochlea. [13]

The most dominant of the above mechanisms seems to be the inner ear inertial mechanism although several other mechanisms contribute as well.

The effectiveness of the individual mechanism depends on the frequency of the signal, place and direction of vibration application, and the status of the outer ear.

The first two factors affect the modes of vibrations of the skull whereas the third depends on the type and quality of the ear occlusion. The last factor dramatically affects the effectiveness of the outer ear compression.[14]

The neural activity of the inner ear is dependent on electro-chemical processes and initial electric potentials between the fluids occupying the various structures of the inner ear. An electric potential is created when there is a difference in the electric charge between two different locations. The area of higher charge is said to be positively polarized while the area of lower charge is said to be negatively polarized. In a biological system, such as the human ear, a difference in chemical charge between two areas is called the bioelectric potential.[11] When the two polarized areas are connected, the charged particles move from one area to another. This occurs because of the electromotive force that is created by the difference in electrical charge. Commonly charged particles in the human ear include positively-charged potassium ions ($K+$), negatively-charged chloride ions ($Cl-$), positively-charged sodium ions ($Na+$) and positively-charged calcium ions ($Ca2+$). In the inner ear, the endolymph contains a large amount of potassium ions and the perilymph contains a large amount of sodium ions. A static bioelectric potential that involves the separation of charged particles by a cell membrane is called a resting potential. The resting potential of the endolymph in the scala media, called the endocochlear potential (EP), is + 80 millivolts (mV) in reference to the resting potential of the perilymph in the two other cochlear channels. The resting potential of the inner hair cells is -40 mV and of the outer hair cells is -70 mV compared with the perilymph. [15] Therefore, the difference in potential between the endolymph and the inner hair cell is 120 mV and between the endolymph and the outer hair cell is 150 mV. This 150-mV potential is a biological battery that supports all inner ear processes. It is a very efficient system that consumes only approximately 14 microwatts (μW) of power while carrying out the equivalent of approximately one billion floating-point operations per second. [12, 13, 15]

A dynamic bioelectrical potential that involves the movement of charged particles from one area to another in response to a stimulus is called a stimulus related potential. There are three stimulus related potentials that are commonly observed in the inner ear in response to an auditory stimulus. The three stimulus related potential are the summating potential (SP), cochlear microphonic (CM), and the compound action potential (CAP). The

former SP and CM are generated by the hair cells and CAP is generated by the vestibulocochlear nerve.[11, 12, 15] The SP is a direct current potential that causes a positive or negative change in the endocochlear potential for the duration of a signal. It is the driving force for moving the charged ions through the stereocilia and membrane separating hair cell from the surrounding endolymph. Both the CM and CAP are alternating current potentials which vary in polarity based on changes in the phase of the signal. The CM is a pre-neural electric potential that mimics the incoming sound signal; it is considered to be a reflection of receptor currents flowing through the hair cells. The CAP is the actual event related potential (ERP) that is generated when the auditory nerve "fires" (transmits a signal) in response to a stimulus. The CAP results from the firing of the auditory portion of the vestibulocochlear nerve in response to the release of the neurotransmitters from the hair cells.[13]

Various ERPs and their changes in time and space can be measured in the central nervous system using electroencephalography (EEG). One example of these measurments is the mismatch negativity (MMN) potential generated in the auditory cortex and having a latency of 150 to 250 ms post-stimulus. The MMN is a negative, task independent neural potential generated in response to an infrequent change in a repetitive sound sequence.[15]

Up and down movement of the basilar membrane causes a shearing force to act on the cilia of the hair cells of the organ of the Corti. The shearing force is a result of different points of attachment of the basilar membrane and the tectorial membrane to the cochlear wall. The force bends the cilia to the left and to the right of the basilar membrane axis.[1]

The stereocilia of a hair cell have gradually changing height and are held together by tip-to-side links that cause the whole bundle to move together when stimulated.[14] Tilting movements of the stereocilia affect the tension on the fiber in the tip link. When the stereocilia are bent toward the largest stereocilium, the tip-to-side links cause mechanically-gated ion channels in the stereocilia membranes to open. The opening of the ion gates allows positively-charged ions (K+) of potassium, which are the main cations in the endolymph, to flow from the positively-charged endolymph into the negatively-charged hair cell.[15] As the fiber tension increases, the flow of ions into the hair cell also increases. When the stereocilia bundle is bent in the direction away from the largest stereocilium, the ion channels close and the excess of K+ in the cell is pushed out of the

cell through a semipermeable membrane via active pumping processes restoring natural negative polarization of the cell (Geisler, 1998). [7,14] However, the effects of stereocilia bending and the in-and-out flow of K+ ions are different in the inner hair cells and the outer hair cells. When the K+ ions enter the inner hair cell, they depolarize the content of the cell, that is, they change to zero the difference in electric potentials between the areas inside and outside the cell. As a result, when the gates are open, the cell becomes depolarized (excited), and when the gates are closed, the cell becomes hyperpolarized or inhibited (e.g. see fig. 9).
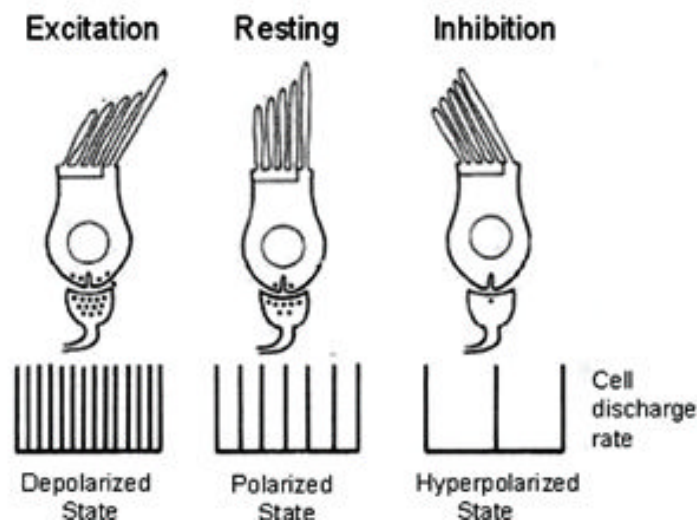
Figure 9. The inner hair cells response to the bending of the steriocilia.
Source: Emanuel D, Maroonroge S, Letowski T. The Hearing System 2009. Chapter 9. Physiology and Function of the Hearing System p320

The transduction of the mechanical actions of the shearing of the stereocilia to the electro-chemical signal transmitted by the nervous system begins when a neurotransmitter is released from the base of the inner hair cell. [17] This neurotransmitter crosses the synaptic cleft and binds to specialized receptor sites located on the post-synaptic membrane of the peripheral processes of the nerve fibers connecting the inner ear with the brainstem. The bundle of nerves connecting the inner ear with the brainstem is called the auditory nerve. If a sufficient amount of neurotransmitters are released, the afferent nerve fibers will fire in response, sending an electric signal down the length of the auditory nerve towards the brainstem. [16, 17]

The response of single auditory nerve fibers to different stimuli has been measured in many experiments. Most of them performed experimentally in which a microelectrode placed in the nerve trunk to isolate the activity myelinated nerve fibers.[17,20]

The auditory nerve has approximately 30,000 fibers in humans and there are approximately 50,000 auditory nerve fibers in cats. Perhaps one of the most important research findings was the observation that 90% to 95% of neurons (type I radial fibers) innervate to the outer hair cells, whereas 5% to 10% (type II, outer radial fibers) innervate to the outer hair radial cells. The radial cells have bipolar cell bodies in the spiral ganglion. Outer spiral fibers are monopolar and unmyelinated.[15,16,17]

On the base of spontaneous discharge, the nerve fibers have been classified into the following three categories: high (18 to 20 spikes per second), medium (0,5 to 18 spikes per second), and low (0 to 0,5 spikes per second). Fibers with high rates of spontaneous activity respond to auditory signals at low levels better than do the fibers with medium or low rates that have thick dendrites which tend to determinate on the side of the inner hair cells facing the outer hair cells. Fibers with low and medium spontaneous rates have thin dendrites on the side of the inner hair cells facing the modeolus.[11]

According to some ongoing studies, the fibers with high rates of spontaneous activity have different terminations in the auditory CNS (cochlear nucleus) than do fibers with low rates of spontaneous activity. In other words, spontaneous activity of nerve fibers is not random but is proving to be anatomically and functionally significant.[11] The tuning curve of the single auditory nerve fiber is perhaps the most basic measure of auditory nerve function. When effectively stimulated by sound, the cochlear afferent responds with an increase in the rate of discharge. At low stimulus intensities, such rate increases are evoked only by a narrow range of stimulus frequencies.[18]

Auditory nerve fibers arrive at the brainstem by forming synapses with large groups of neurons in the cochlear nuclei located in the border between the pons and medulla. The fibers from each ear terminate on the nucleus located on the same (ipsilateral) side of the brainstem from where most of the fibers cross to the opposite (contralateral) side of the brainstem, and either connects to contralateral superior olivary complex or ascends directly to contralateral inferior colliculus in the midbrain. Type I nerve fibers with large

myelinated neurons are responsible for transporting the coded auditory signal from the peripheral to the central nervous system. The function of the smaller and less numerous type II fibers is still largely unknown.[16,18]

The neural cells in the cochlear nuclei have several complex firing patterns and wider dynamic ranges than the neurons in the auditory nerve. In response to simple tonal stimuli, several response patterns have been recorded in the various cells of the cochlear nuclei. These response patterns include the following patterns: 1) a "primary" pattern that is similar to that of the auditory nerve ("primary-like" neurons), 2) a "chopper" pattern that consists of repeated bursts of firing followed by short pauses ("chopper" neurons). The periodicity does not match the periodicity of the stimulus. 3) an "on" pattern, in which the cell fires only when a stimulus begins "on" neurons, and 4) a "pauser" pattern in which the cell fires only at the onset of the stimulus, pauses, and then continues until the stimulus is turned off ("pauser" neurons).[20]

Examples of peristimulus (PST) histograms, i.e., the histograms of the times at which neurons fire, as a function of latency following tonal stimuli (e.g. see fig. 10). The firing patterns shown in figure 10 are the most commonly reported firing patterns. However, there also are other firing patterns observed in response to simple stimuli. Further, there are reports of many different subcategories of firing patterns under each of the main categories, and the response of the cochlear nucleus to complex stimuli varies from the response to simple stimuli.

The type of response recorded from the neurons in the cochlear nucleus depends on a number of physical features associated with the cells (e.g. characteristics of the membrane, type of cell), the connection between the auditory nerve and the cochlear nucleus cells (e.g. many or few axon endings contacting many or few dendrites), and the presence of inhibitory input from other cells. For example, in the anterior ventral cochlear nucleus (AVCN), the most common cell types are the global and spherical bushy cell. These cells receive very few axonal connections from auditory nerve fibers from a localized frequency area of the cochlea and are the most likely contributors to the primary response pattern seen in the cochlear nucleus. Their frequency specificity may also be enhanced by their function as coincidence detectors, which reduce the random noise level from spontaneous activity of the auditory nerve.[18,19] Other cells may specialize in transmitting intensity of

sound (multipolar cells) or temporal order of sound events (octopus cell). In the posterior ventral cochlear nucleus (PVCN), the octopus cell is a common cell type, so-called because these cells resemble an octopus with long tentacle-like dendrites. These dendrites receive many more connections, across a broader frequency range of the cochlea, compared with the AVCN bushy cells, and they are thus more broadly tuned. These cells have been reported to respond well to amplitude modulated tones and clicks, but have a reduced activity in response to steady state noise. In some species, the dorsal cochlear nucleus (DCN) has been recorded to respond to spectral differences that may indicate they provide some coding in response to monaural localization cues in a vertical plane.[17,18]
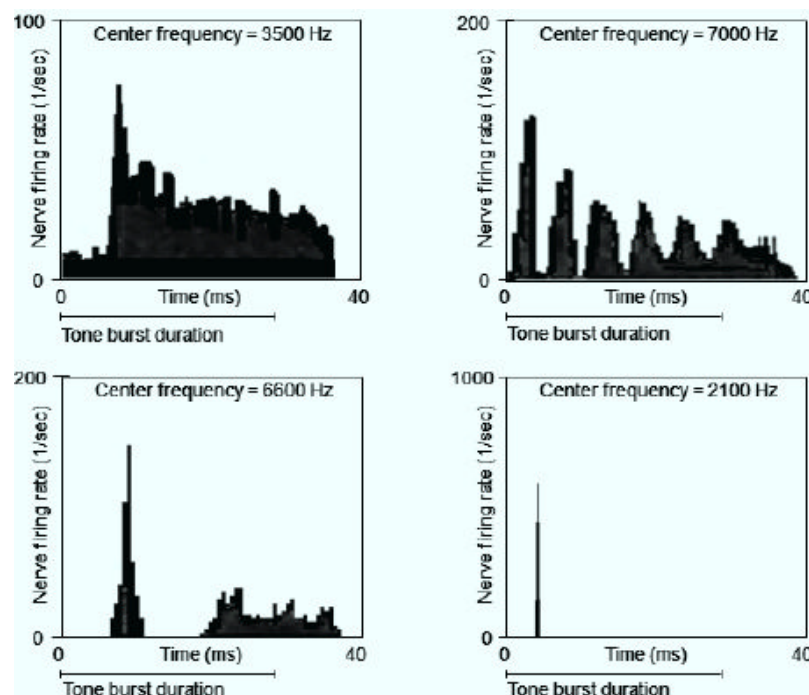
Figure 10. PST histograms illustrating different types of neuron firing patterns in the cochlear nucleus. Source: Pfeiffer R. Classification of response patterns of spike discharges for units in the cochlear nucleus: Tone-burst stimulation. Experimental Brain Research 1966, Volume 1, Number 3, 220-235.

1.3.2 Physiology of superior and inferior vestibular nerves

The vestibular nerves as a sensory nerve conducts vestibular information from the inner ear to the brain.[1,3,7,11]

The peripheral vestibular system includes the paired vestibular sensory end organs of the semicircular canals (SCC) and the otolithic organs (Fig. 11). These receptors are found

within the fluid-filled bony channels of the otic capsule and are responsible for perception of both the sense of position and motion. [19] The vestibular nerves are the afferent connection to the brainstem nuclei for the peripheral vestibular system.
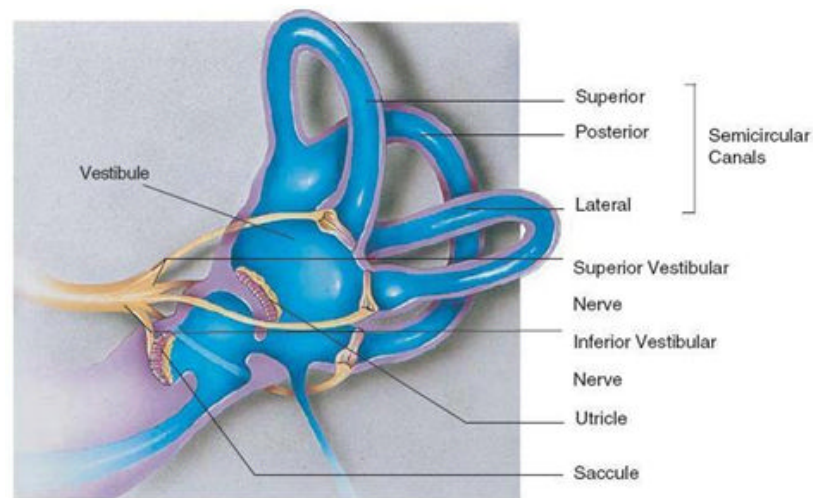
Figure 11. Anatomic organization of the peripheral vestibular system (vestibular end-organs and the vestibular nerve).
Source: http://otorrinos2do.wordpress.com/2009/12/08/physiology-of-the-vestibular-system/

The cells bodies of vestibular nerve afferents are located in the superior or inferior divisions of Scarpa's ganglia, which lie within the internal auditory canal near the emergence of the vestibular nerve into the cerebellopontine angle. [16]

From the vestibular labyrinth, the afferent information travels ipsilateral in 1 of 2 branches of the vestibular nerve. The superior vestibular nerve innervates the lateral and anterior SCC as well as the utricle. The inferior vestibular nerve innervates the posterior SCC and the saccule (e.g. see fig. 11).

Variation of nerve fiber counts among studies appears to be a function of age, although rate of decline of the number of afferent fibers also appears to be variable. The branches of the vestibular nerve travel together into the pontomedullary junction where they bifurcate.[16] Primary vestibular afferents in the superior division of the vestibular nerve include axons that synapse in the superior and medial vestibular nuclei or the uvula, nodulus, flocculus, or fastigial nucleus of the cerebellum. [16-17]

Primary vestibular afferents from the inferior branch synapse with neurons in either the medial, lateral, or inferior vestibular nuclei, which, along with the superior vestibular nuclei and other subnuclei, comprise the vestibular nuclear complex.[16]

Perception of angular accelerations is chiefly the responsibility of the three paired SCCs (superior, posterior, and lateral). Within the ampullated portion of the membranous labyrinth are the end-organs of the cristae, containing specialized hair cells that transduce mechanical shearing forces into neural impulses. Histologically the hair cells of the ampulla are located on its surface. Their cilia extend into a gelatinous matrix better known as the cupula, which acts like a hinged gate between the vestibule and the canal itself (e.g. see fig. 12). The otolithic organs of the utricle and the saccule are found within the vestibule. Chiefly responsible for the perception of linear accelerations (eg, gravity, deceleration in a car), their end-organs consist of a flattened area, rich in hair cells, in the macular area whose cilia project into a similar gelatinous matrix. The matrix, however, differs from the matrix associated with the SCCs in its support of a blanket of calcium carbonate crystals better known as otoliths, which have a mean thickness of approximately 50 μm Information from the vestibular end-organs is transmitted along the superior (which receives information from the superior, horizontal SCCs and utricle) and inferior (which receives information from the posterior SCC and saccule) divisions of the vestibular nerve. Although its role is primarily afferent in the transmission of electrical activity to the central vestibular nuclei of the brainstem, an efferent system does exist that probably serves to modify end-organ activity. Each vestibular nerve consists of approximately 25,000 bipolar neurons whose cell bodies are located in a structure known as Scarpa's ganglion, which is typically found within the IAC.[17, 20]
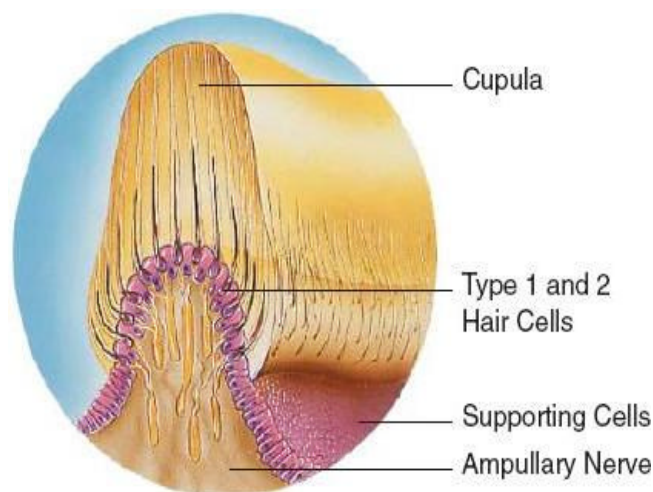
Figure 12. A stylized representation of the crista with the angular acceleration receptor
Source: http://otorrinos2do.wordpress.com/2009/12/08/physiology-of-the-vestibular-system/

53

Introduction

Type I neurons of the vestibular nerve derive information from corresponding type 1 hair cells, whereas type II neurons derive information from corresponding type 2 hair cells at its simplest. The cristae ampullares convey information approximately angular in acceleration of the head to the central nervous system. The maculae convey information about linear acceleration and head position relative to gravity. [18]

The utricular macula is oriented horizontally and the saccular macula is oriented vertically. Tilting the head to the side stimulates the saccular macula and titling the head forward or to the back stimulates the utricular macula.[15] All these sensory organs contain hair cells with their stereocillia responding to the head motion analogous to the way the inner hair cells in the cochlea respond to the acoustic signal. Depending on the head position and the direction of the head movement, the endolymph flow in the semicircular canals and the vestibule stimulates the hair cells of the organs which control balance.[18] For example, the cilia of the maculae are embedded in the gelatinous membrane containing a relatively heavy amount of calcium carbonate (otoconia); movements of the head cause the otoliths to bend the cilia, causing depolarization/hyperpolarization of the hair cells, depending on the direction of movement.[14,18] The signals from the organs which control balance are transmitted through the vestibular portion of the vestibulocochlear nerve to four vestibular nuclei within the brainstem and further to the brain.[18]

The fibers from the vestibular nuclei also crossover to the contralateral nuclei from which they project, among others, to oculomotor nuclei that drive eye muscle activity, resulting in a vestibule-ocular reflex that helps maintain fixation of the eyes on the object moving, in relation to the head position. In this way, the fibers are responsible for a complex coordination between the vestibular system, visual system, proprioceptors, and structures within the cerebellum, brainstem, and the whole cortex.[18]

Primary vestibular afferents enter the brainstem dividing into ascending and descending branches. Within the brainstem there appears to exist a nuclear region with four distinct anatomic types of second-order neurons that have been traditionally considered to constitute the vestibular nuclei. It appears, however, that not all these neurons receive input from the peripheral vestibular system. The main nuclei are generally recognized as the superior (Bechterew's nucleus), lateral (Deiters' nucleus), medial (Schwalbe's nucleus),

and descending (spinal vestibular nucleus). Functionally, in primate models, the superior vestibular nucleus appears to be a major relay station for conjugate ocular reflexes mediated by the SCCs. [14, 15, 18]

The lateral vestibular nucleus appears to be important for control of ipsilateral vestibulospinal (the so-called "righting") reflexes. The medial vestibular nucleus, because of its other connections with the medial longitudinal fasciculus, appears to be responsible for coordinating eye, head, and neck movements. The descending vestibular nucleus appears to have an integrative function with respect to signals from the vestibular nuclei, the cerebellum, and an amorphous area in the reticular formation postulated to be a region of neural integration. Commonly referred to as the "neural integrator" among neurophysiologists, the nucleus is responsible for the ultimate velocity and position command for the final common pathway for conjugate versional eye movements and position. [16]

The vestibular nerve in part also projects directly to the phylogenetically oldest parts of the cerebellum namely, the flocculus, nodulus, ventral uvula, and the ventral paraflocculus on its way directly through the vestibular nucleus. Better known as the vestibulocerebellum, this area also receives input from other neuronal pathways in the central nervous system (CNS) responsible for conjugate eye movements, especially smooth-pursuit eye movements, which, in addition to the VOR, are responsible for holding the image of a moving target within a certain velocity range on the fovea of the retina. [13- 15]

The Purkinje's cells of the flocculus are the main recipients of this information, of which some appears to be directed back toward the ipsilateral vestibular nucleus for the purposes of modulating eye movements in relation to gaze (eye in space) velocity with the head still or during combined eye–head (vestibular signal-derived) tracking. [15] Important for cancelling the effects of the vestibule-ocular reflex (VOR) on eye movement when it is not in the best interest of the individual (think of twirling ballet dancers or figure skaters and how they can spin without getting dizzy), the vestibulocerebellum is also important in the compensation process for a unilateral vestibular loss.

Introduction

The fundamental unit for vestibular activity on a microscopic basis inside the inner ear consists of broadly classified type 1 and 2 *hair cells (e.g. see fig. 13).*
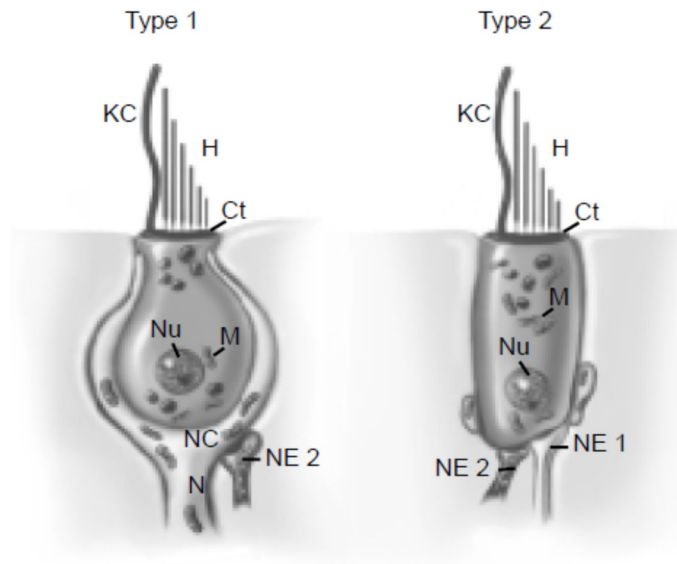
Figure 13. Schematic representation of type 1 and type 2 hair cells: Ct - cuticular plate; H - hairs; KC - kinocillum; M - Mitochondria; NC - nerve chalice; NE - nerve ending; Nu – nucleus
Source: Rutka J. Ototoxicity 2004. Chapter 2, Physiology of the Vestibular System. p21.

Type 1 hair cells are flask-shaped and surrounded by the afferent nerve terminal at its base in a chalice like fashion. One unique characteristic of the afferent nerve fibers that envelop type 1 hair cells is that they are among the largest in the nervous system (up to 20 μm in diameter). The high amount of both tonic (spontaneous) and dynamic (kinetic) electrical activity at any time arising from type 1 hair cells has probably necessitated this feature for the neurons that transfer this information to the CNS. Type 2 hair cells are more cylindrical and at their base are typically surrounded by multiple nerve terminals in contradistinction. Each hair cell contains on its top a bundle of 50 to 100 stereocilia and one long kinocilium that project into the gelatinous matrix of the cupula or macula. It is thought that the location of the kinocilium relative to the stereocilia gives each hair cell an intrinsic polarity that can be influenced by angular or linear accelerations. It is important to realize that an individual is born with a maximum number of type 1 and 2 hair cells that cannot be replaced or regenerated if lost as a result of the effects of pathology or aging. Presumably the same process holds for the type I and II neurons that comprise the vestibular nerve.[17]

At the microscopic level, movements of the head or changes in linear accelerations deflect the cupula or shift the gelatinous matrix of the otolithic organs with its load of otolithic crystals that will either stimulate (depolarize) or inhibit (hyperpolarize) electrical activity from type 1 and 2 hair cells. Displacement of the stereocilia either toward or away from the kinocilium influences calcium influx mechanisms at the apex of the cell that causes either the release or reduction of neurotransmitters from the cell to the surrounding afferent neurons (e.g. see fig. 14).

With Otolithic Displacement
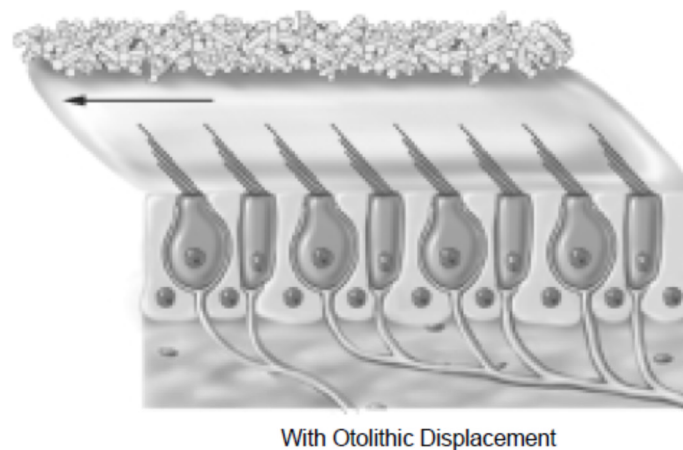
Figure 14. The physiology of macular stimulation and inhibition from otolithic shift and its shearing effect on stereocilia and kinocilium of the hair cells.
Source: Rutka J. Ototoxicity 2004. Chapter 2, Physiology of the Vestibular System. p23

The electrical activity generated is then transferred along the vestibular nerve to the vestibular nuclei in the brainstem.

Information above the tonic (spontaneous) firing rate of the type 1 hair cells transmitted along type I neurons is largely thought to have a stimulatory effect in contrast to a more inhibitory effect attributable to type 2 hair cells and type II neurons. The SCCs largely appear to be responsible for the equal but opposite corresponding eye-to-head movements better known as the VOR. The otolithic organs are primarily responsible for ocular counter-rolling with tilts of the head and for vestibulospinal reflexes that help in the maintenance of body posture and muscle tone. [20]

In order to ultimately produce conjugate versional VOR-mediated movements of the eyes, each vestibular nucleus receives electrical information from both sides that is exchanged via the vestibular commissure in the brainstem. The organization is generally believed to

be specific across the commissure. Neurons in the right vestibular nucleus, for example, that receive type I input from the right horizontal SCC project across the commissure to the neurons found in the left vestibular nucleus that are driven by the left horizontal SCC receiving contralateral type II input and vice versa.[17, 19]

1.3.3   Schwannoma of Vestibulocochlear nerve

1.3.3.1   Background of Vestibular Schwannoma in the history of medicine

"De duro quodam corpusculo, nervio auditorio adherente" – were the first postmortem descriptions made for Acoustic Neuroma (Vestibular Schwannoma) in 1777, by Eduard Sandiford - Professor of Pahology in Leiden, in his book called "*Anatome infantis cerebro destitute*".[22, 26]

He described the appearance of small growth, externally hard like cartilage but internally quite soft. At that time he thought that this cause of deafness clearly beyond the reach of medication or surgery and must be declared incurable. [26]

From 1777, the knowledge about Vestibular Schwannoma (VS) has been accumulating more and more as well as the clinical symptoms in patients with VS which were correlated to the intracranial autopsy findings of several authors.[20]

During the early nineteenth century number of case reports appeared in which antemortem symptoms and clinical signs were correlated with postmortem findings. Early findings have probably been described by the French scientist Leveque-Lasore in 1810. By the mid-1800s, the two neurologists, Toynbee and Stevens, describe a patient, who manifested unilateral deafness, facial numbness and progressive blindness, which was affected by a tumour in the CPA. The first definitively accurate postmortem description of this tumour was not made until Sir Charles Bell carefully presented his autopsy findings in 1830.[21, 23]

Jean Cruveilhier,[21, 25] known for his atlas *Anatomie pathologique du corps humain,* which included the first ever color illustrations of brain pathology,[34] published an unprecedentedly detailed account of the progression of symptoms and autopsy findings in a

26yearold woman with a VS. She became deaf at the age of 19 years and presented seven years later with headaches, progressive blindness, and facial weakness. Although Cruveilhier was unable to correctly localize the tumour until autopsy, he initially believed that the tumour was at the skull base.[21] But no one would correctly diagnose and localize VS prior to an autopsy until almost fifty years later, when Oppenheim in Germany became the first to accomplish this feat.[21,23] In 1900, Sternberg was the first to describe the histopathology of a VS, whereas leading physicians such as Oppenheim, von Monakow, Jackson, Gowers, Babinski, and Starr were refining their knowledge of functional brain anatomy, especially in the cerebellar region.[19,23]

The physician's developments in diagnosis and localization facilitated an earlier diagnosis of VS while the patient was still alive and set the stage for surgical intervention. The concurrent evolution of anesthetic and aseptic techniques during this period fueled the era of surgical exploration in the posterior fossa. Nonetheless, further refinement of the surgical methods available for the supratentorial space and intraoperative control of intracranial tension was necessary to approach the infratentorial space relatively safely.

In 1890, von Bergmann made the first surgical attempt at removing a tumor, which at autopsy was discovered to be a VS; he was unable to intraoperatively localize the tumour before the patient died.[24] The first successful VS surgery was most probably performed by Annandale in 1895. Although a year earlier Ballance resected a tumour that may have been either a meningioma or VS.[26]

Until the 1900s the most physicians has been considering the intracranial surgery to be unwise and irresponsible. [26] But in the early 1900s earlier tumour diagnosis and localization was possible and surgical intervention for intracranial pathology gained some popularity. Prominent surgeons such as von Monakow published optimistic papers encouraging doctors to be less reluctant in attempting intracranial surgery.[23]

As more surgeons independently attempted surgical intervention for VS, a variety of techniques and approaches developed, some of which were early versions of the procedures used today.[19] Woolsey, Fraenkel, and Krause used a unilateral suboccipital approach with some success. Borchardt performed the first "transsigmoid" VS surgery in 1905 and the same year, Horsley first resected a VS.[25] The patient in Horsley's case

survived the operation but became severely disabled, most likely due to a brainstem infarct. In 1903, Garreé was the first to attempt surgery for a bilateral VS and had dismal results, as did Biggs a few years later in 1909.[21]

Four years later in 1913, at the International Congress of Medicine in London, the three well known European surgeons, Horsley (London), Eiselsberg (Vienna), and Krause (Berlin) reported mortality rates for the VS surgeries they performed, with the following resuts: 67% in 15 cases, 77% in 17 cases, and 84% in 31 cases, respectively. [26, 27] They are stated that all of them used a unilateral suboccipital approach and an index finger or spatula to quickly dislodge the tumour, which usually caused injury to the cerebellum and brainstem. Eiselsberg and Horsley further attempted the operation in 2 stages without better success.[26]

The first translabyrinthine approach was described in 1904 by Panse and was similar to the one used today. But the translabyrinthine approach was abandoned because of its high risk of cerebrospinal fluid leakage, destruction of the middle ear, and limited exposure of large tumours.[21, 27] Due to the high mortality rates after the above-stated approaches, some surgeons combined petrosal and suboccipital approaches with little success.[23] But the first successful result towards reducing mortality was obtained by Cushing. In 1904, Cushing began working with Amory Codman to record a patient's pulse, temperature, respiration, and ether dosage during surgery in an attempt to discover the changes indicative of imminent death.[23] This novel idea led to further progress in neuroanesthesia and more specifically in posterior fossa surgery. Cushing also introduced the silver clip in 1911 and electrocautery in 1925 for controlling intraoperative hemorrhage.[26]

Using the new tools as well as his initial experience with intracranial supratentorial surgery, Cushing surgically treated VSs with remarkably lower mortality rates than those of his predecessors. In 1917 he published the results of 30 VS cases in his famous monograph *"Tumours of the Nervus Acusticus and the Syndrome of the Cerebellopontine Angle",* in which he reported a vastly superior mortality rate of 10–15%.[24] Unlike to earlier approaches, Cushing proposed a bilateral suboccipital craniectomy for subtotal intracapsular tumour decompression. He believed that this method was safer than complete resection, allowed decompression of the brainstem, and avoided medullary compression during surgical manipulation of the tumour. Although this was not the first time a bilateral

suboccipital approach had been proposed, Cushing was one of the first surgeons to emphasize the importance of controlling intracranial pressure by using a ventricular tap and therefore avoiding medullary compression and cerebellar herniation.

The bilateral approach allowed surgeons to explore both CPAs, as findings on radiographic images were not always reliable. Cushing's gentle and meticulous methods, combined with his conservative philosophy of performing only intracapsular decompression, proved the safety but not necessarily the efficacy of VS surgery using the now-obsolete technologies of his day. [21]After a few years of partial resection for VS, despite his significantly lower mortality, unfortunately, this method become associated with a higher tumour recurrence rate and the five year mortality rate was 54%.[23] Cushing accepted that another approach for total resection would be far superior if neuroanesthesia, operative, and diagnostic technologies could be improved. After a couple of years Dandy's introduction of air ventriculography (1918) allowed neurosurgeons to localize and operate on smaller tumours partly through the early detection of hydrocephalus. Dandy was very technically skilled, and he believed in his ability to improve on Cushing's results. By this time the syndrome of the CPA was more widely recognized, and surgical intervention was no longer reserved only for patients at the terminal stage of the disease. The above factors assisted Dandy in achieving a gross total resection (GTR) of VSs which were relatively smaller.

Despite the benefits of ventriculography, however, Cushing was extremely reluctant to embrace its clinical use, claiming that it would undermine the importance of a detailed neurological examination.[24] He did not consider Dandy's innovation a next step in the advancement of intracranial surgery.[27] Dandy believed that the 54% 5-year mortality rate Cushing had reported was unacceptable, and he searched for a safe way to perform a GTR of VS despite Cushing's doubts about its feasibility. In his early experience with intracapsular decompression, Dandy was convinced that the residual "shell of tumour" was responsible for delayed neurological deterioration after surgery. He thought he found the answer when in 1922 he published a preliminary report on a successful total VS resection performed 5 years earlier. [23, 24] In this report, he described how he had made a bilateral suboccipital flap, first removing the interior portion of the growth as described by Cushing, then meticulously clipping the veins and arteries surrounding the capsule, and finally pulling the capsule carefully away from the brainstem. Dandy wrote, "As the capsule is

cautiously retracted, several small blood vessels crossing from the brainstem or cerebellum are brought into view and doubly 'clipped' and the vessel divided."[28]

Previously, Horsley had advocated blunt finger removal of an intact large tumour, and Cushing had favored subtotal enucleation of VS as an adjunct to osseous suboccipital decompression. Dandy took the next step in the history of VS surgery by performing extensive intracapsular decompression followed by meticulous tumour capsule excision and careful management of surrounding vasculature to respect important vessels and avoid postoperative hemorrhage. [24] In this 1922 report, however, Dandy failed to mention any of Cushing's 1917 monograph, and so Cushing promptly wrote a letter attacking his manners and professional ethics and dismissed Dandy's success.[26] Rather than considering Dandy's new approach, Cushing rigidly maintained his belief that the high mortality rates of total VS resection would make it irresponsible even to attempt such an approach. He considered Dandy's method to be inconsistent with the standard of care. Some neurosurgeons that had been trained by Cushing followed his recommendations. [21]

In Europe the modern viewpoints of VS has been dominated by the efforts of House, Yasargil and Fisch (1969), Glasscock (1973), Sterkers (1979), King and Morrison (1980), Samii and Wigand (1992).[26] Particularly, surgeons from England, France, Germany and Denmark have made great contribution to the development of knowledge of VS and management of patients with VS.

In Denmark, two CPA tumours were operated on via the translabyrinthine approach by the otologist, EC Schmiegelow, who operated on two patients at the National Hospital, Rigshospitalet, in 1914. [21] It was a huge step forward in VS surgery When William House developed the translabyrinthine approach in 1960. Nevertheless, it resulted in a 20% cerebrospinal fluid leak. But after microsurgical techniques were introduced by M Tos in 1976, who removed a medium size VS via the translabyrinthine approach in the Department of Otolaryngology, Gentofte University Hospital. [23] Even this approach later termed as a Danish VS model, where Tos and Thomsen in close cooperation with the neurosurgeons J Riishede, G Thornval and A Harmsen established one team to manage VS in Denmark.[23]

The invention of the Gamma Knife Machine for the management of patients with VS has revolutionized tumor control. The Gamma Knife Surgery for VS was first conducted by professor Leksell in Sweden in 1969. In 1986, the Leksell Gamma Knife type "B" was introduced. But the worldwide interest in GKS roused only after 1991, when results of GKS for VS were reported at the first international conference on VS held in Copenhagen.[26] GKS was spotlighted as an ideal treatment for patients with a high risk for surgery, old patients, and patients who refused to undergo an operation. Since then, many medical centers have reported good results of GKS for a VS.[28]

Over the years, starting from 2000, the Leksell Gamma Knife type "C" with a robotic automatic positioning system and an automatic helmet changer was introduced, which allowed for more convenient and rapid treatment, and this is still being used today. [28, 30]

In 2004, the Leksell Gamma Knife type "4C" was introduced. It features new Leksell Gamma Plan software, provides the ability to co-register non-stereotactic images, allows planning from various image sources such as computed tomography, magnetic resonance image, and positron emission tomography (PET), and sharing the remote images from the center where a gamma knife is not available.[29]

1.3.3.2   Histopathology of Vestibular Schwannoma

In a majority of literature, different markers in an SV have been revealed such as Luse bodies, fibrous collagen bundles, myelin sheath irregularities, and subepithelial nerve fiber losses and all were observed in the vestibule. But histopathological examinations of VS always detects two tissue types, Antoni "A" and Antoni "B". The Antoni A and Antoni B types are termed after the the Swedish pathologist Antoni.[20]

It is the distal part of the eighth nerve, with Schwann cells enclosing the axons, where an overproliferation of Schwann cells leads to the formation of VS. As a result, acoustic schwannoma cells can survive and proliferate in the absence of axon-derived growth factors, in a similar manner to mature, denervated Schwann cells. [32] The tumours have a remarkably diffuse yellow appearance and as described by Sandiford with it a firm

consistency. When compared to other benign intracranial tumours, VS have the least proliferative status. [30, 31]

Antoni type "A" tissue is type usually described as densely packed cells with small spindle-shaped densely staining nuclei and Antoni "B" refers to a looser cellular aggregation of vacuolated pleomorphic cells. [20] In any particular VS, one tissue type may predominate (e.g. see fig. 15).
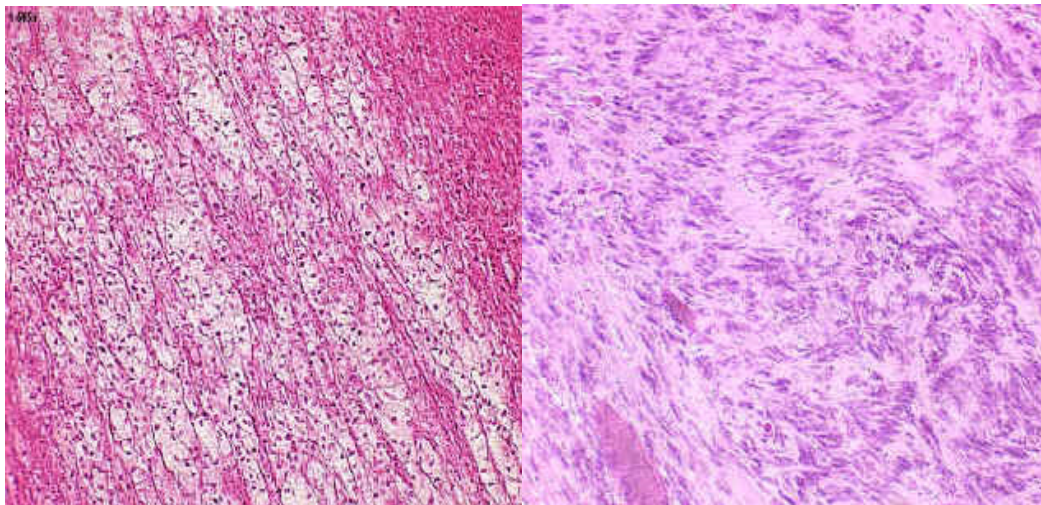
Figure 15. Atoni type A (On the left) is a VS with a thick concentration of cells and the Antoni type B (On the right) is schwannoma. The pattern is a loose texture of cells with a honeycomb appearance. The accumulation of lipids within the cells gives it its characteristic look.
Source: http://www.otopathology.com/acoustic.htm

The cells are dispersed randomly around blood vessels, microcysts, collections of xanthomatous cells and sites of previous hemorrhage. Lymphocytes attest to antecedent degenerative events within Antoni B tissue. The degree of nuclear pleomorphism varies considerably among acoustic neurinomas as well as between different areas within the same tumor. This pleomorphism often contributes to a random population of large and bizarre nuclei that taunt the pathologist with thoughts of anaplasia; however, fortunately, malignant transformation is of a rarity that permits individual case reports. Mitotic figures are most infrequent. Necrosis is commonly present but most often testifies to the meagerness of native blood vessels and their compression by tumor expansion within a restricted compartment.[20, 21]

Schwann cells possess a basement membrane that lies external to the plasma membrane. This feature distinguishes Schwann cells from fibroblasts. In addition, the presence of widely spaced collagen validates this identification. The histological features of a vestibular schwannoma are generally diagnostic, and the assessment of anaplasia or malignancy has already been resolved in favor of benignity by the natural history of this neoplasm.

Russell & Rubinstein (1989) described that mucinous and microcystic changes are especially prone to occur in Antoni B tissue. When confluent, the changes presumably result in the production of large cysts. [20]

In some literature the cystic elements in VS have been reported as a degenerative "A" tissue especially it refers to large and old tumours. But in other literatures this theory has been neglected and criticized along with stating that the distinctive types of Schwann cells could be cultured from "A" and "B" types of human schwannomas. [20]Tumors derived from type "B" tissue had a more pronounced liquificative action upon the culture media than those composed of "A" tissue.

VSs can reach sizes of up to several centimeters in diameter and thus, most of the cells comprising a tumor are not adjacent to the axon. As a result, vestibular schwannoma cells can survive and proliferate in the absence of axon-derived growth factors, and in a similar manner will mature into denervated Schwann cells.[32] A VS receives its arterial blood supply primarily from the branches of the basilar arteries, as well as from branches of the vertebral arteries.[29]

Of course, as the tumor grows, it follows the direction of least resistance, often medially into the CPA, at which stage it may be of considerable size. As a result, a tumor often consists of two parts, the stalk within the IAC and the main portion occupying the CPA.

Schwann cells are multivalent neuro-ectodermal cells, which are considered homologous to oligodendroglia of the central nervous system, both of which form and maintain the myelin sheath.[33] The immunohistochemical identification of nuclear antigen associated with cellular proliferation offered a very promising approach to the measurement of growth fraction in a VS.[20] The occurrence of both sporadic VSs and those associated with

Introduction

Neurofibromatosis NF appears to be associated with an aberration of a tumor suppressor gene on chromosome 22q12. The biological background and reason for the diverse growth patterns of a VS is, however, largely unknown and the natural history of the VS remains enigmatic.

Growth of any solid tumor with a volume of more than 2 or 3mm requires angiogenesis in demand of sufficient tissue supply of oxygen and nutrients through diffusion. Angiogenesis is defined as a process of new blood vessel formation from preexisting vasculature and is characterized by a cascade of processes, during which the vessel basal membrane and the surrounding tissue stroma is degraded by endothelial cell proliferation and migration. Established hypoxia induces paracrine secretion of proangiogenetic factors from the tumor cells, thus activating adjacent endothelial cells, which proliferate and migrate.[34]

The most potent proangiogenetic factor among the several is Vascular Endothelial Growth factor-A (VEGF). VEGF causes vasodilatation, increases vascular permeability, induces angiogenesis through endothelial cell proliferation and migration, and thus plays an important role in regulating angiogenesis. It promotes extravasation of plasma proteins from tumour vessels to form a new and provisory extravascular matrix favoring inward migration and the proliferation of endothelial cells.[34]

1.3.3.3 Clinical manifestations of Vestibular Schwannoma

The clinical presentations of a VS is highly variable and includes unilateral high frequency sensoneural hearing loss, tinnitus, disequilibrium, pressure in the ear, otalgia, and occasionally vertigo, which result from pressure exerted by the tumor upon the cochlear and vestibular portions of the eighth cranial nerve. But hearing loss is the most common finding, occurring in more than 95% of patients over the course of this disease.[35]

While hearing loss is common in a VS there are plenty of other causes of hearing loss. Approximately 10% of cases of unilateral progressive hearing loss are caused by a VS[33] and one out of 100 patients with otologic symptoms will actually have a VS.[1]

66

The sudden hearing loss occurs in about 25% of patients with a VS. However, because a VS is a rare condition, sudden hearing loss attributable to an acoustic tumor occurs in only 1-5 percent of patients with sudden hearing loss, as there are many more common causes.[38] Even a sudden hearing loss with complete recovery can be caused by a VS.[35] The mechanism of hearing loss is related to the direct compression of the cochlear nerve. Hearing loss occurs in VS patients as a symptom may be of several years' duration prior to diagnosis.[33, 36, 37]

The average time from onset of symptoms to clinical diagnosis has been shown to range from approximately 4 to 7.3 years.[33] But in some occasions, this time could last much longer.[36] Nevertheless, as many as 5 to 12 percent of patients with a newly diagnosed VS have normal hearing, in part as a result of the detection of smaller tumors by means of an MRI. In most cases, the onset of hearing loss is gradual, but in 15 percent of cases, it may be sudden if compression of the internal auditory artery occurs.[33]

The subjective tinnitus is another very common consequence of vestibular schwannoma or cochlear nerve dysfunction, it usually presents with concomitant hearing loss which is unilateral and confined to the affected ear. Tinnitus may even be the first symptom of a VS, without the person experiencing hearing loss. Like hearing loss, tinnitus is also present mostly in the high-frequency range. Most of those affected with tinnitus are usually severely impacted.

According to Kim *et al.*,[48] tinnitus is associated with 71% of a VS at presentation. Unlike hearing loss, tinnitus has a low impact on patient functioning; therefore, it rarely serves as the impetus to seek medical attention.[48] Nonetheless, unilateral tinnitus without obvious cause warrants investigation of the auditory brainstem response (ABR) or MR imaging.

Tinnitus in the absence of hearing loss is extremely rare.[10] The pathophysiology of tinnitus associated with a VS is thought to be similar to that of hearing loss, that is, neural or vascular compression. Unlike the asymmetric hearing loss, the tinnitus has low specificity in the diagnosis of a VS.

Approximately 50 percent of all patients with a VS have vestibular symptoms like vertigo and disequilibrium.[49]

Frequency of Symptoms at Presentation of VS.	
Symptoms	Percent
Sensorineural hearing loss	96
Unsteadiness	77
Tinnitus	71
Headache	29
Mastoid pain/otalgia	28
Facial numbness	7
Diplopia	7

Table 1. An analysis of 100 translabyrinthine operations.
Source: Kim Louis, Klopfenstein Jeffrey, Porter Randall, Syms Mark. Acoustic neuroma: Symptoms and diagnosis. Barrow quarterly. Vol 20 No.4.2004. 7-13.

Although, the usual origin of a VS is the inferior vestibular nerve[50] vertigo prior to surgery is not common, occurring in only about 20 percent of persons with a VS.[42] Vertigo may be related to the available compensation of vestibular functions or nerve resistance to the compression. However, it occurs in later stages of the diseases. According to Timothy et al, the hyperventilation induced nystagmus (HVIN) may be far more specific for a VS.[42,43,50] Evaluation of HVIN requires more sophisticated equipment than is available in most offices. It also requires the examiner to be familiar with this condition, and it is somewhat obscure.[50]

Furthermore, the above mentioned signs, in a VS course, may present any symptoms related to any intracranial mass such as sensory changes on the face or tongue, decreased corneal reflex, direction-changing nystagmus, ipsilateral numbness of the face, facial nerve motor dysfunction, a slurring of speech, ataxia, gait disturbance, an incoordination of one or both upper extremities, numbness or tingling of the malar eminence, and occasionally long tract signs.[48] Dysfunction of a facial nerve also can be counted as a symptom presenting in later stages of a VS and/or large VS. For example the facial nerve numbness occurs in 50 percent of cases with the tumor size > 2 cm.[42] Facial twitching, also known as facial synkinesis or hemifacial spasm, occurs in about 10 percent of the patients with a VS.[50] Decreased or absent corneal reflex is a consequence of trigeminal nerve dysfunction, although this deficit is rarely noticed by patients.[33]

Trigeminal nerve dysfunction is, however, responsible for the more common complaint of numbness or tingling of the malar eminence. Brainstem compressive symptoms include

ipsilateral upper or lower extremity dysfunction, and cerebellar symptoms include ataxia and gait disturbance.[33] Usually these symptoms occur in late stages of a VS course and are observed in large-sized tumors. Symptoms from hydrocephalus related to tumor obstruction of the fourth ventricle include headache, nausea, vomiting, diplopia, papilledema, and changes in mental status. The incidence of hydrocephalus in VS patients is low, occurring in 4% of cases according to a University of California-San Francisco series. Significant tumor growth is usually required to produce obstructive hydrocephalus.[49]

Symptoms, like raised intracranial pressure, headaches, nausea, vomiting, and dullness of mental faculties are gradual and persistent symptoms. The symptoms are also characteristic of the later stage of the disease. These symptoms appear gradually and are persistent. An onset of headaches as a symptom of a VS is typically a sequela of hydrocephalus. It occurs prior to surgery in roughly 40 percent of those with large tumors.[39] Therefore, the symptoms of a VS are highly dependent upon the size of the tumor. Patients with small tumors present with unilateral hearing loss and symptoms of vestibular nerve compression.[39] Patients with larger tumors present with symptoms of trigeminal nerve dysfunction, facial nerve dysfunction, and increased intracranial pressure. Finally, continued growth of the tumor are evident in symptoms related to brainstem and cerebellar compression.[33]

1.3.4 Explorations of hearing impairments in Vestibular Schwannoma

1.3.4.1 Conventional Audiometry

The hearing loss is a most frequent initial sign and most common symptom of VS. Over the years the Audiometry became a time-tested useful tool in diagnosis vestibular schwannoma as 95% of all VS patients at early or late stages of the disease would have a hearing loss. [48]

It usually develops over month to year and it associated with impairment of speech disproportionate to the pure tome. In 10% of cases, sudden hearing loss occurs and it attributable to the vascular interruption of the internal auditory artery. [49,50]

A complete audiologic test includes *pure-tone audiometry*, *acoustic reflex* testing with a measurement of *reflex decay* and speech reception audiometry. Figure 16.

Figure 16. Audiometry room and audiometry equippment "*Audiotest 340*"(*Our photo*)

The most frequent hearing impairment in patients with VS has been found to be asymmetrical high-frequency sensorineural hearing loss (SNHL). Although, it should be taken into account that no more than 1 out of 20 patients with large tumours have symmetry within 15 dB at 4000 hz, but only about 1 in 1000 patients with hearing asymmetry have VS.[42] (Figure 17.).
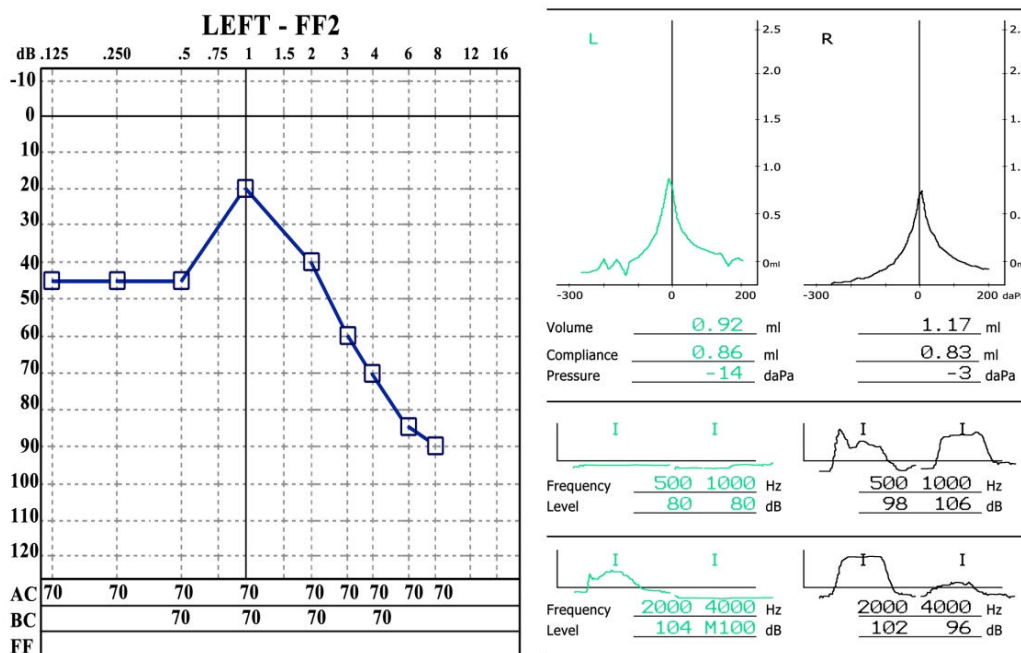
Figure 17. A simple audiogram and tympanogram of a patient with a left-sided vestibular schwannoma (Our photo)

In general, it has been estimated that 5 percent of persons with sensorineural hearing loss have a VS.[48] But in reality, perhaps this number is much higher with a prevalence of VS than is commonly accepted. Usually, the speech reception (SRT) is normal in many patients with small tumors. According to some trials, there are many cases of a VS being registered with symmetrical hearing but with a large VS on one side. Approximately 50% of all VS patients with small tumors normally have excellent speech discrimination, and one third of patients with large tumors still have near-normal (> 80%) speech discrimination.[42] Although a small percentage of patients with asymmetric hearing impairment end up having a VS, a missed early diagnosis of VS may jeopardize hearing and may have legal implications.[51,52]
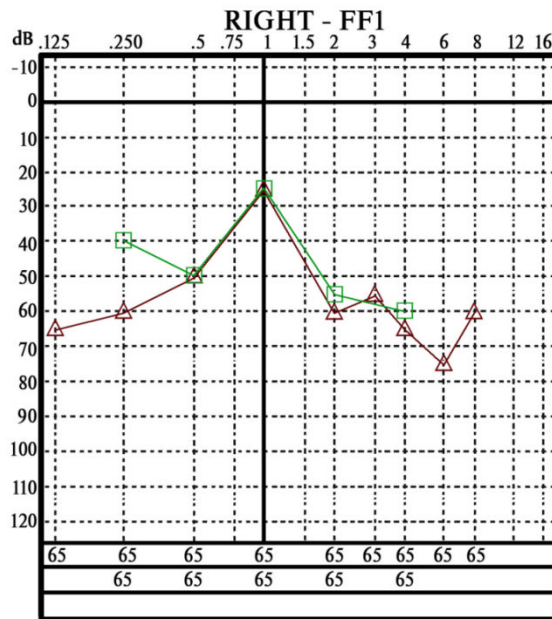
Figure 18. Ipsilateral SNHL in patient with right sided VS (Our photo)

The criteria have not yet been established for identifying the configuration of the pure tone audiogram constituting abnormal results that warrant further investigation using methods such as MRI. Several studies have classified the configurations of the pure tone audiogram among patients with a VS,[1] but few reports have described the prevalence of a VS associated with each of these configurations. The purpose of this study was to retrospectively determine the prevalence of a VS for each configuration of the pure tone audiogram in patients with asymmetric sensorineural hearing loss. By varying the sound intensity, thresholds can be obtained at octave intervals from 250 to 8000 Hz. This test requires the cooperation of the patient, who must indicate every time he is able to hear the pulsed tone, no matter how faint or short it may be. The incidence of normal audiograms in several cases has been reported elsewhere to be 3 to 6 percent.[49] Isolated low-frequency pure tone loss is a rare occurrence in patients with a VS. Audiometry seems to be a poor predictor of tumor size. In a study of 300 patients with vestibular schwannomas, Thomsen and Tos found no significant difference between the degree of pure tone loss and the size of tumors less than 4 cm. A strong correlation was found, however, between the extent of hearing loss and a tumor size greater than 4 cm.[48]

72

There were a few studies conducted to reveal VS related deafness. In some studies (Masaaki Suzuki at all, 2010) the prevalence of a VS in patients with idiopathic sudden deafness (ISD) was 2.8%[52].

Prior to the availability of ABR testing, several additional tests were used to distinguish between cochlear and retrocochlear lesions. These tests included tone decay testing, the suprathreshold adaptation test, the performance intensity function for phonetically balanced words test, the short-increment sensitivity index and the alternate binaural loudness balance test. For the most part, these audiologic tests have been replaced by ABR testing. In one series, an extensive audiologic test battery without ABR testing detected a mixed retrocochlear loss in 69 percent of the cases and pure retrocochlear findings in only 27 percent of patients with vestibular schwannomas. [50,37]

1.3.4.2   Word recognition test (WRT).

WRT (speech discrimination tests) are also useful in the diagnosis of a VS, which assesses the patient's ability to understand speech when presented at a loudness level that is well above the patient's threshold. This test is administered by using single syllable words. The result is presented as a percentage score.[54]

The WRT can be helpful in predicting the usefulness of a hearing aid. An increase in the word recognition score (WRS) with amplification, suggests that a hearing aid might be useful. WRT has some limitations because many patients don't communicate with monosyllabic speech, so a good score on the WRS may not necessarily correlate with good, functional performance.[53] Scores are also weighted towards the perception of high frequency consonants. Poor performance overestimates everyday communication impairment for patients with high frequency hearing loss. The WRT also underestimates hearing problems in noise.[45]

1.3.4.3   Auditory brainstem response (ABR) audiometry

The ABR is the most useful audiometric test in the diagnosis of a VS, and the use of Brain Stem Auditory Evoked Potential (BSAEP) in the VS diagnosis has been established for years. First described by Jewett and Williston in 1971, ABR audiometry is the most common application of auditory evoked responses.[100, 105]

As technology continues to evolve, the ABR will likely provide more qualitative and quantitative information regarding the function of the auditory nerve and brainstem pathways involved in hearing (e.g. see fig. 19).

In the 1980s and 1990s, the ABR became popular as a cost-effective initial screen for patients considered at risk of an VS, with it's performance being judged in light of the size of tumors then being detected radiologically (typically over 1 cm). However, with the advent of gadolinium-enhanced MR imaging in the late 1980s and the subsequent development of noncontrast MR imaging, these tests have allowed much smaller tumors to be detected, leading to improved surgical outcomes and hearing preservation.[129]
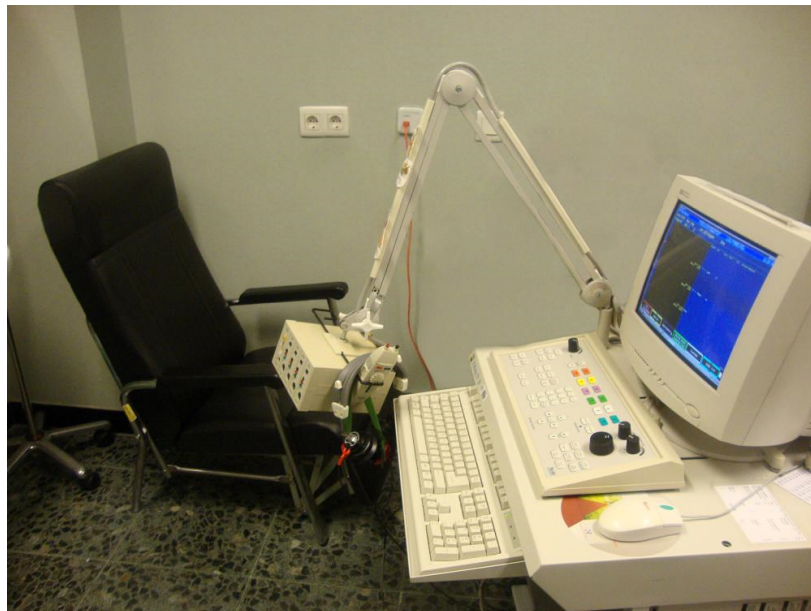
Figure 19. ABR audiometry with the software currently used in CHUS (Our photo)

ABR audiometry refers to an evoked potential generated by a brief click or tone pip transmitted from an acoustic transducer in the form of an insert earphone or headphone.

The elicited waveform response is measured by surface electrodes typically placed at the vertex of the scalp and ear lobes. The microvoltage of the signal is averaged and charted against the time (millisecond), much like an EEG. The waveform peaks are labeled I-VII. These waveforms normally occur within a 10-millisecond time period after a click stimulus presented at high intensities (70-90 dB) of the normal hearing level (e.g. see fig. 20).
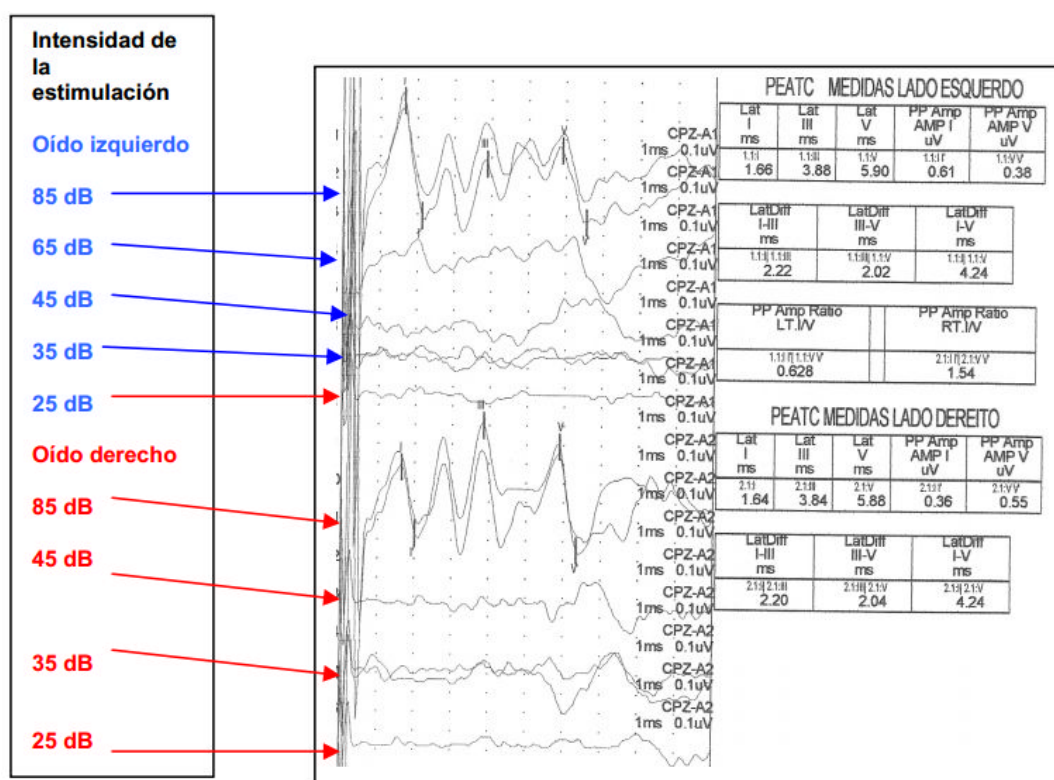
Figure 20. Normal adult auditory brainstem response audiometry waveform response I-V absolute latencies and interpeak intervals (I-III, III-V, I-V) are within normal limits bilaterally (Our photo)

Although the ABR provides information regarding auditory function and hearing sensitivity, it is not a substitute for a formal hearing evaluation, and results should be used in conjunction with behavioral audiometry whenever possible. [106,110, 112.]

ABR audiometry typically uses a click stimulus that generates a response from the basilar region of the cochlea. The signal travels along the auditory pathway from the cochlear nuclear complex proximally to the inferior colliculus. [100, 106, 108]

ABR waves I and II correspond to true action potentials. Later waves may reflect postsynaptic activity in major brainstem auditory centers that concomitantly contribute to waveform peaks and troughs. The positive peaks of the waveforms reflect combined

afferent (and likely efferent) activity from axonal pathways in the auditory brain stem. [100, 102]

Wave I: The ABR wave I response is the far-field representation of the compound auditory nerve action potential in the distal portion of cranial nerve (CN) VIII. The response is believed to originate from afferent activity of the CN VIII fibers (first-order neurons) as they leave the cochlea and enter the internal auditory canal. [105, 100] Wave II: The ABR wave II is generated by the proximal VIII nerve as it enters the brain stem. [100] Wave III: The ABR wave III arises from second-order neuron activity (beyond CN VIII) in or near the cochlear nucleus. Literature suggests wave III is generated in the caudal portion of the auditory pons. The cochlear nucleus contains approximately 100,000 neurons, most of which are innervated by eighth nerve fibers. [102, 103] Wave IV: The ABR wave IV, which often shares the same peak with wave V, is thought to arise from pontine third-order neurons mostly located in the superior olivary complex, but additional contributions may come from the cochlear nucleus and nucleus of lateral lemniscus. [109, 110]

Wave V: Generation of wave V likely reflects activity of multiple anatomic auditory structures. The ABR wave V is the component analyzed most often in clinical applications of the ABR. Although some debate exists regarding the precise generation of wave V, it is believed to originate from the vicinity of the inferior colliculus. [100] The second-order neuron activity may additionally contribute in some way to wave V. The inferior colliculus is a complex structure, with more than 99% of the axons from lower auditory brainstem regions going through the lateral lemniscus to the inferior colliculus.

Wave VI and VII: Thalamic (medial geniculate body) origin is suggested for generation of waves VI and VII, but the actual site of generation is uncertain.

ABR audiometry is considered an effective screening tool in the evaluation of suspected retrocochlear pathology such as vestibular schwannoma (Figure 21). [100, 101, 105] However, an abnormal ABR finding suggestive of retrocochlear pathology indicates the need for MRI of the cerebellopontine angle. [104, 105]
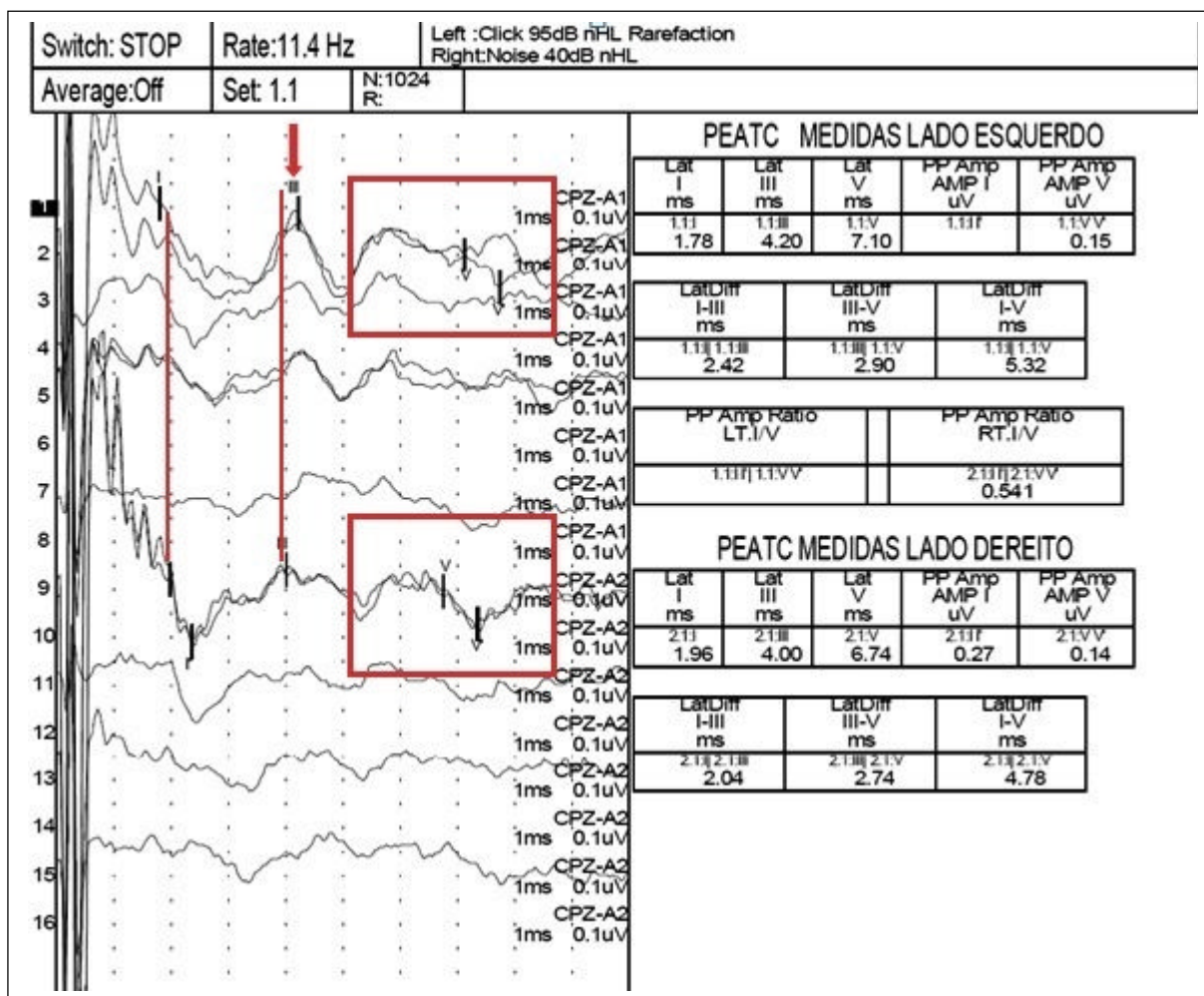
Figure 21. Abnormal ABR (Our photo)

In addition to retrocochlear pathologies, many factors may influence ABR results, including the degree of sensorineural hearing loss, asymmetry of hearing loss, test parameters, and other patient factors. These influences must be factored in when performing and analyzing an ABR result. [100, 102,110.]

In general, ABR exhibits a sensitivity of over 90% and a specificity of approximately 70-90%. [106, 107]

Sensitivity for small tumours is not as high. For this reason, a symptomatic patient with a normal ABR result should receive a follow-up audiogram in 6 months to monitor for any changes in hearing sensitivity or tinnitus. The ABR may be repeated if indicated. Alternatively, MRI with gadolinium enhancement, which has become the new criterion standard, can be used to identify very small (3-mm) VS.

Introduction

The ABR sensitivity in the diagnosis of CN VIII tumours by size according to several studies is as follows:

In a 1994 study by Dornhoffer, Helms, and Hoehmann, the sensitivity was 93% for tumours smaller than 1 cm. [100]

In 1997, Zappia, O'Connor, Wiet, and Dinces reported a sensitivity of 89% for small tumours smaller than 1 cm, 98% for medium tumours 1.1-2 cm, and 100% for tumours larger than 2 cm. The overall sensitivity was 95%.[102] In a 1995 study, Chandrasekhar, Brackmann, and Devgan reported a sensitivity of 83.1% for tumours smaller than 1 cm and a sensitivity of 100% for tumours larger than 3 cm. Overall sensitivity was 92%.[103] In 1995, Gordon and Cohen reported the following sensitivities: 69% for tumours smaller than 9 mm, 89% for tumours 1-1.5 cm, 86% for tumours 1.6-2 cm, and 100% for tumours larger than 2 cm.[103, 104]

In a 2001 report by Schmidt, Sataloff, Newman, Spiegel, and Myers, the sensitivity was 58% for tumours smaller than 1 cm, 94% for tumours 1.1-1.5 cm, and 100% for tumours larger than 1.5 cm. The overall sensitivity was 90%.[105, 106] In a large prospective study that compared ABR with contrast-enhanced MRI (the criterion standard) in 312 patients with asymmetric sensorineural hearing loss, Cueva found that ABR yielded a sensitivity and specificity of 71% and 74%, respectively, in revealing the cause of lesions for asymmetric sense and oral hearing loss (including, but not limited to, vestibular schwannoma). The ABR-positive predictive value was only 23%, whereas its negative predictive value was 96%. Seven of 31 positive cases had other lesions that ABR could not identify as a cause of the hearing loss. [106]

Although traditional ABR measures decrease in sensitivity as a factor of tumour size, recent studies have shown that by using a new stacked derived-band ABR that measures amplitude, very small tumours may be detected more accurately. [100, 108]

This new technique, combined with traditional ABR audiometry, may soon make possible the detection of very small tumours with accuracy approaching 100% using ABR audiometry.

Other applications of ABR continue to evolve as some reviewed literatures suggests that although the overall ABR wave latencies are within normal limits in patients with tinnitus,

those patients have longer latencies than control patients without tinnitus.[107] It almost means that ABR may be useful in monitoring and understanding tinnitus.

They are variety of scientific viewpoints and opinions regarding diagnostic value of ABR. The results of individual trials are also controversial.

Several investigators have reported the sensitivity of ABRs testing as 93% or greater. [119, 120, 121] However some other authors stated that in their trial 85% of VS patients had abnormal ABRs. [122]

Of course the tumour size and nerve of origin is important factors affecting the ABR sensitivity. Wilson DF at all, states that in their group of patients one of 25 patients with extracanalicular tumours had normal ABRs for a false-negative rate of 4%; however, 5 of 15 patients with intracanalicular tumours had normal ABRs for a false-negative rate of 33%. [118] Figure 22.
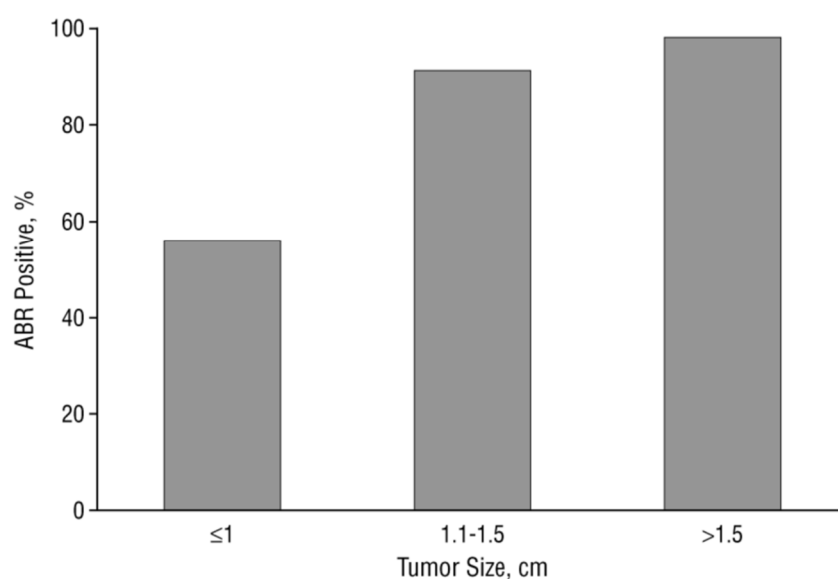
Figure 22. Sensitivity of ABR testing by tumour size

Source: Wilson DF. Talbot JM, Mills L. The sensitivity of auditory brainstem response testing in small VSs. Laryngoscope. 1992 Sep; 102(9):961-964

The ABR was less sensitive in detecting intracanalicular VS than in detecting extracanalicular VS. [118]

1.3.4.4 Otoacoustic emissions (OAE) testing

An otoacoustic emission is a low-level sound emitted by the cochlea either spontaneously or evoked by an auditory stimulus. Specifically, OAEs provide information related to the function of the outer hair cells. [62, 66]

Over the past 20 years, their use in routine audiological assessments has increased significantly. Today, OAEs are used commonly in the audiological assessment of difficult to test patients, such as persons who cannot or will not volunteer reliable behavioral responses.

Otoacoustic emissions were first reported by Kemp in 1978. The primary purpose of OAE tests is to determine cochlear status, specifically hair cell function. [57, 58]

Present OAEs in an ear indicate many things about the auditory system. First, a present OAE tells us that the conductive mechanism of the ear is functioning properly. This includes proper forward and reverse transmission, no blockage of the external auditory canal, normal tympanic membrane movement, and a functioning impedance matching system. Present OAEs also indicate that outer hair cells (OHC) function is normal, which, in most cases, correlates with normal hearing sensitivity. OAE testing does have some limitations. OAE testing does not evaluate the inner hair cells, CN VIII, ascending central auditory pathway, or auditory processing function. [67,80]

Understanding the cochlear anatomy and physiology must exist to understand OAEs. Generally speaking, OAEs are waves generated by movement of the basilar membrane and are measured in the external auditory canal.[80] However, with an in-depth understanding of cochlear anatomy and physiology, OAEs can be directly related to OHC function. There are many events leading up to this. First, there is a stimulus delivered to the ear. This stimulus invokes movement of the basilar membrane, which in turn causes the OHCs to move, or be deflected. [80, 83]

When the OHCs move, their stereocilia bend in one direction or the other. Ions rush in and rush out, changing the membrane potential within the hair cell. The changes in voltage across the plasma membrane lead to OHC length changes, which are called electromotility. The electromotility of the OHCs has a feedback effect on the basilar membrane, causing it

to vibrate. Therefore, the electromotility of the OHCs is thought to be the mechanism which underlies OAEs. Furthermore, research studies over the past 25 years have demonstrated that when the OHC electromotility is blocked, OAEs are absent, which solidifies the relationship between OHC motility and OAEs. [80, 83]

This information can be used to screen hearing, partially estimate hearing sensitivity within a limited range, differentiate between the sensory and neural components of sensorineural hearing loss, and test for functional hearing loss. [62,63] The information can be obtained from patients who are sleeping or even comatose because no behavioral response is required. [61-63]

The normal cochlea does not just receive sound and produces low-intensity OAEs. These emissions are produced most probably, by the cochlear outer hair cells as they expand and contract. [61] The presence of cochlear an emission was hypothesized in the 1940s on the basis of mathematical models of cochlear nonlinearity. [63] However, OAEs could not be measured until the late 1970s, when technology created the extremely sensitive low-noise microphones needed to record these responses (e.g. see figure 23).

Figure 23. TEOAE software "*ILO 292*"; Contents: Ear probe, Small speaker, Microphon and Response Analyzer connected to computer (Our photo)

Introduction

The 4 types of otoacoustic emissions are as follows:

- Spontaneous otoacoustic emissions (SOAEs) - Sounds emitted without an acoustic stimulus (ie, spontaneously)
- Transient otoacoustic emissions (TOAEs) or transient evoked otoacoustic emissions (TEOAEs) - Sounds emitted in response to an acoustic stimuli of very short duration; usually clicks but can be tone-bursts
- Distortion product otoacoustic emissions (DPOAEs) - Sounds emitted in response to 2 simultaneous tones of different frequencies
- Sustained-frequency otoacoustic emissions (SFOAEs) - Sounds emitted in response to a continuous tone. [62, 67]

The PTA measures throughout the outer ear, middle ear, cochlea, cranial nerve (CN) VIII, and central auditory system. However, OAEs measure only the peripheral auditory system, which includes the outer ear, middle ear, and cochlea. The response only emanates from the cochlea, but the outer and middle ear must be able to transmit the emitted sound back to the recording microphone. [66, 68]

OAE testing often is used as a screening tool to determine the presence or absence of cochlear function, although analysis can be performed for individual cochlear frequency regions. [61] OAEs cannot be used to fully describe an individual's auditory thresholds, but they can help question or validate other threshold measures or they can provide information about the site of the lesion. [65,66]

Using current technology, most researchers and clinicians find a correlation between frequency-specific analysis of TOAEs/DPOAEs and cochlear hearing loss. However, at this juncture, the correlation cannot fully describe auditory threshold. Naturally, a correlation would not be expected for noncochlear hearing loss. [65, 67, 68]

Multiple responses are averaged. All OAEs are analyzed relative to the noise floor; therefore, reduction of physiologic and acoustic ambient noise is critical for good recordings. Because no behavioral response is required, OAEs can be obtained even from patients who are comatose. For a quiet and cooperative patient, recordings usually require less a few minutes per ear. [78, 80] For uncooperative or noisy patient, recordings may take significantly longer or may be impossible to obtain on a given visit.

In spontaneous otoacoustic emissions (SOAE) This nonevoked response is usually measured in narrow bands (< 30 Hz bandwidth) of frequencies recorded in the external ear canal. No stimulus is required. Obtain multiple recordings to ensure replicability and to distinguish the response from the noise floor. SOAE recordings usually span the 500-Hz to 7000-Hz frequency range. [82,84]

In transient otoacoustic emissions cicks are the most commonly used stimuli, although tone-burst stimuli may be used. Most commonly, 80- to 85-dB sound pressure level (SPL) stimuli are used clinically. The stimulation rate is less than 60 stimuli per second. TOAEs are generally recorded in the time domain over approximately 20 milliseconds. Alternating responses are stored in alternating computer memory banks, A and B. Data that correlate between the 2 memory banks are considered a response. [80] Data that do not correlate are considered noise. When present, TOAEs generally occur at frequencies of 500-4000 Hz. Data in the time domain then are converted to the frequency domain, usually in octave band analysis.[82]

In Distortion product otoacoustic emissions the stimuli consist of 2 pure tones at 2 frequencies (ie, f1, f2 [f2>f1]) and 2 intensity levels (ie, L1, L2). The relationship between L1-L2 and f1-f2 dictates the frequency response. An f1/f2 ratio yields the greatest DPOAEs at 1.2 for low and high frequencies and at 1.3 for medium frequencies. To yield an optimal response, set intensities so that L1 equals or exceeds L2. Lowering the absolute intensity of the stimulus renders the DPOAEs more sensitive to abnormality. A setting of 65/55 dB SPL L1/L2 is frequently used [88, 89] (e.g. figure 24).
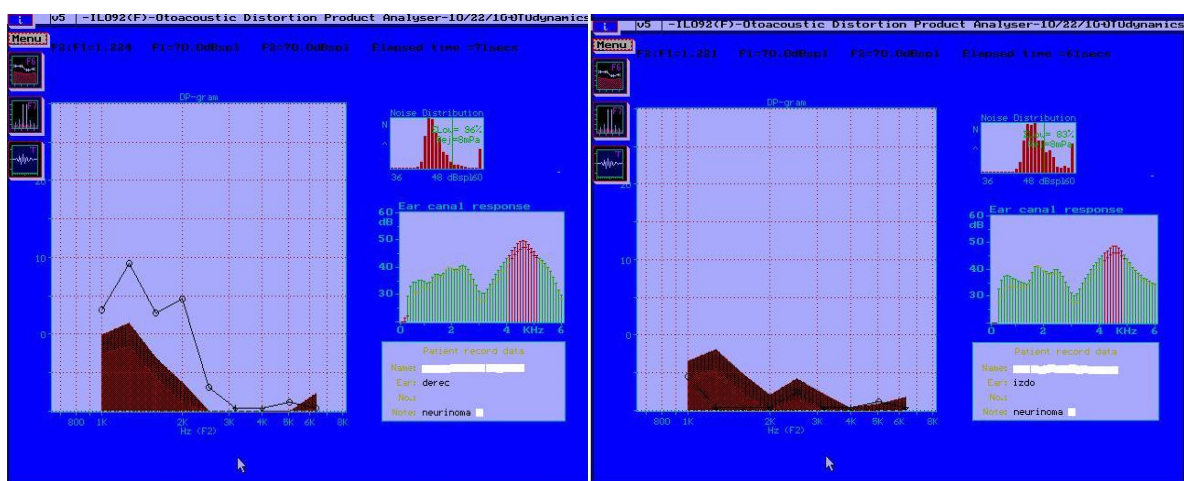
Figure 24. An example of DPOAEs recorded from 80 year old female patient with left sided VS (Our photo)

Introduction

Responses are usually most robust and recorded at the emitted frequency of 2 f1–f2; however, they generally are charted according to f2 because that region approximates the cochlear frequency region generating the response. [80, 90]

But anyway, most investigators believe that otoacoustic emissions whether they be spontaneous, product distortion, or evoked are present in healthy cochleae. [96, 97]

Studies have shown that TEOAEs are lost on the lesioned side in a variable number of patients with VS, probably because of cochlear vascular damage [90, 95] According to Singh et al [94] the presence of TEOAEs on the lesioned side in 63 patients with VS who were surgically treated with the aim of saving hearing function was a favorable prognostic factor for hearing preservation, probably as a result of better cochlear vascularization.

An Otoacoustic emission testing is regarded as the only test capable of demonstrating the function of the organ of Corti, especially in the outer hair cells, in an objective, noninvasive, and reproducible way. There is also a consensus that different noxious factors that can affect the cochlea such as ototoxics and acoustic disorders diminish or eliminate otoacoustic emissions. [94, 96]

It is accepted that otoacoustic emissions are modified by stimulation of the efferent auditory system, as contralateral acoustic stimuli reduce distortion product and evoked emissions.[98] For these reasons, the use of otoacoustic emissions testing is widely acknowledged as useful for making auditory assessments of newborns and patients who have been exposed to ototoxics or environmental noise, and for controlling cortipathy that is, damage to or a lesion in the organ of Corti.[98]

In cases of a VS and other central auditory system disorders, the OAEs presents but ABR altered. Interestingly, a number of reviewed literatures have indicated that OAEs (TEOAES or DPOAEs) can be both affected and unaffected by the presence of a VS.[54,57]

An explanation for such data can be derived from information of how the growth of the tumor affects the vascular supply of the cochlea or how the growth of the tumors induces mechanical pressure alterations on the vascular supply and the cochlea itself. The OAE-based measures can provide information on the sensory component of any hearing disorder; thus, they can provide precise indexes of evaluating sensorineural hearing impairment cases which can play an important role in the detection of a VS.[57]

1.4   Explorations of balance dysfunctions in Vestibular Schwannoma

1.4.1   Posturography.

Posturography is a general term that covers all the techniques used to quantify postural control in an upright stance, in either static or dynamic conditions. Among those techniques is computerized dynamic posturography (CDP), also called test of balance (TOB). [200-201]

CDP is a non-invasive specialized clinical assessment technique used to quantify the central nervous system adaptive mechanisms involved in the control of posture and balance, both in normal and abnormal conditions (e.g. see fig. 25)

Figure 25. Assessment of VS patient with Computerized Dynamic Posturography equipment from "Smart Balance Master Neurocom[®]" (Our photo)

Due to the complex interactions among the sensory, motor, and central processes involved in posture and balance, CDP requires different protocols to differentiate among the many defects and impairments, which may affect a subject's postural control system. CDP challenges that system by using several different combinations of visual and support

surface stimuli and parameters. It has been proven effective in assessing vestibular as well as some neuromuscular disorders affecting balance. [202]

Computerized Dynamic Posturography is an integral component in the diagnostic workup of imbalance or dizziness when used to identify the underlying sensory (vestibular, visual, somatosensory) and motor control impairments. CDP is not considered to be a site-of-lesion test nor is it pathonomonic for vestibular disease.[24]

Balance and dizziness disorders often have multiple causes that cannot be isolated to a single localized pathology. Clinical evidence indicates that an impairment reduction strategy is the most effective way to reduce the symptoms associated with imbalance and dizziness with multiple causes.[23, 27]

Whereas traditional site-of-lesion tests are designed to confirm the presence and anatomical location of pathology, CDP, in contrast, documents the physiological impairments that are the functional manifestations of pathology. Because the balance system is highly adaptive, patients with similar pathology can present with different impairments, depending on the stage (progression) of the disease or disorder. [123]

In many patients with chronic balance disorders, no anatomical pathology can be identified that accounts for the patient's symptoms and impairments. Because of the "disconnect" between pathology and impairments, CDP and traditional site-of-lesion tests provide complementary rather than redundant information in the diagnostic workup of the dizzy and/or unsteady patient.[128]

The Sensory Organization Test (SOT) objectively identifies problems with postural control by assessing the patient's ability to make effective use of (or suppress inappropriate) visual, vestibular, and proprioceptive information. [200] During the SOT, useful information delivered to the patient's eyes, feet and joints is effectively eliminated through calibrated "sway referencing" of the support surface and/or visual surround. The support surface and/or visual surround tilt to directly follow the patient's anteroposterior body sway, eliminating orientation information. By controlling the usefulness of the sensory (visual and proprioceptive) information through sway referencing and/or eyes open/closed conditions, the SOT protocol systematically eliminates useful visual and/or support surface information and creates sensory conflict situations. These conditions isolate vestibular balance control, as well as stress the adaptive responses of the central nervous system. In

short, patients may display either an inability to make effective use of individual sensory systems, or inappropriate adaptive responses, resulting in the use of inaccurate sense. [202]

The CDP has become an increasingly popular modality for evaluating balance function. Most clinicians and researchers use the equipment, protocol, and normative values developed by NeuroCom International of Clackamas, Ore., as the standard for testing and comparison. [200]

A central aspect of the CDP protocol is SOT and it helps the physician evaluate how visual, somatosensory, and vestibular inputs affect a patient's ability to maintain functional balance. This objective test measures the extent of a patient's sway while standing on a force platform during six conditions (e.g. see fig. 26-27).

SOT 1   SOT 2   SOT 3

SOT 4   SOT 5   SOT 6
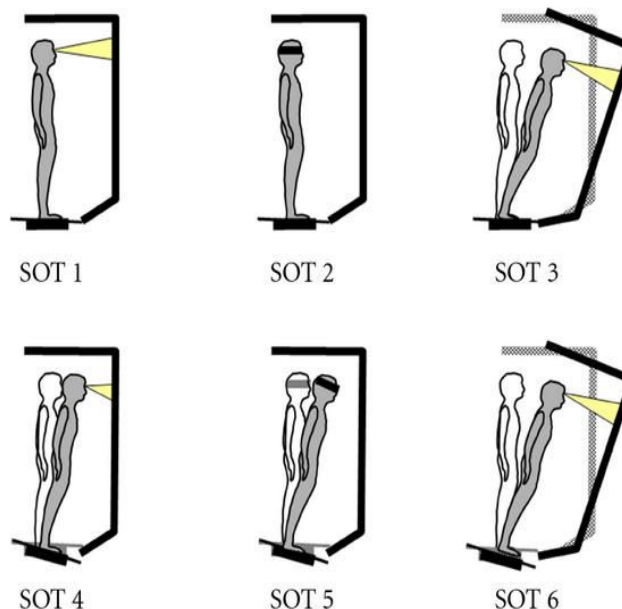
Figure 26. Test conditions SOT 1 to 6 (Our photo)

Condition 1 is a simulation of a common, normal state. With eyes open, and the platform and visua*l* surround are stable; In **condition 2**, the platform and visual surround are both still fixed, but the patient's eyes are shut; In **condition 3**, the eyes are open and the platform is fixed, but the visual surround tilts in the direction of the patient's sway, thereby delivering inaccurate visual information about orientation in space; **Conditions 4, 5,** and **6** are the same as conditions 1, 2, and 3, respectively, except that the platform moves. The sway-referenced platform tilts with the patient's sway, thereby altering somatosensory

input. As a result, conditions 5 and 6 effectively force a patient to rely on vestibular inputs alone to maintain balance.
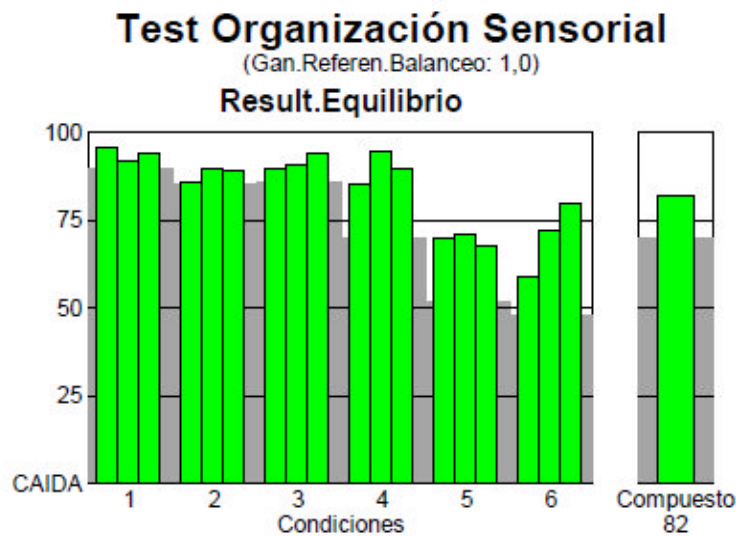
Figure 27. Normal SOT in a patient with left sided Antoni type "B" Vestibular Schwannoma (Our photo)

Some authors indicate that in their studies 83% of all patients with VS before the surgical removal of tumour shows abnormalities during CDP conditions 5 and 6. But postoperative follow-up of this patients shows that three month after the operation only 21% of patients shows abnormal CDP. [123]

In case of VS patients undergoing to surgical removal of tumour the CPD performs usually only once for diagnostic purposes. However, after the surgical removal of VS the patients periodically follows up with CDP, where CDP in the one hand rehabilitates the patients but in the other hand patients will physically adapts to the movements of CDP platform, thus it doesn't mean that the vestibular function of patients getting to be improved. These patients most probable will have problems with daily gait. [200]

CDP Information is critical to planning treatment focused on impairment reduction, and is therefore indicated whenever an impairment reduction strategy is appropriate. Based on a retrospective study of the treatment planning process in more than 4000 chronic dizzy patients, the following guidelines were developed for the use of CDP in treatment planning.[126,200]

1.4.2 Craniocorpography

The Craneocorpography (CCG) is an objective and quantitative testing method of vestibulospinal function and balance.

The GCC consists of photo-optical recording of movements of the head and body during standing and stepping tests. [198] The stepping test was first described by Unterberger and colleagues in 1963. In 1978, Claussen described the photographic technique for recording results of the stepping test, which he called the craniocorpography test [216] (e.g.see fig 28).

The CCG uses light markers placed on the forehead, the occiput, and both shoulders of a patient. Such lights are reflected through a mirror system on the ceiling into a recording video camera and on to a computer that receives, analyzes, and prints the signal.[198, 216] While testing process the patient is blindfolded by means of a sleeping mask, cutting off visual stimuli, and the patient loses contact with the ground while stepping; hence the proprioceptive stimuli are also gradual [217, 218] (e.g. see fig 28-29).

Figure 28. In craniocorpography, the patient is blindfolded by means of a sleeping mask, cutting off visual stimuli, and the patient loses contact with the ground while stepping; hence the proprioceptive stimuli are also gradual (Our photo)

Introduction

The patient will maintain balance only through the stimuli received from both vestibular systems. Any deviation, rotation, or sway beyond the normal range will indicate the involvement of the peripheral or central systems. [198]

The GCC can record easily, quickly and inexpensively vestibulospinal reactions, both qualitatively and quantitatively analyze, archive and compare them subsequently can be obtained at the same or other patients.

The Unterberger-Fukuda test requires a patient to step at least 80 steps on the spot. The test evaluates longitudinal displacement from the starting point to the end point; lateral sway, which is the width of the head movement curves; angular deviation, which is the angle between the directions at the starting point and at the end point; and body spin, which is the rotation around the body axis. [217, 218]

For the evaluation of the stepping test, mainly uses two parameters: lateral sway, which is the lateral displacement of the shoulders and head between steps and is measured in centimeters, and angular deviation, which is the angle between the initial and final position of the patient and is measured in degrees. Lateral sway is assumed to be related to central disorders and angular deviation to peripheral lesions. [198, 217-219]

With these two parameters, we define, basically, four types of CCG assumed to be related to a specific site of lesion. This provides a very important clue for the topographical diagnosis, as follows:
- **type I**, normal;
- **type II**, peripheral lesion or an enhanced angular deviation with normal lateral sway;
- **type III**, central lesion or an enhanced lateral sway and normal angular deviation;
- **type IV**, combined, central plus peripheral lesion or an enhancement of the lateral deviation and the lateral sway [218-219] Figure 30.

Claussen et al. [198, 217, 218] reported that the parameters obtained through the CCG and the TOB (test of balance) are significant for the final diagnosis. CCG and the TOB are useful techniques for assessment of vestibular function in cases of vestibular disorders caused by VS. CCG and the TOB are significant tests for scrutinizing peripheral, central, and combined lesions in cases of vertigo. Vestibular functions can be tested simultaneously on

both sides.These tests can be easily performed in the outpatient department and are not time-consuming or expensive even for the long term follow up of VS patients.
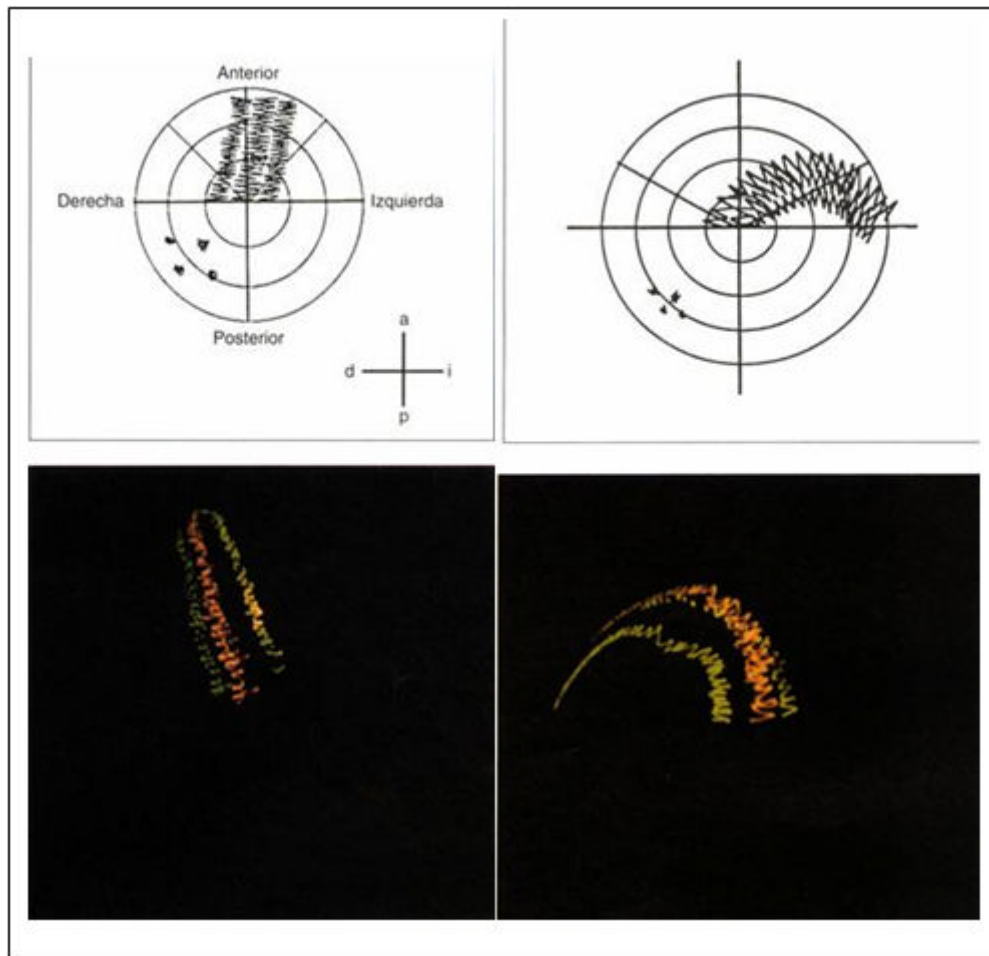
Figure 29. <u>On the left:</u> CCG type I normal, with shematic interpretation of normal CCG. Bottom - an example of CCG in healthy subject. <u>On the right:</u> CCG typy II corresponding unilateral vestibular weakness (Our photo)

1.4.3 Caloric testing

Caloric testing assesses and records the function of each labyrinth separately, making it possible to define which side is compromised. [203, 204]

The caloric response is connected with the central nervous system, which is important in differentiating between central and peripheral vestibular diseases. It is a part of Electro or Videonystagmography (ENG/VNG) reflecting an attempt to discover the degree to which the vestibular system is responsive and also how symmetric the responses are, between left

and right. It is a test of the lateral semicircular canals alone it does not assess vertical canal function or otolithic function. [205]

VNG testing is used to determine if a vestibular disease may be causing a balance or dizziness problem, and is one of the only tests available today that can decipher between a unilateral and bilateral vestibular loss. VNG testing is a series of tests designed to document a patient's ability to follow visual objects with their eyes and how well the eyes respond to information from the vestibular system.

It is based on the principle of generating thermal variation within the external auditory canal; by changing the temperature of the middle ear, this thermal variation changes the density of endolymph within the lateral semicircular canal, producing convection currents that stimulate the sensorial cells located in the ampullary crest. [203]

The patient is placed in dorsal decubitus at 30º relative to the horizontal plane. This position places the lateral canal vertically, as a liquid column, and places the ampullary crest superiorly.[203-204, 206] By having the patient more comfortable and relaxed, consistent and accurate test results are more easily achieved (e.g. see fig 30).

Figure 30. Caloric test - patient is lying on the table while water is being squirted into her ear, and drains into a basin. The goggles on the patient are being used to record her eye movements (Our photo)

The bithermal caloric test is performed using 50 ml of water at 44°C and 30°C to irrigate the tympanic membrane over a period of 30 seconds. The irrigation is done through a 3 mm diameter catheter introduced into the external auditory canal with its tip lying just a millimeter away from the tympanic membrane. The caloric test results are evaluated using culmination frequency as the parameter and are plotted on the butterfly chart (e.g. see fig 31). [207]
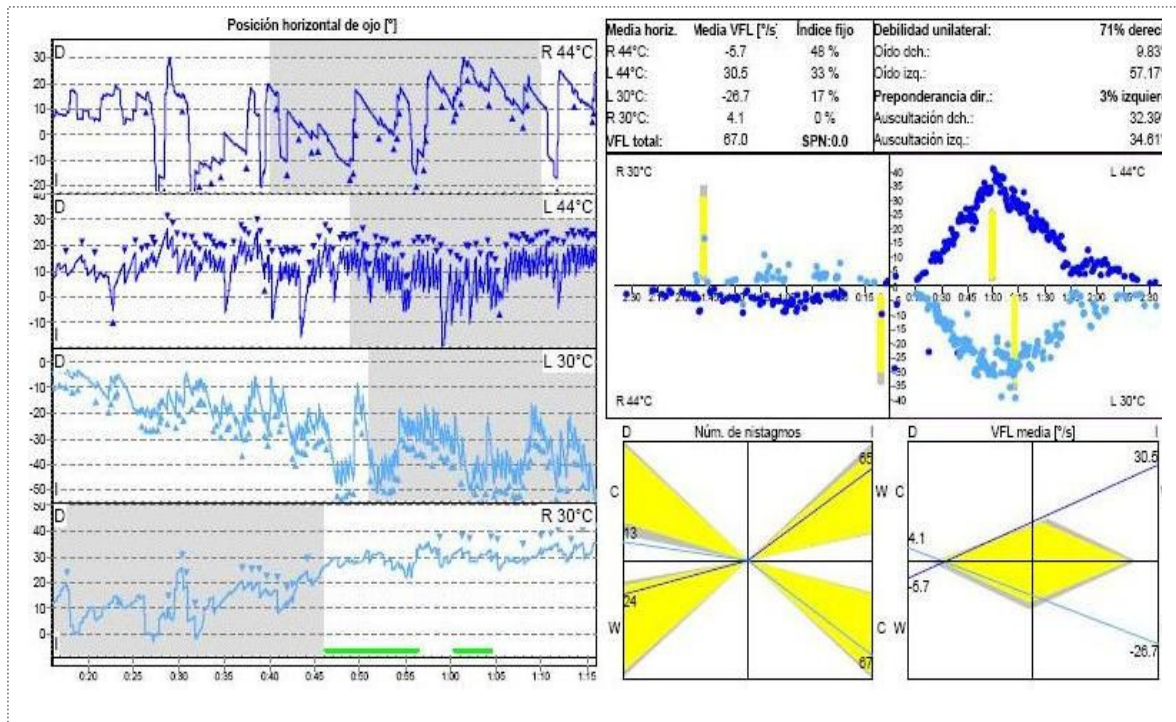
Figure 31. The Results of Standard VNG testing shows 71% right/unilateral weakness in a patient with right sided VS (Our photo)

From the peak slow-phase velocity of nystagmus following numbers are obtained - cold right, cold left, warm right, and warm left. Spontaneous nystagmus (SN) should be subtracted from these, and then the absolute value taken. From these responses, Left cool (LC), Left warm (LW), right cool (RC), right warm (RW) three additional numbers are derived:

Total response - absolute sum of all appropriately directed responses which is usually should be 20 or greater. TR= (RC+LC+RW+LW). The goal is to detect bilateral weakness. When responses are corrected for spontaneous nystagmus, the procedure here is to sum the absolute value of responses that go in the right direction, left cold and right warm should be right-beating, right cold and left warm should be left beating.

Introduction

Directional preponderance (right beating - left-beating/total) should be 35% or less. There is little if any clinical value in DP.

Unilateral paresis or RVR, RVR = (RC+RW-LC+LW)/TR. This is called "Jongkee's formula". It should be 25% or less. If all responses are appropriately directed (see commentary on TR above), one can simply take the sum of the absolute values of responses due to the right ear, subtract the sum of the absolute responses due to the left, and normalize to the sum of the absolute values of all responses.

An upward change in the middle ear temperature above the body temperature causes the endolymph to move upwards, generating an endolymphatic current within the canal towards the ampulla. If the stimulus temperature is lower than the bodily temperature, there is the opposite movement, which generates an ampullary current towards the canal, away from the ampulla.

The action of these convection currents on the ampullary crest alters the action potential of this sensory receptor, stimulating or inhibiting these currents. Stimulation initiates the VOR, a simple reflex arc from the vestibular nucleus to the oculomotor nuclei, which generates the vestibular nystagmus. The nystagmographic response is evaluated and compared with a normal standard. Caloric testing does not assess the function of the sacculus or the utricle of the vertical canals. [203-204]

In the literature there are almost no work has been done regarding the results of VNG in a group of patients with VS, except ENG.

Kirtane et al 207, studied 30 cases, 16 were found to have large schwannomas compressing the cerebellum or brainstem as proved on surgical exploration or at autopsy. The ENG showed evidence of a central lesion in these patients in the form of an abnormal pendular eye tracking test, an abnormal gaze test, failure of visual fixation suppression or hyperactive contralateral caloric response. [206]

The pendular eye tracking test, if abnormal, indicates a central lesion. They observed to occur in 10 patients, each of whom had large VS compressing the cerebellum and/or the brain stem. Significant spontaneous nystagmus was recorded in only 12 patients (40%). Linthicum et al 209, reported recordable SN in only 10% of their cases. However in series

of patients studied by Kirtane et al 207, the direction of the spontaneous nystagmus beat was nonlocalising, beating towards the side of the tumour in 5 cases and away from the tumour in 6 cases.

The results of bithermal caloric test seem to be most important and valuable test of the entire ENG test battery. [207] Kirtane and his colleagues twenty seven patients (90%) had the anticipated ipsilateral, hypoactive, warm and cold, caloric responses. Attention, however, must be paid to the caloric responses elicited from the normal ear. Normal contralateral caloric responses are to be expected. They were seen in 11 cases (36.7%), all of whom had small or moderate-sized schwannomas. [207,208] Interestingly, in their group of patients, 10 cases (33.3%) demonstrated hyperactivity of both warm and cold caloric responses on the contralateral side. These patients were found to have fairly large neuromas compressing the brain stem which probably caused compression of the cerebello-vestibular fibers to the contralateral vestibular nuclei. These cerebello-vestibular fibers passing through the inferior cerebellar peduncle cross in the midline close to the restiform body and are mainly inhibitory. A lesion in these fibers as is caused by a large VS leads to a release of the contralateral vestibular nuclei from the inhibitory influences of the cerebellum, thus explaining the noninhibition of the contralateral caloric responses. [207,209]

Nowadays the VNG testing is considered the new standard for testing inner ear functions over ENG, because VNG measures the movements of the eyes directly through infrared cameras, instead of measuring the mastoid muscles around the eyes with electrodes like the previous ENG version. VNG testing is more accurate, more consistent, and more comfortable for the patient.

Bilateral hypoactivity in their series was found in 9 patients (30%). Of these, only 2 patients had bilateral VSs. A schwannoma situated medial to the porus acousticus and arising from the inferior vestibular or cochlear nerve may give a normal caloric response since the impulses resulting from lateral semicircular canal stimulation pass in the superior vestibular nerve which may yet be free from compression. This occurred in 3 of their patients (10%).[209]

Thus, in conjunction with audiological and radiological findings, ENG is a valuable aid in establishing a definitive diagnosis of a VS and in evaluating its probable size and extent.

Hence the complete ENG test battery should be performed in every case suspected to have VS. [207, 210]

1.4.4 Vestibular Evoked Myogenic Potentials

The Vestibular Evoked Myogenic Potentials (VEMPs) is a diagnostic tool in the process of which investigated patients with specific vestibular disorders.

Basically, the VEMP is a biphasic response elicited by loud clicks or tone bursts recorded from the tonically contracted sternocleidomastoid muscle, being the only resource available to assess the function of the saccule and the lower portion of the vestibular nerve. It is known to be inhibitory electrical potentials generated after a sound stimulus (clicks or pure tones), originated in the saccule and conducted by the lower portion of the vestibular nerve all the way to the CNS, generating inhibitory electrical responses picked up by electrodes placed on the sternocleidomastoid muscle (SCM). [211]

The patients are put in a chair, seated and instructed to turn their heads to the opposite side of the sound stimulus, in order to contract the contralateral SCM muscle. VEMPs are read by electrodes placed on the patient's SCM (ipsilateral to the sound stimulus), the positive electrode is placed on the upper third of the muscle, while the negative electrode is placed on the muscle tendon, just above the clavicle. [212] (e.g. see fig. 32).

Figure 32. VEMPS software and electrode placement (Our photo)

The electrical responses from these potentials are made up of two biphasic waves, the first is positive, with a latency around 13ms, known as p13; followed by another wave, this time negative, with a latency around 23ms, known as n23 (e.g. see fig. 33-34).
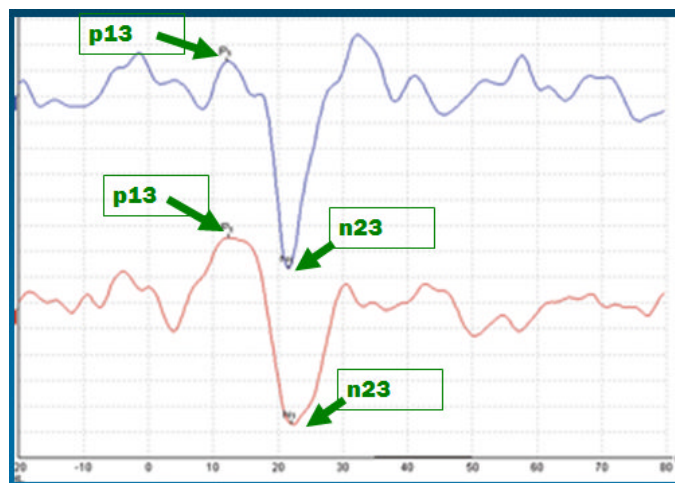
Figure 33. Parameters of Evaluation of VEMPs (Our photo)
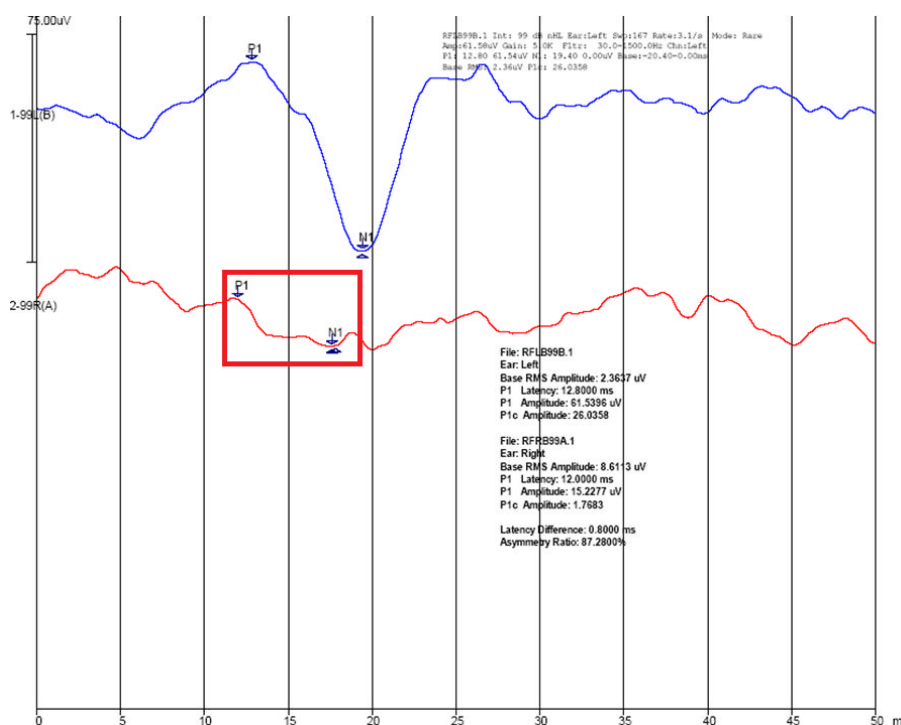
Figure 34. VEMPs showing 87% asymmetry rate in patient with right sided VS (Our photo)

These responses are present in most of the normal individuals studied, differently from a second biphasic complex known as n34-p44, which according to Colebatch would be absent in 40% of the normal individuals studied, while Robertson described that this second complex would be present in 68% of normal individuals. [211,212]

In spite of several conducted studies there are still exist some controversial points regarding the VEMPs. One of those controversies is the relationship observed between the electrical response amplitudes and the level of contraction of the muscles tested (usually the SCM).

Because it becomes very hard to be able to compare the test of an elderly patient with that from a young athlete, who very likely has a much higher level of muscle contraction.

Following important controversy regarding VEMPs could be the index of sound stimulus generated through clicks or tone bursts.[212]

As we know that VEMPs neural pathways involve lower portion of the vestibular nerve, so it can be used in diagnosis of vestibular schwannomas. Some studies in the literature already show this important contribution of VEMPs, such as the one developed by Murofushi et al. in 1998, who observed 80% of altered VEMPs in 17 patients with established diagnosis of vestibular schwannoma. In 2001, Takeichi et al. performed a similar study in which he observed altered VEMPs in 13 of 18 patients diagnosed with vestibular schwannoma confirmed by MRI. In a general way, VEMPs can contribute to the diagnosis of vestibular tumors, but must not be used as the sole diagnostic method, because it only assesses the function of the inferior vestibular nerve. Nonetheless, when performed together with MRI, the ABR, audiometry and caloric test, they may help in the exact location of the tumor in the vestibular pathways.[212]

1.5   Neurologic examinations in Vestibular Schwannoma

Neurological examination plays an important role in diagnosing acoustic tumours. Because it assesses motor and sensory skills, the functioning of one or more cranial nerves, hearing and speech, vision, coordination and balance, mental status, and changes in mood or behavior, among other abilities. Items including a tuning fork, flashlight, reflex hammer, ophthalmoscope, and needles are used to help diagnose brain tumours.[133]

Otoneurologic testing includes otoscopy, exploration of muscular strength, sensibility, cranial nerves, cerebellar testing, and exploration of spontaneous or induced nystagmus

with head shaking, absence of saccadic movements by Halmagy testing, Romberg and Unterberger Testing.

Usually the VS is a cause of positive otoneurological findings such as pathologic nystagmus, positive pastpointing and postural instability, a conclusion regarding the involvement of the vestibular system can usually be reached on bedside examination. Moreover, the presence or absence of signs of brainstem or cerebellar dysfunction, are sometimes sufficient to determine the nature of the disturbance without any need to conduct laboratory tests.[124,138]

Examinations of patients in otoneurology room can be performed in following order. First of all the examiner will check the eye movements of patient via asking the patient to keep their head perfectly still directly in front of examiner. The patient will follow the finger of examiner without head movements. It is important to ask patient if the patient experiences any double vision and if so when is it worse. This is to check the oculomotor nerve function.[133] Following the trigeminal nerve function can be assisted. It has sory supply to the face and motor supply to the muscles of mastication.

Initially test the sensory branches by lightly touching the face with a piece of cotton wool and then with a blunt pin in three places on each side – around the jawline, on the cheek and on the forehead.[11]

The corneal reflex would also be examined as the sensory supply to the cornea is from this nerve. This is done by lightly touching the cornea with the cotton wool. This should cause the patient to shut their eyelids. So we will ask the patient to look in the other direction, so we will not be testing the blink reflex. Then gently but firmly will touch the cornea at its junction with the sclera. Sensitivity to pain increases medially from this point and decreases laterally. The junction of the cornea and sclera is a good compromise between causing pain to the patient and obtaining the reflex.[133]

There is a rapid blink of the eye being tested and a consensual blink of the other eye. If there is seventh nerve weakness on the side being tested, then observe the consensual reflex.The patient will close his/her eyes tightly and the examiner will look for

completeness of eye closure. Also the nasolabial folds and mouth will be observed while the patient is concentrating on the eyes.[134]

As the orbicularis oculi contract tightly, there are milder associated contractions of muscles about the mouth and nose; these milder contractions are better suited to displaying slight weakness than when these muscles are tested directly.[124]

Additionally it can be asked a patient to smile, show you teeth, or pull back the corners of the mouth. Look for asymmetry about the mouth. The most subtle signs of mild facial weakness are the blink reflex and incomplete lid closure. More often we in otoneurology practice will ask to patient to get out the tongue and move to right and left side.

To test the sensory fibers of the facial nerve, we can apply sugar, salt, or lemon juice on a cotton swab to the lateral aspect of each side of the tongue and have the patient identify the taste. Taste is often tested only when specific pathology of the facial nerve is suspected.[4]

The eighth cranial nerve carries two special sensory afferent fibers, one for audition and one for vestibular function. The cochlear division of CN 8 is tested by screening for auditory acuity. This can be done by the examiner lightly rubbing his fingers together next to each of the patient's ears and comparing the left and right side responses. [124]

In addition, the Rinne and Weber tests are easy to perform and can help differentiate conductive deficits from neurosensory lesions. The Weber test consists of placing a vibrating tuning fork on the middle of the forehead and asking if the patient feels or hears it best on one side or the other. The normal patient will say that it is the same on both sides. The Rinne test consists of comparing bone conduction, assessed by placing the tuning fork on the mastoid process behind the ear, versus air conduction, assessed by holding the tuning fork in air near the front of the ear.

Normally, air conduction volume is greater than bone conduction sound volume. For neurosensory hearing loss, air conduction volume is still greater than bone conduction, but for conduction hearing loss, bone conduction sound volume will be greater than air conduction volume.[133]

1.6 Diagnostic Imaging in Vestibular Schwannoma

Imaging has become a sensitive method of evaluating patients with possible VS.[130] MRI continues to evolve but is already considered the preferred imaging study for the evaluation of a patient with suspected VS. Other imaging techniques remain as useful tools in certain clinical settings, but many techniques, considered state of the art less than a decade ago, have faded into almost complete obsolescence. [29, 131]

Because of the increasing acceptance of MRI as the imaging procedure of choice, much of discussions deal with MRI. Other modalities, such as CT, are discussed where appropriate. It should be remembered that either gadolinium enhanced MRI or contrast-enhanced CT can demonstrate almost any VS.[132] The usual clinical situation, however, is that the clinician is trying to ensure that the patient does not have an VS, and so the most desirable test is the one that is the most sensitive.

1.6.1 Magnetic Resonance Imaging (MRI)

MRI has largely replaced other radiological and clinical investigations in the screening of patients with audio-vestibular symptoms for the presence of vestibular schwannoma. Smaller tumours can now be detected, leading to earlier surgical intervention with improved rates of hearing preservation. [132]

Since the introduction of MR imaging technology, the number of patients with relatively small, incidentally found, asymptomatic VS has increased. A recent study estimates the incidence of VS at 0.2% of all scans done in asymptomatic patients. [137]

There has been a significant increase in the incidence of VS over the past 30 years, from 5 tumours per million per year in 1976 to just under 20 per million per year in 2001.[52, 53] Much of this increase in incidence is due to the advent of better noninvasive diagnostic techniques, especially MRI. [53]

Introduction

Noncontrast high-resolution MRI, the recommended method for diagnosis of VS, enables accurate evaluation of the cranial nerves within the cochlea, labyrinth, internal auditory canal, and cerebellopontine angle. Furthermore, the incidence of giant tumours has recently dropped, whereas that of small and medium-sized tumours has increased.[52] Thus, in some occasions the CT may not visualize the intracanalicular region well, and it is here that MRI establishes its advantage [130] (e.g. see fig 35).

Figure 35. MRI scanner MAGNETOM Symphony Maestro Class (CHUS) (Our photo)

Thin section fast spin echo T2 weighted sequences are capable of clearly demonstrating the auditory nerves and, on the basis of small studies, this unenhanced MRI sequence has been advocated as a screening technique for detecting vestibular schwannoma [133] (e.g. see fig 36).
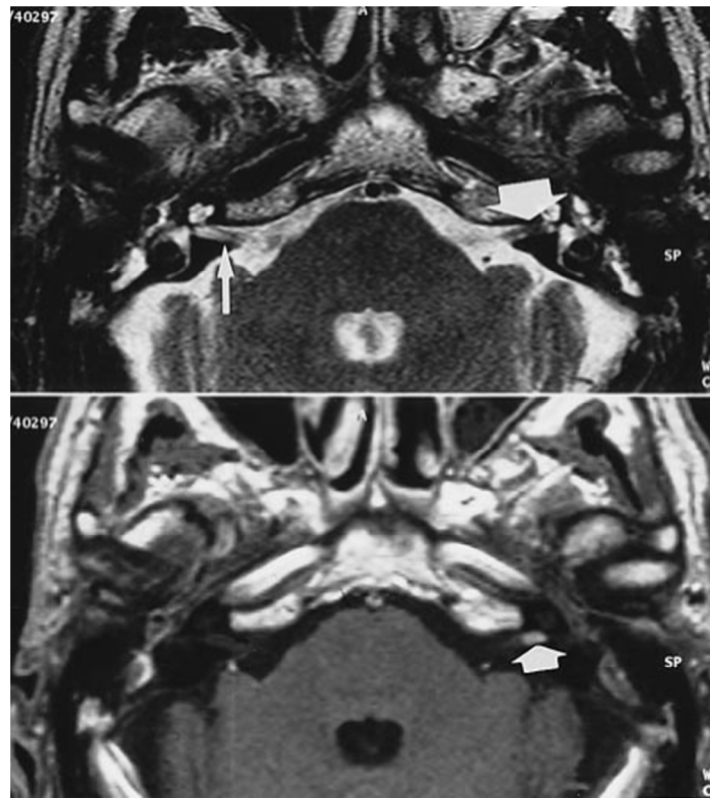
Figure 36. Axial fast spin echo T2 weighted *(top)* and gadolinium enhanced T_1 weighted *(bottom)* images from one patient. On the left the fast spin echo images clearly demonstrate a 3 mm intracanalicular intracanalicular VS
Source: O'Rourke B, Wallace R. Imaging of VSs. Barrow Quarterly 2004,Vol 20, (4)

However, the presence of audiovestibular symptoms and studies with large numbers of patients are required for the proper assessment of alternatives to gadolinium enhanced imaging for VS screening.

The vestibular schwannoma is a soft tissue tumour. Although the lesion can certainly come into contact with the brain, the role of imaging is usually to try to contrast the lesion against the CSF. It may be difficult to appreciate VS on CT done without contrast administration because the density differences are insufficient for consistent visualization of a tumour. [22]

MRI, on the other hand, gives excellent soft tissue visualization but does not show the bony detail nearly as well as CT. Cortical bone gives a lack of signal or signal void on MRI. Air also is seen as a lack of signal on the MRI scan. In a normal situation, therefore, the observer is not able to differentiate the otic capsule from the air filled middle ear. Both appear black. The petrous apex often contains fat, which is seen as bright signal on the T1-weighted (short TR/TE) image. [130]

Fluid does give some signal on the T1-weighted image. Fluid is not nearly as bright as fat but still can be seen quite easily, especially when contrasted against the signal void of the dense bone of the inner ear. Thus the perilymph/endolymph in the labyrinth and the CSF in the IAC can be seen on the image. On the T1-weighted image, the soft tissue and the CSF have different signal intensities. [132]

Soft tissues such as the nerves or brain have somewhat greater signal than the CSF. Often the nerves can be seen crossing the CPA cistern and occasionally can be followed into the IAC. [132]

The appearance of VS depends on the internal architecture of the tumour, its site of origin along the neural pathway, and the size of the lesion as well as the specifics of the imaging procedure being performed. The tumour can have a somewhat variable internal architecture. The tumour is made up of various concentrations of Antoni A and Antoni B type histological patterns. Both types can often be identified within the same tumour. This variability of histology along with the presence of cystic areas and even small hemorrhages is thought to account for the wide spectrum of appearance of the VS. [133]

MRI is sensitive enough to define intracanalicular nerves for clinical purposes. Although contrast-enhanced T1-weighted imaging remains the most commonly employed method for evaluation, high-resolution T2-weighted imaging allows delineation of the individual nerves and evaluation of their relative sizes. [134]

When combined with knowledge of normal anatomy, this information can also be used to detect tumour. Sagittal oblique imaging in a plane perpendicular to the long axis of the internal auditory canal provides a cross-sectional view of the canal and allows individual nerves to be depicted (e.g. see fig.35). The high T2-weighted signal of the surrounding cerebrospinal fluid (CSF) provides excellent contrast between the relatively T2- weighted hypointensity of nerves. T2-weighted fast spin-echo (FSE) MR imaging acquired on a 1.5 Tesla-strength magnet with thin-section thickness, a small field of view, and a large matrix (512 x 512) provides excellent anatomic detail. Direct two-dimensional (2D) acquisition in the axial, coronal, and sagittal oblique planes through the internal auditory canal is typical.

The three dimensional volume acquisitions can be obtained as a single axial acquisition, and that data set can then be used for multiplanar reconstructed images. The high-resolution anatomic detail of these T2-weighted images not only detects nerve sheath tumours but also allows tumour volume and the degree of nerve involvement to be evaluated. The ability of high-resolution T2-weighted imaging to depict tumour involvement of individual nerves may provide prognostic information that can help preserve hearing in selected patients.
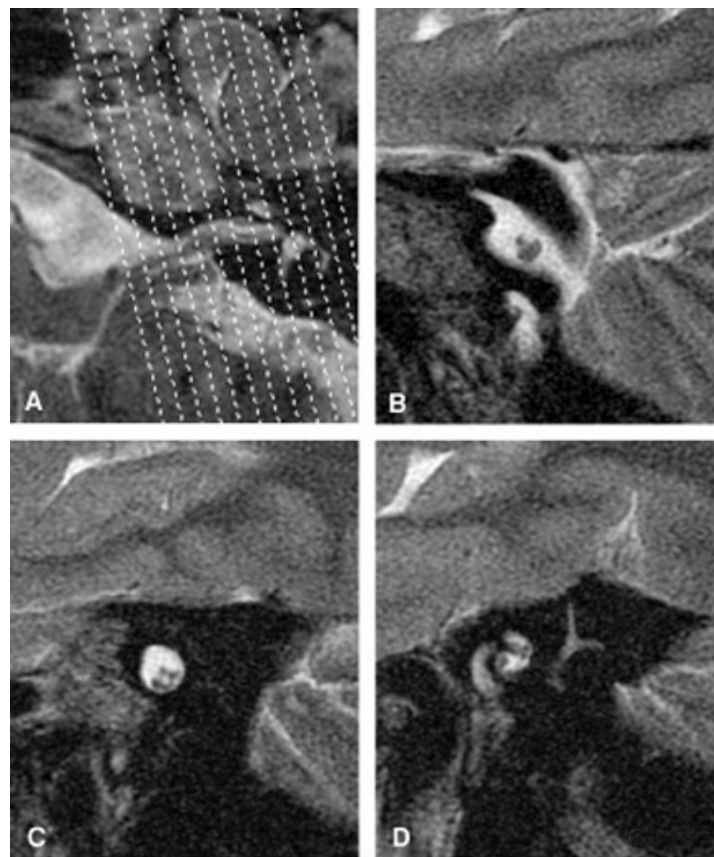
Figure 37. High-resolution T2-weighted images of the left internal auditory canal showing the localization of facial and vestibulocochlear nerves within the IAC
Source: O'Rourke B, Wallace R. Imaging of VSs. Barrow Quarterly 2004,Vol 20, (4)

In terms of cisternal vestibular schwannomas, meningiomas within the cerebellopontine angle cistern are probably the most common differential consideration. Both can appear as large, round, densely enhancing, extraaxial masses causing significant local mass effect. Meningiomas typically arise adjacent to the porus acousticus but sometimes extend into the internal auditory meatus itself. The presence of a 'dural tail' or an obtuse angle with respect to the petrous bone can also help differentiate a meningioma from a schwannoma (e.g. see fig.).[149]
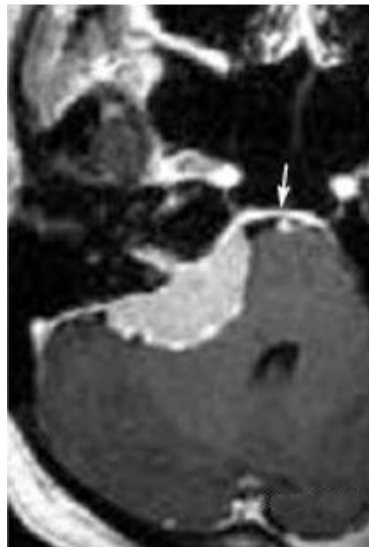
Figure 38. An extraaxial, enhancing tumour is shown in the right cerebellopontine angle with typical characteristics of a meningioma. *While this lesion does extend into the internal auditory canal, the cisternal component is hemispherical and forms obtuse angles with the petrous bone. A thin 'dural tail' (arrow) extends along the ventral aspect of the prepontine cistern.
Source: Curtin DH, Hirsch W. Imaging of VSs. Neurosurg Clin N Am 19, 2008. 175–205

Other common cerebellopontine angle masses such as epidermoids and arachnoid cysts are easily distinguished by their hyperintense T2-weighted signal characteristics and lack of enhancement (e.g. see fig.). On postcontrast T1-weighted imaging, an intracanalicular lipoma can appear as an ovoid hyperintense mass that can be differentiated from a schwannoma on precontrast T1-weighted images. (e.g. see fig.39).
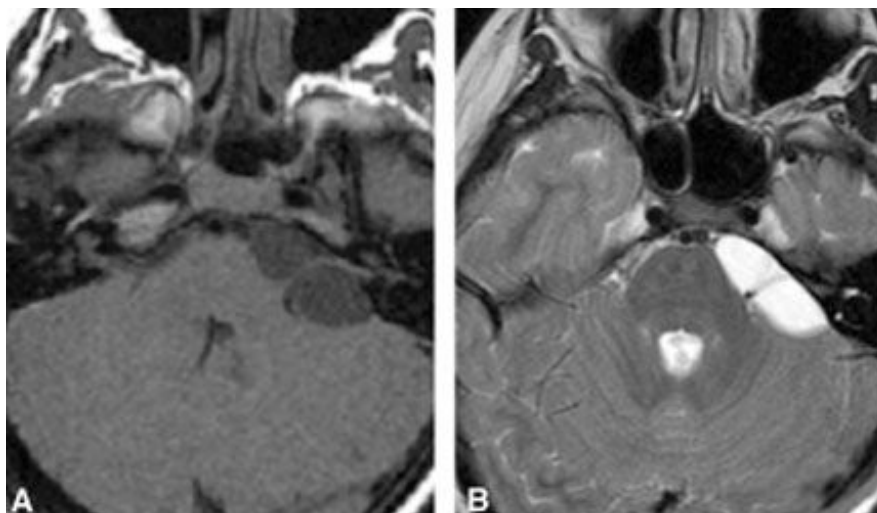
Figure 39. (A) T1- and (B) T2-weighted images of a cerebellopontine angle arachnoid cyst.
The cyst matches the signal of cerebrospinal fluid on all sequences and is not enhance. Note the mass effect and distortion of the left vestibulocochlear nerve complex
Source: Curtin DH, Hirsch W. Imaging of VSs. Neurosurg Clin N Am 19, 2008. 175–205

Performing contrast enhanced imaging alone will pick up all detectable VSs [135, 136] as well as some other causes of abnormal enhancement. Some disease processes that may present with similar audiovestibular symptoms are more readily identifiable on gadolinium enhanced MRI than on non-contrast images [135]. However, this strategy may overlook some other disease processes for example, localized ischemic changes or demyelination in the brain stem and cerebellum which may be relevant to a patient's clinical presentation and which may only be evident on T2 weighted images. Many radiologists and referring clinicians appreciate the additional information that the rapid, inexpensive, fast spin echo sequence provides.

Satisfactory fast spin echo images, where two normal nerves are seen within the internal auditory canal on the symptomatic side, appear to exclude the presence of VS. We would expect to identify all detectable tumours if contrast enhanced images were only acquired in patients whose initial fast spin echo images did not fulfill this criterion. This strategy would yield a sensitivity of 100% for detection, and a negative predictive value of 100% for exclusion, of VS.[135]

The prevalence of vestibular schwannoma in patients undergoing contrast enhanced imaging, that is the positive predictive value of a fast spin echo scan that has not excluded VS, would be 6.5%. [134, 136]

The MRI imaging strategy intended to identify small intracanalicular VSs cannot rely on fast spin echo T2 weighted imaging alone. Gadolinium enhanced T_1 weighted imaging could be restricted to patients where fast spin echo images do not exclude VS but this strategy requires continuous supervision by an experienced radiologist. [132]

In most practices the screening examination should continue to include a gadolinium enhanced sequence in order to optimize the detection of small VSs. [134-136]

1.6.2   Computed Tomography imaging (CT)

Although the MRI considered as a gold standard testing which gives excellent soft tissue visualization but does not show the bony detail nearly as well as CT.[132]

Introduction

The bony anatomy is demonstrated in excellent detail by high-resolution CT when performed with a bone algorithm. The cortical edges of the IAC are sharply defined, and intricate internal anatomy of the labyrinth is routinely visualized. [136]

The bone algorithm allows limited visualization of the soft tissues, however, and the contents of the IAC are not seen.

Air contrast high resolution CT is the most accurate method available for detecting small VSs. Indications for this technique are discussed along with general approaches to these patients. [136]

The tumour shows as a bright white lesion protruding from the IAC on CT. On the MRI, the bright white of the high signal from the enhancing tumour is seen on the T1-weighted image (Figure 38).There have been scattered reports of nonenhancing VSs, but if they exist, they are too rare. [133]

Calcifications are occasionally mentioned as rarely being present in VSs. They are extremely uncommon. In fact, if anything more than minimal calcification is present, an alternative diagnosis, such as meningioma, should be considered. Calcifications, when present, are expected to be tiny, and they are unlikely to be seen on MRI, where small calcifications are averaged together with contiguous soft tissue and become virtually invisible. CT is much more likely to show small flecks of calcium if they are present.
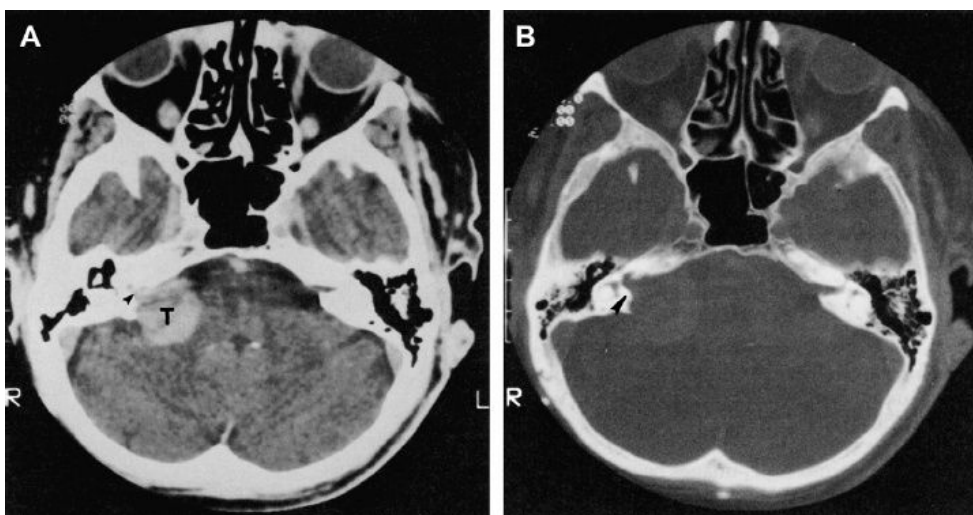
Figure 40. (*A*) A VS with high resolution computed tomography showing contrast. Soft tissue algorithms show the tumor (T) protruding into the internal auditory canal (IAC). (*B*) A Bone algorithm shows the enlargement of the IAC
Source: Curtin DH, Hirsch W. Imaging of VSs. Neurosurg Clin N Am 19, 2008. 175–205

Lesions arising in the temporal bone such as a cholesterol cyst, cholesteatoma, or one of a variety of bone tumours are usually easily distinguished from VS. The origin outside the IAC is usually obvious. Occasionally a tumour, such as a paraganglioma, can have a substantial component protruding into the CPA cistern, but once again the finding of the characteristic erosion of the jugular fossa on CT or the characteristic black dots on MRI representing rapid flow inlarge tumour vessels indicate the true identity of the tumour.

Following a piece of Teflon made polytef incerts in place to separate a vessel from a nerve can sometimes resemble a schwannoma (e.g. see fig. 41). It can be dense on CT. There can be some enhancement of the contiguous tissues on CT or MRI. The site of the previous craniotomy is obvious, and the patient gives the appropriate clinical history.
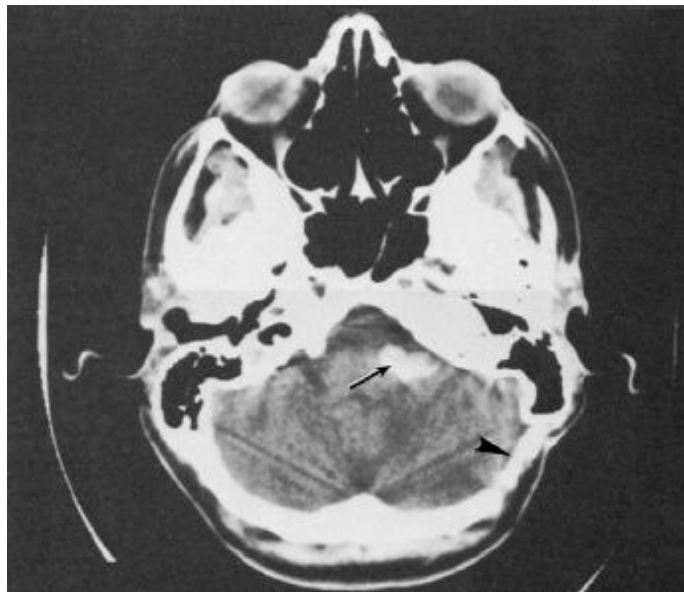
Figure 41. A Polytef in the CPA cistern. Increased radiodensity represents a piece of Teflon used to separate the nerve from the vessel. Source: Curtin HD, Hirsch WL Jr. Imaging of acoustic neuromas. 1992. Neurosurg Clin N Am. 2008 Apr;19(2):p202

On some occasions, some patients cannot undergo an MRI. When a patient cannot undergo an MRI, a contrast enhanced, high resolution CT scan is still a highly reliable examination.[136] When the primary question is whether the patient has a VS, a gadolinium enhanced MRI scan is the preferred imaging modality. In the past, one could not be completely sure that there was no VS unless the nerves could be visualized all the way through the IAC and no enlargement was present (e.g. see fig. 42).
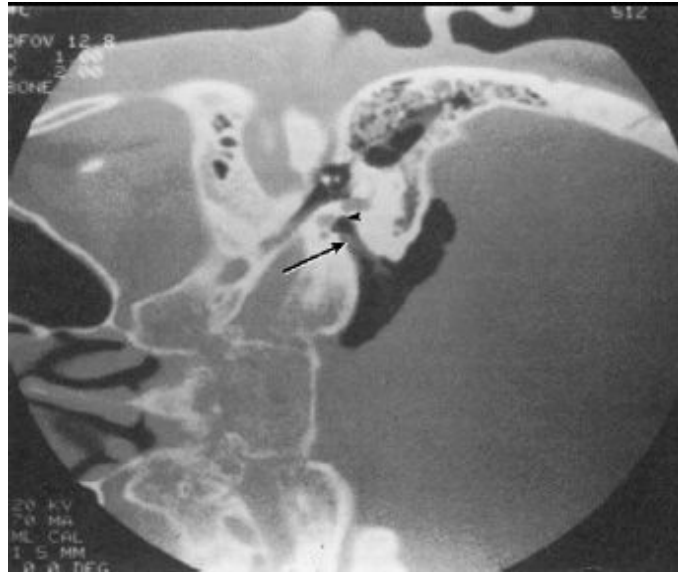
Figure 42. The Air cisternogram shows the infilling of the internal auditory canal (IAC), with air outlining the nerves. Note that the air passes all the way to the extreme lateral portion of the IAC
Source: Curtin HD, Hirsch WL Jr. Imaging of acoustic neuromas. 1992. Neurosurg Clin N Am. 2008 Apr;19(2):p202

Almost all VSs will be found by high quality modern CT scanning. Some clinicians prefer CT scanning, especially when the clinical picture is not as clear cut and high quality images of the otic labyrinth are desirable at the same time that the IAC is evaluated. [132, 133]

Also CT remains more available in some locations and so becomes the initial study, with MRI reserved for the few cases in which the CT scan is considered equivocal.[123]

1.7   The natural Evolution of Vestibular Schwannoma

Follow up management is an important part of any pretreatment discussion with patients who have VS, because excision or radiosurgical treatment can potentially compromise function.[138, 139, 140]

Despite the availability of published data highlighting clinical, radiographic, and biological parameters of significance when managing VS conservatively, deciding between early treatment and expectant management remains a significant challenge for practitioners. [138]

Observation management with serial MR images has provided useful information about the variability in natural history of untreated VSs. [141]

Increasing utilization of MRI has revealed that the growth rate of VS can vary unpredictably from case to case, and observation of early stage patients in whom no increase in volume was detected over the years (or even decades) has permitted surgical treatment to be deferred and in some cases avoided altogether.

According to some authors the difference incidence between its postmortem and clinical diagnosis suggests that in a significant number of cases the tumour's growth rate can be extremely limited, if not absent. [144]

However, the practical implications of this finding have been a cause of controversy: although it has facilitated the planning of increasingly conservative surgical treatment, the specific indications for immediate surgery remain a matter of debate. [143]

In order to search for a possible predictive factor of growth rate Modugno [155] *et al.* performed analysis using 6 clinical variables (tumour size, sex, age, initial symptoms, ABR pattern and duration of the symptoms). According to their results in 30/47(63.8%) cases, no growth was detected during the entire period of follow-up, while in the remaining 17/47 (36.2%) patients, a volumetric increase was recorded. Growth was observed within the first year in 10/17 (58.8%) cases, at 2, 3 and 4 years from diagnosis in 1/17 (5.8%), 3/17

(17.6%) and 1/17 (5.8%) cases respectively, after 6 years in 2/17 (11.7%) cases (e.g. see fig. 43).
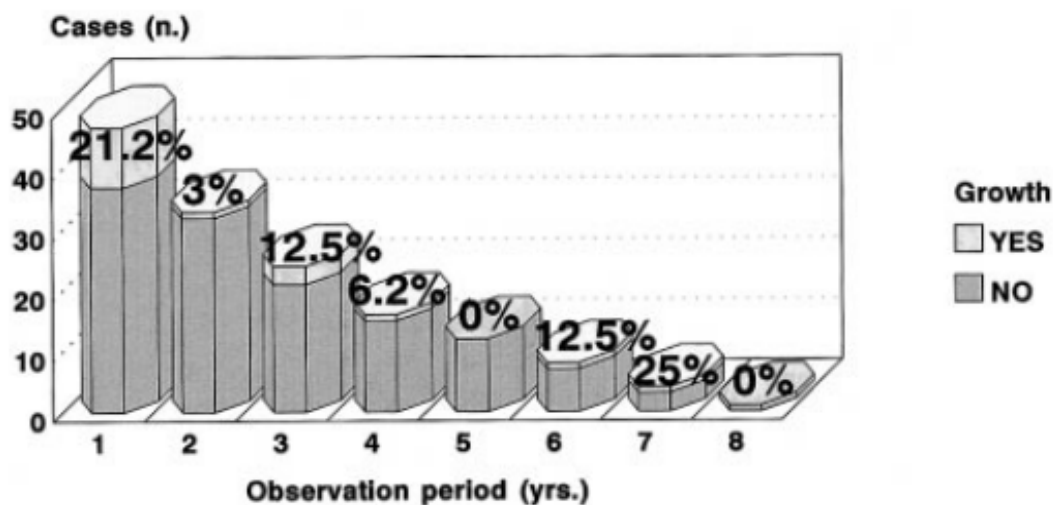
Figure 43. A chart showing the rate of growth of a VS during the follow-up years
Source: Modugno GC et al. Small VSs: Monitoring the Growth Rate by MRI. Acta Neurochir (Vienna) 1999. 14.141: 1063-1067

The growth rate, according to Modugno[155] *et.al.,* expressed in absolute millimetric increase of the greatest axis of the neoplasm, ranged from 1 to 12mm/year with a mean value of 4.0mm/year. In 5/17 (29.4%) cases the growth was < 2mm/year; in 10/17 (58.8%) cases it was between 3 and 6mm/year; in the remaining 2/17(11.7%) cases it was > 9mm/year. In this case the relative increase ranged from a minimum of 11.1% to a maximum of 150%, with a mean value of 55.9%. When growth was recorded, the therapeutic choice varied considering different parameters. The results of comparative analysis of literature, between different works are quite interesting (e.g. see table 2).

Author	Case (n)	Age (Years)	F.U years	RM	No Growth (%)
Valvassori (144)	35	16-81	1-2	-	43
Thomsen (145)	21	37-79	4,2	-	85
Ogawa (148)	36	15-73	4,5	-	19
Bederson (146)	70		2,2	- +	47
Sterkers (147)	21	49-79	3,5	- +	47
Nedzelski (149)	50	50-83	3,4	- +	52
Woods (151)	27	55-80	2,1	- +	40
Noren (152)	98	16-82	2,5	- +	30
Rosenberg (153)	16	65-86	4,3	-	44
Strasnick (154)	50	40-90	2,6	- + +	32
Charabi (150)	97	<81	3,4	- +	26

Table 2. Percentage of cases with a VS growth and a review of literature.
Source: Modugno GC et al. Small VSs: Monitoring the Growth Rate by MRI. Acta Neurochir (Vienna) 1999. 14.141: 1063-1067

By contrast, Thomsen, *et.al.*,[145] reported no growth in as many as 85% of cases submitted in a longitudinal follow-up study for a mean period of observation of 4.2 years. However, it is noteworthy that in a 5-year multicenter study, which included Thomsen's group, a much lower overall percentage (26%) of cases without growth was reported.[2]

It is possible to conclude from the literature that in about 45% of the patients with a diagnosis of a VS, the MRI did not reveal any growth for an average period of 2±4 years of follow-up. [155]

Several investigators have published their institutional results, but to date, there have been few efforts to combine these experiences to achieve the statistical power needed to determine the suitability of follow-up management for these tumors.

Sughrue, *et.al.*,[138] performed a comprehensive review of the literature on the hearing preservation and intervention rates, with special emphasis on tumor growth rates, in a large population of patients with a VS who were treated conservatively. Their results suggest that the patients with tumors that grew $\leq$ 2.5mm/year had better hearing outcomes than patients with tumors that grew > 2.5mm/year. They did not find a similar relationship between initial tumor size and rate of hearing preservation.[139]

In fact, patients with preserved hearing had statistically larger tumors on average at presentation, but the 2mm difference in average size must be interpreted within the context of limitations associated with imaging resolution and observer reliability. This suggests that for patients with tumors $\leq$ 2.5 cm, the tumor growth rate is a more important indicator of who is at risk for progressive hearing loss than tumor size at presentation. The mechanism behind this observation is unclear;[138] however, it has been hypothesized that faster growing tumors represent a biologically more aggressive subset of lesions, which are more likely to infiltrate and disable the cochlear nerve, regardless of the initial size of the tumor.

Facial nerve outcomes in patients with a VS in whom the disease is managed conservatively, have consistently excellent outcomes throughout the series reports. The patients with faster growing tumors had a nearly identical reported rate of subsequent intervention to that of patients with slow growing tumors, despite poorer hearing

outcomes.[138]   In literature, some authors performed studies analyzing predictor factors where the mean age of the patients in whom growth was recorded was slightly higher, but the difference did not appear significant. As for the initial symptoms, tinnitus was more frequent in cases with growth, but even this difference was not significant.[140] ABR also showed a greater frequency of electrophysiological patterns correlated with a block of the central pathways in the cases with growth, although this difference was not significant.

As regards the relation between tumor growth and duration of the symptoms, variance analysis showed only a tendency towards an inverse correlation: the average duration of the symptoms was shorter in patients who presented with tumor growth.[150]

Regarding growth patterns, in a recent multicenter study, Charabi, et.al.,[23,150] recognized the following five different types of behavior: 1) continuous growth (40%), 2) non-visible growth (18%), 3) continuous growth after a variable period of quiescence (18%), 4) a regressive tendency (8%), and 5) irregular growth (16%). The fact that the third subgroup had the longest mean period of observation led Charabi, et.al.,[23,150] to argue that, in a percentage of cases with apparently no growth, a volumetric increase could be revealed at a later date (a finding which could be in keeping with the observations of Thomsen, et.al..[145]

However, the fact that the mean age of the patients with no growth was significantly higher than that of the patients with linear growth, after a period of quiescence, could also suggest the following opposite hypothesis: that patients who do not present any growth could belong to a separate, independent population. A larger series of experiments with longer follow-up periods must therefore be accomplished before any clear conclusions can be drawn.

Tumour size, age and sex have been particularly considered in the literature. However, no significant correlation has been found between any of these parameters and tumour growth. Ogawa et al.[148] maintain that older age, female sex and bigger tumour size are likely to predict a volumetric increases of the neoplasm, but their data do not reach statistical significance. A different predictive factor was proposed by Charabi et al.[23, 150], who found a significant inverse correlation between tumour growth and the reported duration of symptoms before diagnosis.

114

1.8   Treatment modalities of Vestibular Schwannoma

Present day there are 3 treatment modalities or options exists for patients with VS.

- Watch and Wait;
- Conventional neurosurgery;
- Radiosurgery with Gamma Knife.

1.8.1   Follow up or observation with serial MRI

In recent years, the wide diffusion of the Internet has meant that many patients come to consultation with prior knowledge about the various treatment options, which far from making matters clearer, often mislead patients due to incomplete and biased information. It is very important for all patients to be informed of the 3 treatment modalities. [156]

In majority of cases above listed treatment options would be informed or presented to patient to choose the treatment option.[145]

With the exception of some situations where the choice of treatment is clear, for example observation for a 90-yearold patient with a 3 mm tumour or surgery for a 30-yearold patient with a 5 cm tumour, the decision on the best therapeutic option for patients with VS is very difficult to take. In this case otoneurologist would recommend the best option and the patient would accept ether will look for the second opinion. The ideal situation for such patients could be to consult the ideal situation is for a patient to consult a multidisciplinary team in a center with experience. It is important to take into account that the majority of patients with VS present only hearing loss and/or tinnitus at the time of diagnosis, and disabling symptoms are rare. [23, 150, 156] Thus, the vast majority of preoperative patients have very good quality of life despite having a tumour. [156] After the chosen treatment regardless the type of it, even if there are no serious or unforeseen complications, this quality of life worsens.[153] Obviously, this situation is exacerbated if severe complications or sequelae appear.[143]

That is why it is very important that the patient understands - the goal of VS treatment is to avoid problems derived from the growth of the tumour, which by its nature and location can lead to intracranial hypertension and death. [23, 155, 150, 156] But these problems can appear after many years, so the treatment involves, at the present time, a reduction in the quality

of life to avoid serious complications in an uncertain future.[156] Exceptions to this rule are patients with large and symptomatic tumours, in which treatment is imperative, and patients with severe vertigo. In these cases, quality of life may improve after treatment.

Follow up or observation/ wait-and-scan treatment approach consists in performing serial MRI, the first one generally 6 months after diagnosis and, if there are no significant changes, every year.[156, 155, 149]

Along with serial MRI, it is important to perform audiometric test in each review. Even some clinical hospital's ORL dept. includes otoneurology divisions which equipped with other machines and of course they afford to perform some other tests like Craneocorpography, posturography, Videonystagmography/caloric test etc.

In older patients with small tumours where the expected growth of the tumour is not life-threatening in the years they presumably have left to live, this attitude would be the treatment indicated. [156] In these cases, as long as no significant changes are observed in the symptoms, an annual MRI is carried out (e.g. see fig 44).
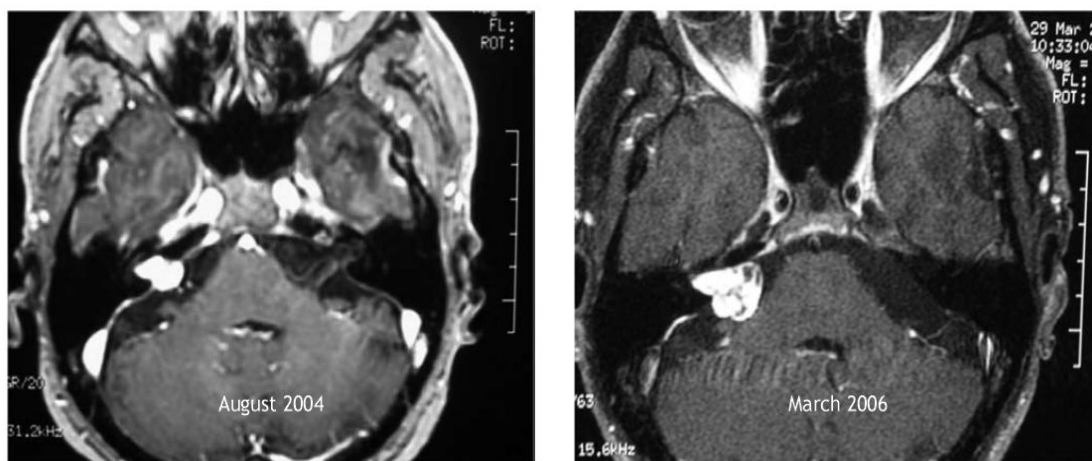
Figure 44. Image shows the growth of a VS after one and a half years of observation
Source: Lassaletta L et al. An update on the treatment of vestibular schwannoma. Acta Otorrinolaringol Esp. 2009;60(2): pp131-140

Advanced age, deterioration of general condition, absence of relevant symptoms, longstanding clinical condition indicating slow growth, are all factors in favor of this wait-and-scan treatment.

Age factor and the size of the tumour, hearing level could be predict the exact type of the treatment. If the combination of advanced age and small tumour size is hardly questioned as an indicator for observation, there are other situations which may also indicate the same treatment. But the most case could be a case of young patient with a small tumour and good hearing. In this case, all 3 therapeutic options could be considered: microsurgery to resect the tumour and preserve hearing while the tumour is still small; radiosurgery to control the growth of the tumour, thus avoiding the potential morbidity of surgery, relying on preserving hearing; and observation, as the rate of tumour growth is not initially known and the possibility exists that it may not grow or it does so at a normal rate, in which case the injury will not become life-threatening for many years. And lastly, the slow rate of growth of most tumours makes observation a valid option as an initial approach in almost all tumours, except in very large ones which may become life threatening in the short or medium term. [156]

The main advantage of observation is that it avoids the complications of surgery or radiation. A theoretical disadvantage of this wait-and-scan approach is the delay in providing definitive treatment if the growth of the tumour is established, although it has not shown that this delay has a negative impact on the quality of life. Other drawbacks are the need for lifelong imaging tests and the psychological factor, due to knowing that there is an untreated intracranial tumour. [156] Along the recommendation or just when the observation is chosen as a therapeutic option, it is important to inform the patient that it is likely that the hearing loss will increase, even if the tumour does not grow.[158]

According to several authors the decision of conservative management is not straightforward, although some treatment guidelines have been proposed. An algorithm designed by *Smouha et al. (2005)* recommends observation in elderly patients, with small tumours, and no symptoms other than hearing loss. [196-197] They define elderly patients as over 45 years and small tumours as less than 25 mm in diameter. Upon observing growth beyond 2 mm/year or changes in symptoms, intervention is indicated. Unfortunately there is little correlation between symptoms and tumour size, and patient quality of life may diminish even without growth. [189] Therefore, treatment may also be indicated when symptoms progress but the tumour size remains static. Concerns about patient compliance have also been voiced, and high attrition rates were noticed in some conservative

management studies.[197] Nonetheless, observation remains a practical choice for many patients. [196-197]

1.8.2   Conventional neurosurgery

The introduction of the microscope, microsurgical techniques, monitoring of the facial nerve, the refinement of anesthesia and the experience acquired at some centers have helped to generate new targets in VS surgery. Present day, the goal is not just excision of the tumour with minimal mortality, but also the preservation of facial function and, where possible, hearing. While mortality has fallen to values below 1%-2% at experienced centers, and preservation of facial function is achieved in most cases, the preservation of hearing is achieved in only a select few. As in other areas of otolaryngology falling between different specialities, there is controversy about which specialist should carry out VS surgery. The answer is usually neurosurgeon, but whether the neurosurgeon or not it should be performed by the person with most experience in it.[149]

In theory, any otoneurology surgeon or neurology surgeon with enough experience can carry out the complete surgery, although it is rare for a neurosurgeon to have experience in the milling of the IAC. In some medical centers that's why VS surgery performs by the otolaryngologist and some others it performs in cooperation between otolaryngology specialists and neurosurgeons which has been enriching and brought several advantages: each specialist provides their expertise in different fields, allowing for shifts to be set up so that, in patients with large tumours, dissection of the cranial pairs can be performed more restfully, and all approaches can be used, some of which are not accessible to certain specialist. [156]

In conventional neurosurgery there are three different surgical approaches could be applied: Retrosigmoid (RS), translabyrinthine (TL) and the middle cranial fossa (MCF). [156] In many occasions the surgical removal is only treatment for large VSs because stereotactic radiosurgery is not applicable. The translabyrinthine,[161-162] retrosigmoid suboccipital, [163-164] and middle fossa approaches[165] are the three basic approaches for the removal of these tumours. Recent papers recommend the translabyrinthine approach for the removal of large tumours and have reported good results with this technique. [160]

The selection of surgical approach is based on multiple factors, including pure tone thresholds, speech discrimination score, auditory-evoked responses, tumour size, hearing status of both ears, and patient age and preference. Surgery practices vary in degree of experience and preferred techniques.[166] Despite these differences, however, imaging directs preoperative management by addressing tumour size, extent of IAC penetration, cerebellopontine angle involvement, relationship of the tumour to cranial nerves, and relevant anatomic variants. [167] Preoperative MR imaging is generally considered the standard procedure unless contraindications exist. (e.g. see fig 45).
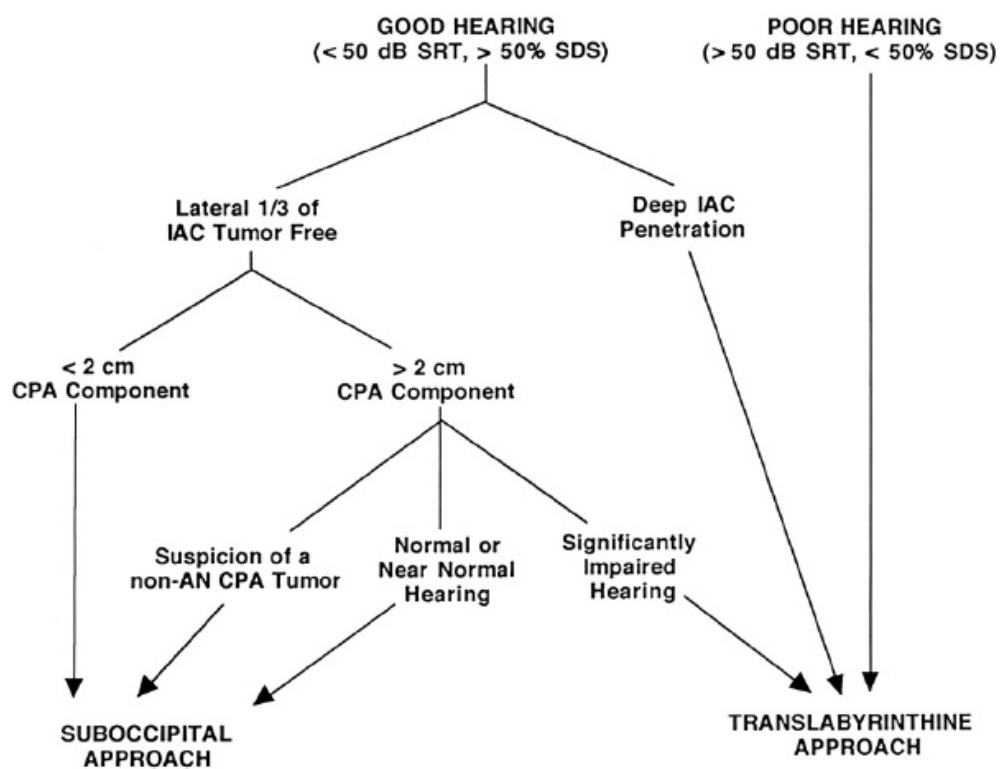
Figure 45. Selection criteria for the surgical approach
Source: Whittaker CK, Luetje CM Vestibular schwannomas. J Neurosurg 1992;76:897–900

1.8.2.1   The retrosigmoid (suboccipital) approach (RS)

The retrosigmoid or suboccipital approach used to attempt hearing preservation. Success rates vary from 30-65% in CPA tumours smaller than 1.5 cm with good hearing and limited involvement of the IAC. However a tumour extending to the fundus is a

contraindication to the RS approach for hearing preservation. The tumour removal is accomplished with mirrors. [144, 157.]

All the patients in the authors series have, however, been operated through the retrosigmoid route as this is the only route that is not only adequate for all sizes of tumour but also suitable for preservation of facial function and hearing. No doubt enough literature is available now to document TL and MCF approaches as good means of tackling selected tumours (e.g. see fig 46).
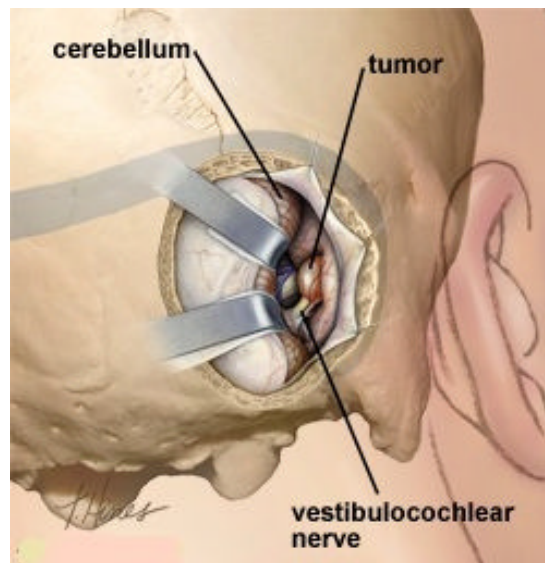
Figure 46. The suboccipital approach
Source: http://www.mayfieldclinic.com/PE-AcousticSurgery.htm

1.8.2.2   The translabyrinthine approach (TL).

The translabyrinthine approach is oldest surgical approach applied to VSs. William House developed the translabyrinthine approach for excision of VSs in 1964. [160] This approach is familiar to most neurosurgeons and otoneurologists and is frequently used to remove VSs. This procedure provides the best line of sight of the facial nerve and consequently offers the highest success rate of facial nerve preservation for a patient. [158]

The translabyrinthine approach (Fig 42) eliminates hearing but generally results in the lowest tumour recurrence rate.[168] Cerebellopontine angle exposure is adequate even for very large tumours, but an anterior sigmoid sinus or high-riding jugular bulb can make dissection of the cerebellopontine angle component more difficult compared with the

suboccipital approach. Differences in retraction, resection, and wound closure unique to the translabyrinthine approach are described later and are readily apparent at MR imaging.

Translabyrinthine approach is the preferred surgical choice by most doctors when the hearing level is no longer useable. It is also a good choice when a tumour is above 20 mm as, statistically, facial nerve damage increases with large tumours. [160]

This approach also makes use of a postauricular incision. [159-160] A complete mastoidectomy is performed, and bone over the sigmoid sinus and tegmen is skeletonized. Ossicles may or may not be removed, depending on the surgeon, to facilitate packing the middle ear to lessen the risk of CSF leak. Bone is removed from the adjacent middle and posterior fossa and from around the sigmoid sinus. The sigmoid sinus can then be retracted, unlike with a suboccipital resection. A labyrinthectomy is performed by removing the three semicircular canals and opening the vestibule after identifying the jugular bulb, which marks the inferior extent of dissection. Bone around the superior, posterior, and inferior portions of the IAC is removed, the IAC fundus lying just medial to the vestibule. After tumour removal, surgeons use a number of techniques to limit the risk of CSF leak. [160]
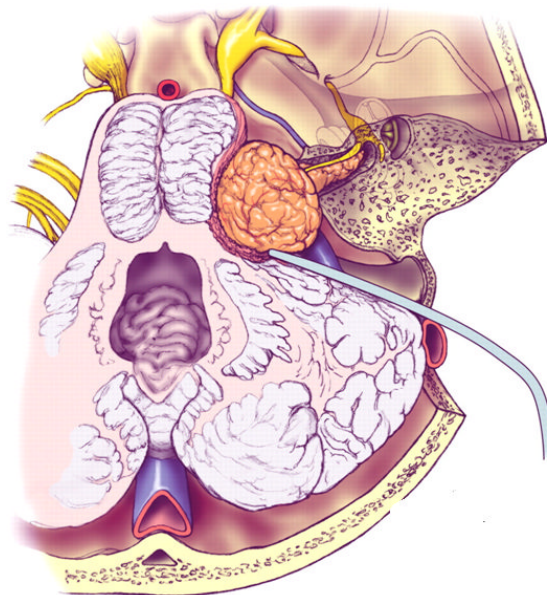
Figure 47. Drawing illustrates the translabyrinthine approach
Source: Silk PS, Lane JI, Driscoll CL. Surgical Approaches to Vestibular Schwannomas: What the Radiologist Needs to Know. November 2009 RadioGraphics, 29, p1962

The main disadvantage of this approach is that this procedure sacrifices an individual's hearing and other complications associated with this surgery is CSF leaks, meningitis, and rarely fat graft prolapsed.[160] In addition, the dural based blood supply to tumours in this region is encountered and may be interrupted early in the course of dissection. That's why it should only be selected when a person has severe hearing loss or the tumour is too large for hearing preservation surgery. [159]

1.8.2.3   Middle Cranial Fossa approach

The MCF approach is generally reserved for small tumours, which are mainly intracanalicular and have less than 1 cm of cerebellopontine angle extension, and for patients with good hearing. This is the only technique that allows complete access to the IAC without violating inner ear structures. [167, 169] However, exposure of the cerebellopontine angle cistern is limited, and tumours with a large cerebellopontine angle component cannot be easily and safely addressed with this method. [169]

This procedure begins with a preauricular skin incision and temporal craniotomy. The middle meningeal artery may require division. The dura mater over the petrous ridge and adjacent MCF floor is dissected to allow placement of a retractor over the petrous ridge. [169] The temporal lobe is then elevated. Exposure is limited due to the risk of temporal lobe injury if retraction is too aggressive. [170]

1.8.3   Radiosurgery with Gamma Knife

Stereotactic radiosurgery (SRS) is an accepted alternative to microsurgery for smaller tumours and non-surgical candidates, offering similar tumour control rates. [182-185]

Ideal active management for small-to-medium-sized vestibular schwannomas is still disputed and unclear, as some recent studies favored the radiosurgical over microsurgical approach, while others showed no difference between groups of patients that were treated microsurgically, radiosurgically, or untreated with observation (Figure 48). [179-181.]
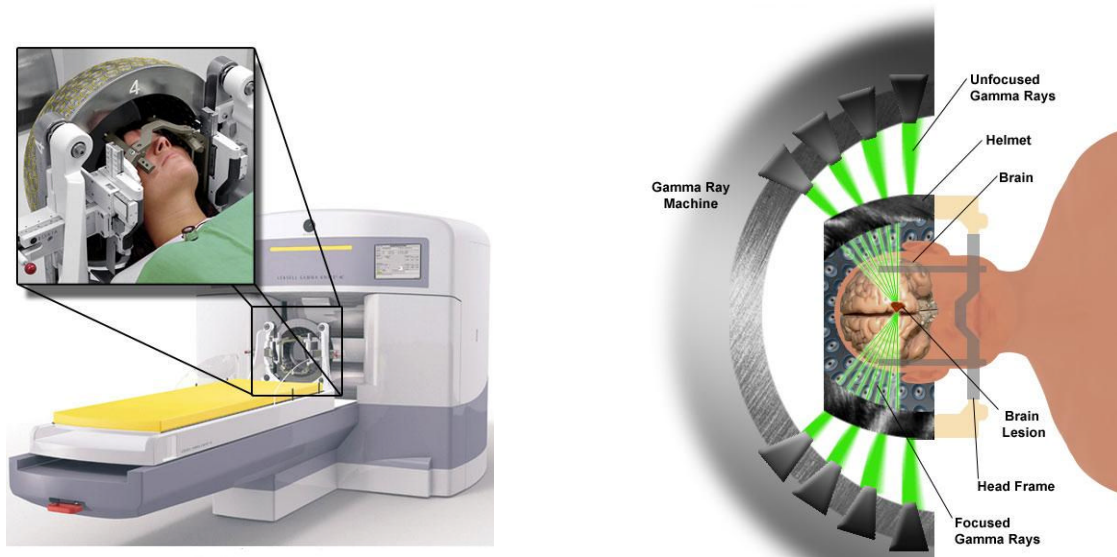
Figure 48. Schematic of stereotactic Radiosurgery with the Gamma Knife®
Source: http://www.yalemedicalgroup.org/stw/Page.asp?PageID=STW029077 (12.11.2013)

Meta analysis including studies from the 1990's identified an average tumour control rate of 91% with Gamma Knife radiosurgery (GKRS).[186] A more recent review identified a range of control rates, from 89-100% reported in various studies. Complicating the interpretation of such results, many of which report on patients first treated over a decade ago, is that Gamma Knife technology and treatment planning continues to undergo significant evolution. Improvements in imaging resolution and computer planning software, have allowed physicians to better spare adjacent brainstem and nerve structures.[187,188] Furthermore, the therapeutic dose used for treating VS has decreased over the past two decades, with marginal doses of 12 Gy and maximum doses of 20-25 Gy identified as current standards.[189] Therefore, controlling vestibular schwannomas with fewer risks may be accomplished with contemporary SRS.

The effect of irradiation on tumour tissue is shrinkage of tumour cell by DNA damage and intratumoural vascular obliteration. Ionized irradiation causes DNA damage to cells, and the apoptosis of cells promotes early tumour shrinkage.

In the case of late responding tissues, a long cell cycle time causes delayed tumour shrinkage. Meanwhile, the irradiations of the blood vessels of the tumour interrupt the blood flow through hyalinization of arterioles, myointimal cell injury, and endothelial

proliferation, which slowly reached to ischemia, hypoxia of the tumour cells, and damage to the cells.[190]

Regarding the natural course or conservative management for VS, Yamakami et al.[183] reported on the natural course of 903 patients who underwent conservative treatment; in the average observation period of 3.1 years, 51% of the tumours had grown and the mean growth rate was 1.87 mm /year. In the end, 20% of the patients needed surgical treatment. The tumour size may not grow within a certain time, but surgical treatment becomes necessary at some point in a long-term follow-up observation for VS in a young patient. Considering this fact, treating the tumour when it is still small will help the patient and provide a better prognosis.[191]

The outcome for patients managed conservatively has been the subject of several reviews. *Yamakami et al.* reported that over a mean follow-up of 3.1 years, 51% of tumours grew, 20% eventually required intervention, and 37% of patients ultimately lost useful hearing (N = 903 patients). [183] In a meta-analysis by *Smouha et al (2005).*, 43% showed growth, 20% required treatment, and 51% of patients experienced hearing loss over a mean follow-up of 3.2 years (N = 1345 patients). [183, 196-197]

Myrseth et al (2007)., reviewed the literature and determined that over a 3 year period 30-50% of patients undergoing conservative management will lose useful hearing and 15-50% will ultimately require active treatment. [189, 196] Patients must be aware that a significant fraction managed conservatively will eventually require intervention or experience progression of symptoms.[196]

1.9   Complications of Vestibular Schwannoma treatment
1.9.1 Complications conventional microsurgery

Postoperative Hearing Loss and Delayed Complications include headache, CSF leak, meningitis, facial nerve weakness, and, occasionally, vascular injury. Headaches of varying severity occur in approximately 46% of postoperated patients and resolve within 1 year in one-half of cases.[171]

CSF rhinorrhea remains a significant cause of morbidity after resection of VS, with rates of rhinorrhea after this procedure reported to range between 0 and 27%.[221]

According to Brennan *et al.* 226, the CSF leak and its association with the risk of meningitis remain as important issues in the surgical treatment of VS. An incidence between 0 and 30%, with an approximate rate of 12% is reported. [226] The CSF leak often manifests as otorhinorrhea and can originate from inadequate sealing of exposed mastoid or petrous air cells, poor wound closure, or hydrocephalus. CSF otorhinorrhea is more common with the RS approach, with a prevalence of approximately 2.2% in a recent large series. CSF wound leak was seen in 6% of cases in the same series (Figure 49-50).

A larger series by Falcioni *et al* [173] published in 2008 reported an overall CSF leak rate of 8.3%. Diaz Abadon *et al* [224] studied 170 postsurgical patients operated due to VS (163 cases) and other (7cases) CPA tumours. In their series 27 patients (15,9%) presented CSF leake as complication VS surgery. Also they are performed comparative study of current complication depending on applied surgical approach with literature review. (Table 3).

Author/year	Case (n)	CSF fistulae, %	TL, %	CSF fistulae, TL%	RS, %	CSF fistulae RS, %	MCF, %	CSF fistulae MCF, %
Shea MC, 1979	80	15	37,5	30	62,5		0	0
Jacob A, 2007	359		64,3	14,2	13,9	13,2	19,5	11,4
Selesnick SH, 2004	5964		-	9,5	-	10,6	-	10,6
Sanna M, 2004	707	2,8	84,9	1,8	5,4	18,4	7,6	3,8
Darrouzet V, 2004	400	6,9	57,2	-	32		-	-
Fishman AI, 2004	215	6,6	52	5	36	8,5	12	8.3
		17 [*]						
Becker SS, 2003	300	11	33,3	13	33,3	10	33,3	10
Kalamarides M, 2004 [14]	220	12	63	-	27		10	-
Cueva RA, 2005	343	0,8	51,6	-	47,1		1,23	-
		1,2 [*]						
Coca A, 2007	120	12,5	36,6	-	62,5		0,8	
Leonetti J, 2001	589	0,5	35,5	3,8	32,4		0,51	0
		0 [*]						
		6,9 [*]						
Lee SH, 2002	160	10,5	0		100		0	
Wu H, 1999	277	3	100		0		0	
		28,2 [*]						
Díaz Anadon, 2008	170	15,9	24	17,1	66	17	5	0

Table 3. Incidence of CSF fistulae as a postsurgical complication depending on applied surgical approaches to CPA. *FM: fosa media aproach; RS: retro sigmoid aproach; TL: translaberintine aproach.* Prevous series. Source: Diaz Anadon A et al. Fístulas de LCR tras la cirugía de tumoures del ángulo pontocerebeloso y su relación con el índice de masa corporal; Published in Acta Otorrinolaringol Esp.2009; Vol.60.N 05. p321
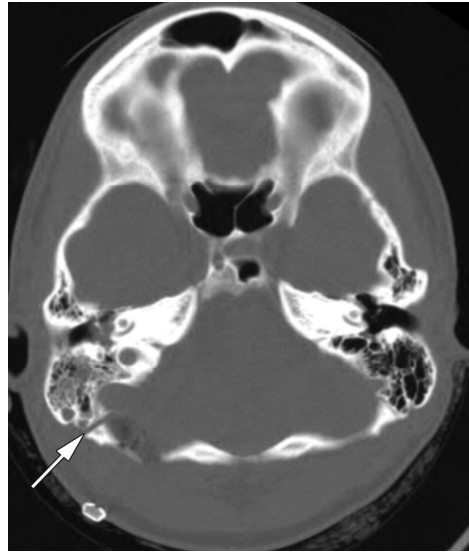
Figure 49. Image of a CSF leak following suboccipital resection of a VS. *A craniotomy defect is seen traversing mastoid air cells (arrow), allowing an egress of CSF into the middle ear cavity.
Source: Silk PS, Lane JI, Driscoll CL. Surgical Approaches to Vestibular Schwannomas: What the Radiologist Needs to Know. November 2009 RadioGraphics, 29, p1965

Following severe facial nerve injury is uncommon with microscopic techniques, and most tumours are now being removed by experienced teams of neurosurgeons and neurotologists.[223]

Transient facial nerve palsy is more common with the MCF approach as mentioned earlier. Vascular injury occurs infrequently, but the sigmoid sinus and jugular bulb can be directly compromised or may potentially thromboses after retraction, possibly with devastating consequences.[225]

It is important to assess for an intact torcula and the potential for adequate contralateral venous flow should there be injury to the sigmoid sinus or jugular bulb. In the rare case of absent flow on the contralateral side, the translabyrinthine approach would be contraindicated. Parenchymal venous injury can also occur as a result of large adherent tumours with complicated dissection. Arterial injuries occur rarely, with the anteroinferior cerebellar artery being most at risk. [169,223,225]

Figure 50. CSF wound leak. Axial nonenhanced CT scan shows changes from suboccipital resection, with a CSF wound leak that resulted in a pseudomeningocele

Tinnitus is a most frequent also remaining most challenging issue among postoperative complications of VS.

Kameda and colleagues (2010) [174] report their single-institution, retrospective study of tinnitus outcomes after resection of VS via the retrosigmoid approach.

Of their 242 patients with VSs, 171 (70.7%) complained of tinnitus before surgery. This symptom disappeared in 25.2%, improved in 33.3%, remained unchanged in 31.6%, and worsened in 9.9% after tumour removal.[174]

Another study conducted by Levo et al. [227] observed 251 cases of postsurgical VS and according to their results: Preoperatively, 62.6% of the patients had experienced tinnitus. Of those with preoperative tinnitus, 47.4% also had it postoperatively, but of those 93 patients without preoperative tinnitus, 39.8% had tinnitus postoperatively. Tinnitus is one of the primary symptoms of VS, together with hearing impairment and disequilibrium.

The risk of postoperative tinnitus is almost 40%, and with preoperative tinnitus, the risk is 7.6% higher. Even though the cochlear nerve was resected in 45 cases, tinnitus later was noted in 3 patients. The status of postoperative tinnitus was not associated with useful hearing preservation (p = 0.153) or tumour size.

Kameda and colleagues [174] conclude that retrosigmoid tumour resection may provide some chance (~ 60%) for improvement of and some risk (10%) of worsening tinnitus.

Outcomes of VS surgery depend on the size and adherence of the tumour, the use of cranial nerve monitoring, and of course the skill of the surgical team.

According to Acoustic Neuroma Association reports 60% of members have acceptable facial function after surgery. The medical literature reports vary, but overall, facial movement is preserved in 75% and useful hearing is preserved in 20% of patients[228, 229].

Delayed hearing loss may occur after surgery in 30 to 50% of patients who had useful hearing immediately after surgery. Partial-removal techniques have higher rates of hearing and facial function preservation; however, the long-term results of these techniques are still being investigated.[227-229]

1.9.2   Complications of Gamma Knife Radiosurgery

Complications that are associated with stereotactic radiosurgery for vestibular schwannoma include hearing deficits, facial palsy, hydrocephalus, and brain stem damage, although the incidence of some of these conditions is much lower than with microscopic open surgery.[231]

In the literature there are many reports on postradiosurgical complications such as cranial neuropathy, cerebellar infarction and edema, cyst enlargement, malignant transformations, intratumoral hemorrhage, and hemifacial spasm in relatively large VS. [139,190, 196]

Bush and colleagues looked specifically at Gamma Knife patients who had "useful audition" pretreatment and found that, at a tumor marginal dose of 13.8 Gy mean at the 50% isodose line, 42% maintained useful hearing posttreatment.[60]

Regarding trigeminal and facial nerve dysfunctions after radiosurgery for VS, Kondziolka et al.160) reported in 1998 that the application of 16.6 Gy marginal dose on average resulted in facial dysfunction 15% and trigeminal dysfunction 16%.

However, many authors reported lower incidence of complication (<4%) with low dose radiosurgery (Table 4).

Author, year	Number of patients	Mean tumor volume, size	Mean maximal /marginal dose	Mean follow up period	Tumor control rate (%)	Hearing preservation rate (%)	Facial palsy (%)	Trigeminal neuropathy (%)
Kandziolka[190] 1998	162	Diameter 22 mm (8-39)	32,7 (24-50)/16,6 (12-20)	5-10 years	97	47 (G-R* I-III)	15	16
Moller 2000	111	-	40-12	0.25-10 years	96	80	14	4
Prasad 2000	200	0.02-18.3cc	34 (17-53)/13(9-20)	4,3years	92	58	2	4
Regis 2004	1000	12.7 mm^3	-/-	-	97	77.8 (G-R I) 47.6 (G-R II)	1.3	0.6
Flickinger 2004	313	1.1 ml (0.04-21.4)	26 (20-26) 13 (12-13)	24 months	93.5	78.6 (G-R I,II)	0	4.3
Hasegawa 2005	73	6.3 cm^3	28.4 (16-36) / 14.6 (10-18)	135 months	87	37 (G-R I,II)	-	-
Chung 2005	195	4.1 cm^3	21.9(17.1-34.0)/ 13 (11-18.2)	36 (1-110)	93.6	60 (G-R I,II)	1.4	1.1
Lunsford 2005	829	-	-/13 (10-20)	6 years	98.6	78.60	<1	<3.1

Table 4. Published results of gamma knife radiosurgery for VS. *G-R Gardner Robertson grade
Source: Lim YJ, Choi SK. Gamma Knife Radiosurgery for Vestibular Schwannomas. J Korean Neurosurg Soc 2007 (42), p164

In cases of residual or recurred mass after microsurgery, the repeated operation was recommended generally, however, recently radiosurgery is considered as a secondary treatment instead of reoperation. On the other side, in case of increased tumor size due to failed radiosurgery, microsurgery is indispensable. However, many authors reported that it may be difficult to remove the tumor due to fibrosis after radiosurgery.[230]

Hearing preservation is another important issue to consider in the treatment of vestibular schwannoma with either microsurgery or radiosurgery. The hearing preservation rate following microsurgery was reported to be 40-70% in patients with serviceable hearing (Betchen et al., 2005)[231]

Introduction

Hearing preservation is an important issue in gamma knife radiosurgery as well. As the experience with gamma knife radiosurgery has grown, the radiation dose has decreased. Currently, a marginal dose of 12 or 13 Gy is the standard dose for treating vestibular schwannoma. Regis et al. (Regis et al., 2008) reported a 60% hearing preservation rate in patients in a large study with a mean follow-up of 7 (minimum 3) years. These authors also mentioned that patients who were not treated using gamma knife radiosurgery lost an average of 9-39 dB compared with an average loss of 2 dB at 3 years following radiosurgery, which corresponds with a preservation of hearing functionality of 60-75%. The probability of preserving functional hearing was higher in patients who had initial symptoms that were other than a decrease in hearing, in patients who were younger than 50 years, and in those patients whose cochlea received a dose of less than 4 Gy during treatment. (Tamura, et al., 2009).

The mechanism that underlies hearing deterioration following gamma knife radiosurgery is not fully understood. Some of the mechanisms that have been proposed include a temporary expansion of the tumour in the canal, vascular insufficiency of the auditory system, the toxic dispersion of free radicals, among others (Wackym et al., 2010).

Hayhurst et al. (Hayhurst, et al., 2011) reviewed the non-auditory complications that were associated with gamma knife radiosurgery in 80 patients who were followed for more than 2 years. Twenty-seven (33.8%) of their patients developed non-auditory adverse radiation effects, and patients with a target volume that exceeded a threshold of 5 cc were more likely to develop complications.

Other complication of GKRS can be Hydrocephalus occurring in approximately 14% of cases and in 4% to 6% of cases after gamma knife treatment.[232, 233] Although it has been reported that gamma knife radiosurgery may contribute to the development of hydrocephalus, a causal relationship has not been established and remains controversial. [232]

Elevated CSF protein levels are thought to then obstruct CSF resorption at the level of the arachnoid granulations.These events are reported to occur in acoustic schwannomas without radiosurgical treatment, though Radiosurgery may exacerbate these events in some patients. [234]

The condition of patients with significant dysequilibrium or recurrent vertigo is not improved and may actually worsen by stereotactic radiation. Patients who are poor candidates for stereotactic radiation should still be informed of the availability of the therapy and be told why they are poor candidates, in the context of the relative risks and benefits of radiotherapy as opposed to microsurgery.[235]

1.10 Tumour Recurrence

After VS surgery, the rate of tumour recurrence is generally very low, ranging from <1% to 9%. [175-177]

According to reviewed literature, the most common cause of VS recurrence after surgery is from incomplete tumour removal, when some of the tumour had to be left behind. This usually happens unplanned, and depends on what happens during surgery.[177]

An increased risk of residual or recurrent tumour is seen with the suboccipital approach due to relatively blind dissection of the IAC fundus. Residual tumour is deliberately left in approximately 1%–2% of patients if dissection is complicated or vital structures such as the facial nerve are at risk for injury. [178]

In 2007 Balasubramaniam and colleagues reviewed 20 cases and revealed 10 de novo secondary tumors, of which eight were malignant, with six being malignant gliomas. The majority of thier cases (14 of 20) involved AN, with most being in patients with neurofibromatosis-2 (8 of 14), reflecting the large numbers and long-term use of radiotherapy for AN. Accelerated growth of primary benign VS and subsequent resection with histopathological confirmation of malignant transformation was found in 6 patients, all of whom had NF-2.[235]

Objectives

2 Objectives

1. To conduct an epidemiologic analysis of patients with Vestibular Schwannoma diagnosed in our Department.

2. To evaluate the utility of different tests for audiologic and vestibular explorations in the diagnosis of Vestibular Schwannoma.

3. To analyze the natural history of Vestibular Schwannomas, both morphologically and in terms of their functional repercussions.

4. To compare the efficacy of two different therapeutic strategies (the wait-and-watch policy and Radiosurgery) in the management of small Vestibular Schwannomas.

5. To establish a therapeutic protocol for small Vestibular Schwannomas.

Materials and methods

3   Materials and Methods

3.1   Materials

3.1.1   Patients

One hundred seven (107) patients with Vestibular Schwannoma (VS) underwent a retrospective study which has been implemented in the Galicia population which attended Santiago de Compostela University Hospital from the period between February 21, 1992 and May 05, 2011.

In this study, we have included only cases of VS and most of which were diagnosed by the means of gadolinium-enhanced MRI. As criterions of exclusion we have used the tumors apart from a VS or cases of CPA/IAC tumors of unknown origin.

Among the studied cases, there was 1 (0, 92%) young male, at the age of 36, who was diagnosed with a bilateral VS due to Neurofibromatosis Type II (NF2). In spite of knowing the clear distinct origin of the NF2, we have included this patient as a clinical presentation and the nature of the tumor was absolutely the same.

3.1.2   Technical support

3.1.2.1   Audiometer

The Audiometric testing was performed mainly by the clinical audiometer labeled "Audiotest 340" (Interacoustic Incidencia, Barcelona) with the background noise less than 5dB (Figure 17). The results of audiometric testing were found from the patient's case records folder in paper form. In the event that some of the patients were diagnosed primarily at the other provincial hospitals, the testing results have been found in the Hospital Electronic Medical History (IANUS) of Galicia which connects 14 hospitals and 440 health centers.

3.1.2.2   The Craniocorpography

For the analyzing the craneocorpographic (CCG) tests, we used the results of the CCG model Eymasa CCG600SE® consisting of lights and a Polaroid® (Polacolor® PRO 100) camera with the size of objective 127mm, angle of coverage 41º and the convex mirror

with the angle of coverage 93° (e.g. see fig. 48). The results were found in patient case reports and as well as at IANUS in e-versions.

3.1.2.3   Computerized Dynamic Posturography software

For the estimation of balance or equilibrium, we have used the posturography testing results realized by the means of the Posturography machine labeled Smart Balance Master Neurocom® (e.g. see fig. 26). The CDP in our case was first recognized at the time of diagnosis and then through the follow-up years.

3.1.2.4 Caloric testing tool and software

In order to assist and analyze the vestibular functions since 1992, the following computerized caloric analyzers were used: *"Nystar plus"* manufactured by Nicolet Instrumental®, "Veonus" from Biodigital® and later more modern VNG software from "Intracoustics®" (e.g. see fig. 31). The VNG consists of infrared goggles (video Frenzel goggles) for the recording of eye movement during the irrigation and cables transmitting the information into the PC.

3.1.2.5 Otoacoustic emissions

The OAE has been applied for a VS patient at the prediagnostic stage, especially when the patient presented severe hearing loss. So, the purpose of this testing was to reveal whether the patient was definitely deaf or hard of hearing. Because the OAE has four different types, in our case we have used the results of the Distortion product otoacoustic emissions (DPOAEs) realized by the means of TEOAE software *"ILO 292"* (e.g. see fig. 23-24).

3.1.2.6 Auditory Brainstem Response audiometer and software

Usually, before getting an MRI, the ABR audiometry was administered for the patients suspect for a VS. The results were realized by *"Nicolet Viking IV P System"* from Nicolet Biomedical, Inc., (e.g. see fig. 20) in the Neurophysiology department of CHUS.

3.1.2.7 Vestibular Evoked Myogenic Potential tool and software

In addition to above mentioned tests, we have analyzed the results of VEMP testing implemented by the SmartEP system from *"Intelligent Hearing Systems"* (e.g. see fig. 51).
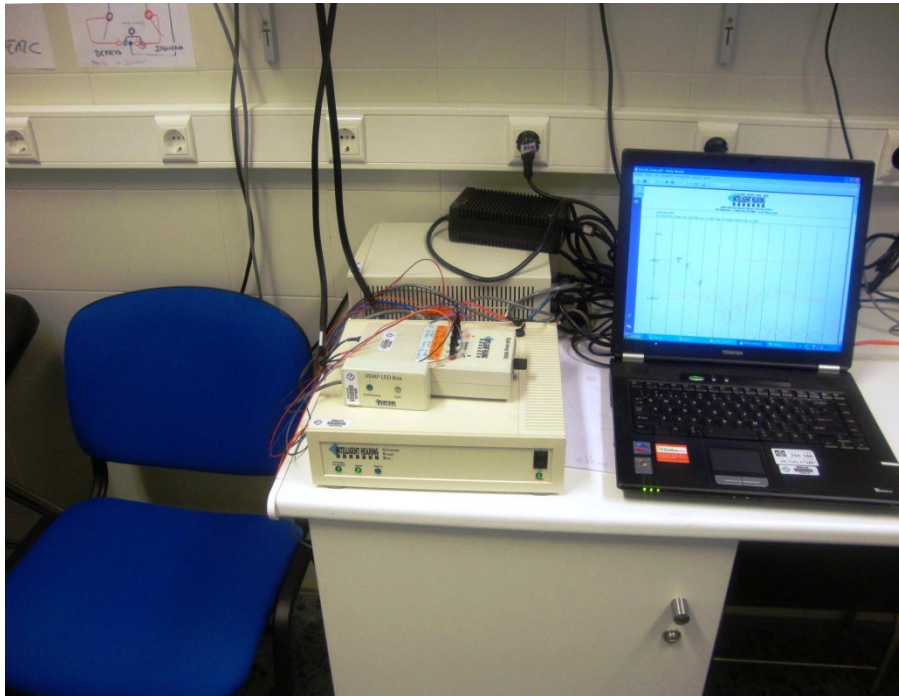
Figure 51. VEMP software with the SmartEP system from "Intelligent Hearing Systems" used for current study (Our photo)

3.1.2.8 Magnetic Resonance Imaging

We have used MRI testing reports performed by Gadolinium contrast. Almost in all cases, MRI testing has been realized in the Radiology division of CHUS (e.g. see fig. 32). We obtained the results from patient's case records as well as e-versions from IANUS.

3.2   Methods

The study included 107 (100, 0%) patients which clinically followed up from July 21.1992 to May 05, 2011, with the mean follow up period 56.52 ±10.79 (range 25.02-71.74) months.

This work consists of both retrospective and prospective clinical observations. The retrospective study based on the investigation of patients having undergone treatment for VS. Data were collected from patient records, outpatient consultations, telephone interviews and re-evaluations of MR scans series.

3.2.1 Audiometric testing

The audiometric testing has been realized for all VS patients at the outpatient department of the Otolaryngology division of Santiago de Compostela University Hospital Clinic from the period between February 21, 1992 and May 05, 2011.

The measurement of PTA implemented was done by the adding up the following threshold levels: 500Hz, 1000Hz, 2000Hz and 3000 Hz and dividing the sum of the values by the four and further revealing the mean. The found number expresses the pure tone average in decibels (dB). It can be explained with following simple formula:

Threshold value at 500Hz + threshold value at 1000Hz + threshold value at 2000Hz + threshold value at 3000Hz= x / 4 = Pure Tone Average

Apart from the calculation of PTA, in each follow up revision, starting from 6 months, one year, two years, until ten years, depending on the remoteness of VS diagnosis of each VS case, we have calculated the Difference of PTA (DPTA) in order to know how the hearing will be changed over time. For example, if the primary PTA of the patient equals 68,75dB and after 5 years it equals 80dB, in this case we will find DPTA by the means of subtraction of primary PTA from the PTA value after 5 years. It can be illustrated with the following expression:

PTA at the time of diagnosis (68, 75)-PTA after x (5) years (80dB) =DPTA (-11, 25).

3.2.2 Testing of balance with Dynamic Craneocorpography

The CCG testing has been realized in the CCG room of the outpatient department of CHUS. The CCG equipment uses light markers placed on the forehead, the occiput, and both shoulders of a patient, which reflects through a mirror system on the ceiling into a motion recording video camera and on to a computer that receives, analyzes, and prints the result (e.g. see fig. 52).

Figure 52. The Craneocorpography device (Our photo)

During the realization of the Unterberger stepping test, the camera records the movements of light markers placed on the forehead, the occiput, and both shoulders of a patient.

In order to cut off the visual stimuli of the patient, we have used the sleeping mask. In this way, the patient loses contact with the ground while stepping and will maintain balance

only through the stimuli received from both vestibular systems. The records of the CCG testing have been analyzed according to Claussen which described 4 different types (page 85).

3.2.3 Computerized Dynamic Posturography (CDP)

In our group of patients the CDP, like other vestibular tests, were initially realized for prediagnostic VS patients and then checked up during each follow up revision. In all cases, the center of gravity was determined under six sensory conditions, the analysis of which makes up the Sensory Organization Test (SOT):

1.   Immobile surface, immobile visual surround, eyes open.

2.   Immobile surface, eyes closed.

3.   Immobile surface, mobile visual surround, eyes open.

4.   Mobile surface, immobile visual surround, eyes open.

5.   Mobile surface, eyes closed.

6.   Mobile surface, mobile visual surround, eyes open.

Each of the six conditions was performed in triplicate, giving a total of 18 tests per session and each test lasts 20 seconds. The following parameters were considered in the data analysis:

- Balance score (0–100%) obtained in each condition, calculated as the arithmetic mean of the three individual test scores.

- Mean overall balance score (0–100%), calculated as the arithmetic mean of the 18 individual test scores.

- Somatosensory ratio, SOM= [condition-2 score]/ [condition-1 score]·100; a measure of the patient´s ability to use somatosensory information for maintenance of balance.

- Visual ratio, VIS= [condition-4 score]/ [condition-1 score] ·100; a measure of the patient´s ability to use visual information for maintenance of balance.

- Vestibular ratio, VEST= [condition-5 score]/ [condition -1 score] ·100; a measure of the patient´s ability to use vestibular information for maintenance of balance.

- Preference ratio, PREF= [condition-2+condition-5 score]/ [condition-3+condition-6 score] ·100; a measure of the patient´s reliance of visual information, even when that information is incorrect.

3.2.4   Caloric testing with Videonystagmography (VNG)

We realized the VNG for the diagnostic purposes at the time of diagnosis and also for the estimation of vestibular functions of VS patients over the follow-up years.

We have revealed the functionality of each ear and if a VS may be the cause of a dizziness or balance problems. To monitor the movements of the eyes, VNG goggles are placed around the eyes to record eye movements during testing.

1. Ocular Mobility;
2. Optokinetic Nystagmus;
3. Positional Nystagmus;
4. Caloric Testing.

For the caloric testing, we used 50 cc of water in 44 ºC to 30 ºC with the period of stimuli being 40 seconds following the indications of Bartual;[112] first, right ear with 44 ºC of water; second, left ear with 44 ºC of water; third, left ear with 30 ºC of water; fourth, right ear with 30 ºC of water. The interval between the each irrigation was 5 minutes and the patient was placed in the Hallpike position. The evaluation is both qualitative and quantitative, being most useful at slow phase of nystagmus.

For the interpretation, we used Jongkee´s[213] formula:
% Caloric paresis = 100 x [(LC + LW) - (RC + RW)/(LC + LW + RC + RW)].
The strength of left-beating nystagmus to right-beat calculated:
% Directional preponderance (DP) = 100 x [(LC + RW) - (RC + LW)/ (LC + LW+RC+RW.
Greater than 30% of directional preponderance is considered to be abnormal, although this is a rather nonspecific finding in isolation.   The result is said to be normal when this index is lower than 25%. In turn, the vestibular areflexia (100% canalicular paralysis) is considered if there is no response to cold water.

3.2.5   Otoacoustic emissions

As a screening tool to determine the presence or absence of cochlear function in VS patients with different sizes of the VS tumour, we have investigated the results of DPOAEs by the sounds emitted in response to two simultaneous tones of different frequencies. Each test has been performed by the audiologist in a special cabin designed for OAE.

The technique of performing of DPOAE starts from inserting a properly sized probe, according to ear canal volume, with a soft flexible tip to obtain a seal. Stimuli consisted of two pure tones at two frequencies (i.e., f1, f2 [f2>f1]) and two intensity levels (i.e., L1, L2). The relationship between L1-L2 and f1-f2 dictates the frequency response. An f1/f2 ratio yields the greatest DPOAEs at 1.2 for low and high frequencies and at 1.3 for medium frequencies.

In order to obtain or yield an optimal response, intensities are tuned up so that L1 equals or exceeds L2. Lowering the absolute intensity of the stimulus renders the DPOAEs more sensitive to abnormality. A setting of 65/55 dB SPL L1/L2 is frequently used.

Responses are usually most robust and recorded at the emitted frequency of 2 f1–f2; however, they generally are charted according to f2 because that region approximates the cochlear frequency region generating the response. The result we have registered to our database is simple "present" or "absent" of response to stimuli.

3.2.6   Auditory Brainstem Response (ABR) audiometry

Auditory brainstem response was performed with the Nicolet Viking IV (Nicolet Biomedical Instrument Inc). Active electrodes were attached to the ipsilateral mastoid region and were referenced to a vertex electrode. A ground electrode was placed on the forehead. The latencies of wave I and wave V, the I-V interpeak interval, the interaural latency difference of waves V (ILD V) and I-III, III-V the interaural differences between I-V interpeak intervals (ID I-V) were evaluated. The interaural differences were determined by subtracting the value of the left side from the value of the right side (Table 5).

Wave	Media	DS (±)	Wave	Media	DS (±)
I	1.7	0.15	I-II	2.1	0.15
II	2.8	0.17	I-V	4	0.23
III	3.9	0.19	III-IV	1.2	0.16
IV	5.1	0.24	III-V	1.9	0.18
V	5.7	0.25	IV-V	0.7	0.19
VI	7.3	0.24	V-VI	1.5	0.21

Table 5. The normal value of waves in ABR (CHUS)

Results were considered normal if the interaural difference was 0,2 milliseconds (ms) or less for the wave I-V IPLs. Results were considered borderline if the interaural difference for the wave I-V IPLs was between 0.2 and 0.3 ms. If the interaural difference was 0.3 ms or greater for the wave I-V IPLs, ABR results were considered abnormal. Also the absence of wave III-V or the absence of ABR was considered suggestive of retrocochlear pathology.

3.2.7   Vestibular Evoked Myogenic Potentials (VEMP) testing

The VEMPS has been performed like other tests have been performed in the otolaryngology outpatient department of CHUS. The test records information using an evoked response laptop, a sound generator, and surface electrodes to pick up neck muscle activation or other muscles, if this is of interest.

There are different methods of obtaining the VEMP. Our method of obtaining activation is to have patients sit upright with their chin turned over the contralateral shoulder to tense the SCM muscle.

Electrode montage for VEMPs records information in the following places:

- The ground electrode placed on the forehead;
- The reference electrode placed on the sternum;
- Active electrodes to the medial third of SCM muscle.

We explained to the patient to sit in an upright position and to rotate the chin to the opposite side while trying to tighten the neck muscles. The device has visual feedback that

indicates whether the intensity of muscle contraction is satisfactory (50 - 200µV). An average we have realized is150 stimuli in each ear with clicks at 99 with the duration of 0.1 ms. In interpretation, we have focused primarily on P1/N1 (P13/N23) amplitude measurements or threshold asymmetries between the right and left sides. Side-to-side differences in VEMP amplitude as an asymmetry ratio we have calculated with the following formulas:

Asymmetry Ratio = $100 (A_L - A_R)/(A_L + A_R)$

Where A_L equals the peak-to-peak amplitude (P1/N1) on the left side and A_R equals the peak-to-peak amplitude on the right side.

We have considered normal AR to be less than 35% [211].

3.2.8   Magnetic Resonance Imaging

Our group of patients were being followed up over the years, therefore in each revision in the ENT department, they were directed to the Radiology Department to perform an MRI scan for comparing the size of the VS with the previous MRI. All MRI scans of the VS patients were performed with gadolinium contrast.

According to the radiologists of CHUS, to enable an accurate and consistent comparison of findings on MRI images, tumour size is defined by calculating the mean intracranial diameter according to the measurements along three easily defined axes on Gd-enhanced T_1-weighted images.

Thus, the maximum anteroposterior and mediolateral distances were measured on axial images, parallel and perpendicular to the sagittal plane. The maximum craniocaudal diameter was determined by assessing coronal images.

The mean diameter as well as the greatest intracranial dimension was noted for each tumor. A decrease or increase in size was regarded as significant if the change of mean diameter was at least 2mm. This cutoff was chosen based on limitations in spatial resolution of the standard 1.5-tesla MR imaging used for most follow-up studies. Intracanalicular tumors, without intracranial extension, were measured in all three dimensions, with a change in size being defined as significant if the transverse diameter had decreased or increased 2mm or more.

From the radiologist's report, we always picked up the maximal size of the VS. For example, according to above measurement methods, if they reported the following dimensions: 22x17x14mm in this case as the maximum size of the tumor, in the follow-up revision we registered it to be 22mm.

Moreover, by using the previous reports of the radiologists, we compared the size of the VS tumor with current and primary scan. In this way, we had a size difference for each follow-up year.

All the information in numbers from the radiologist's reports were downloaded to the Microsoft Excel 2007 file.

Results

4   Results

4.1.1   Demographic and Epidemiological characteristics of patients with VS

4.1.2 Gender

A current study included 107 (100.0%) patients who attended to the Santiago de Compostela University Hospital for the period between February 21, 1992 and February 26, 2013 with the overall average observation period of 56.52 ±10.79 (range 25.02-71.74) months. Among the 107 (100.0%) patients, there were 57 (53.8%) females and 50 (46.2%) males, (e.g. see fig. 53) including 1 (0.9%) male patient with a bilateral VS due to NF2. Because of its genetic origin, we analyzed the bilateral VS separately and we will describe it at the end of the results.
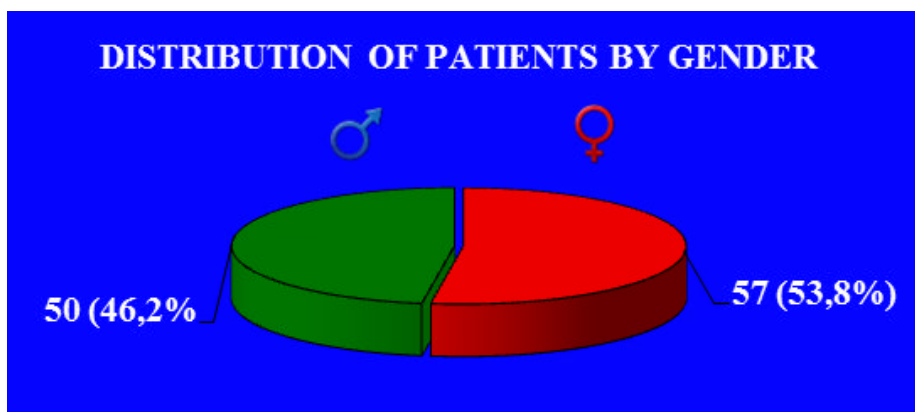
Figure 53. Chart showing the distribution of patients by gender

4.1.3   Age

Among investigated unilateral VS patients there were 57 (53,8%) females with the median age of 57,45 ±14,24 (range, 24-86) and 49 (46, 2%) males with median age of 56,16 ±15,14 (range 24-85). Although the number of females was slightly higher than the number of males, but this difference was statistically not significant (Table 6).

Gender	Number of cases & percentage	Age at the time of diagnosis		
		Median age/±	Age range	IQR
Female	57 (53, 8%)	57,51 ±14,20	24-86	48-69,0
Male	49 (46, 2%)	56,21 ±14,97	24-85	43,5-69,5
Total	106 (100,0%)	57,0 ±14,50	24-86	46,7-69,0

Table 6. Distribution of VS patients by gender

4.2 Clinic Characteristics of patients with VS

4.2.1 Primary symptom

First of all, we have revealed the primary symptoms of a VS which brought the patient to the physician (Table 7). In the majority of cases, 68 (64.1%), the primary symptom of a VS was hearing loss in the affected ear. The second major presenting symptom of a VS was tinnitus. The first sign of a VS in 24 (22.1%) of the patients was the complaint of having tinnitus (Table 7).

Primary sign of VS	Number of patients	Percentage
Hearing loss	68	64,1%
Tinnitus	24	22, 1%
Vertigo	9	8, 3%
Unsteadiness	4	3, 7%
Dizziness	1	0,9%
Total	106	100,0%

Table 7. Distribution of patients regarding the type of presenting symptoms of a VS

4.2.2 Symptoms at the time of diagnosis

Apart from the symptoms of presentation reported by patients, there were additional symptoms found at the oto-neurologic examination which immediately brought about their diagnosis.

In 11 (16.1%) out of 68 (63.2%) patients, the hearing loss was the only presenting symptom of a VS and there were no any other symptoms at the time of diagnosis. But in 54 (59.0%) of the patients with hearing loss, the tinnitus and vestibular symptoms presented were associated with hearing loss.

Only in one case (0.94%) out of 106 patients, did the tinnitus purely present a VS at the pretreatment stage. In contrast, in 23 (21.6%) cases of hearing loss, vestibular and other symptoms, were associated secondly to tinnitus. The cases of vertigo and unsteadiness

never presented as an only sign of a VS and the patients were always associated with either symptom. But in the case of one (0.94%) patient, the dizziness was purely presented as a VS. The detailed clinical symptoms and their association can be seen in Table 8.

Presenting symptom	Additional symptoms found at the time of diagnosis		
Hearing loss (68)	Only hearing loss (11)	
	Tinnitus (40)	Only tinnitus (26)
		Instability and/or vertigo (10)
		Hypoesthesia in Ramsay-Hunt area (2)
		Instability and hypoesthesia in R-H area (1)
		Vertigo and facial palsy (1)
	Vertigo, dizziness and/or instability (14)	Only vertigo, dizziness and/o instability (13)
		Dysphony (1)
	Other: earache (1), pain in hemifacial area (1) and lack of speech indelibility (1).	
Tinnitus (24)	Only tinnitus (1)	
	Hearing loss (19)	Only hearing loss (18)
		Headache (1)
	Other: vertigo (1), instability (1), plugged ear (1) and dizziness, nausea and vomiting (1)	
Dizziness (1)	Only dizziness (1)	
Instability (4)	Hearing loss (1)	
	Hearing loss, dizziness and loss of consciousness (1)	
	Tinnitus (1)	
	Clumsiness of right hemisphere and facial paresis (1)	
Vertigo (9)	Hearing loss (6)	Only hearing loss (3)
		Instability (1), tinnitus (1) and hypoesthesia in Ramsay-Hunt area (1)
	Tinnitus (2)	
	Instability (1)	

Table 8. Distribution of presenting symptoms (which brought the patient to a physician) and symptoms found at the time of diagnosis of a VS

4.1.1. Side of the lesion.

According to the gadolinium contrast and the enhanced MRI, a total of 55 (51.9%) patients presented with a right-sided VS and 51 (48.1%) patients presented with a left-sided VS. Among the patients with a right VS, there were 30 females (52.6%) and 25 males (50%). In a group of patients who presented with a left-sided VS, there were 27 females (47.4%) and 24 males (51.0%). We did not find an association between the side of affection and gender (p value =0.87 (Chi- squared test)).

4.2.3 Localization of VS

Regarding the localization of a tumor, there were, in general, 25 (23.6%) patients who presented with an extracanalicular VS, 41 (38.7%) who presented with a pintracanalicular VS, and 40 (37.7%) patients who presented with an intra-extracanalicular VS. Among the patients with an intracanalicular VS, there were 27 (65.8%) females and 14 (34.1%) males. In a group of patients with an intra-extracanalicular VS, there were 19 (47.5%) females and 21 (52.5%) males. In Table 10, is the presentation of distribution of patients regarding the localization of a VS.

Patients			Localization of VS			Total
			Extracanalicular	Intracanalicular	Intra-extracanalicular	
Gender	Female	Number of gender	11(19,3%)	27(44,4%)	19(33,3%)	57
		% of affected side	44,0%	65,9%	47,5%	53,8%
	Male	Number of gender	14 (28,6%)	14(28,6%)	21(42,9%)	49
		% of affected side	56,0%	34,1%	52,5%	46,2%
Total		Number of gender	25(23,6%)	41(38,7%)	40(37,7%)	106
		% of affected side	**100%**	**100%**	**100%**	100%

Table 9. Distribution of VS patients regarding gender and localization of a VS

In order to know if there is any correlation between the localization of a VS and the gender of the patients, we have applied the Chi-squared test which didn't show statistical significance (p-value 0.09).

The following graph 2 illustrates the frequency of VS related symptoms and information regarding the localization of a VS.
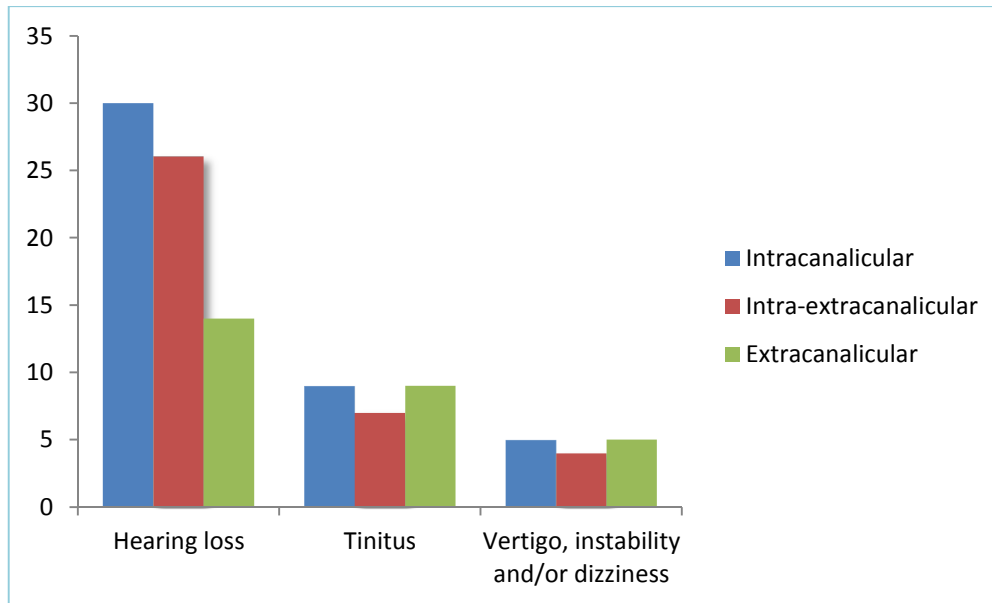
Figure 54. Distribution of presenting symptoms regarding the localization of the tumor

The plotted graph above shows a visual relationship between localization and primary symptoms of a VS and the applied two tailed Pearson and Spearman test equally showing the significant relationship between localization and initial symptoms ($p=0.01$).

4.3 Exploration

4.3.1 Audiologic Testing

4.3.1.1 Pure Tone Audiometry

4.3.1.1.1 Pure Tone Thresholds

We found that in the cases of the 68 (63.5%) patients, the early symptom of a VS noticed by the patients was hearing loss. But the loss of hearing was not always the patient's reason for coming to the hospital; therefore, in diagnostics testing, we have revealed 96 (90.56%) patients with hearing loss. Among the patients with hearing loss, there were 51 (53.1%) females with the mean PTA of 64.93dB and 45 (46.8%) males with a mean PTA of 60.96dB. Ten (8.4%) patients presented with a normal PTA (e.g. see table 10).

Hearing level at diagnostic stage	Number of patients	Percentage
SNHL	89	83,9%
Deafness	7	6,6%
Normal hearing	10	8,4%
Total	106	100%

Table 1. The results of early conventional audiometry of patients with a VS

As we see from the above table, at the time of diagnosis, a total of 96 (90.56%) patients presented with hearing loss, including 89 (83.9%) SNHL. Seven patients (6.6%) with deafness had a PTA of 58.80dB. The overall average PTA was lower in patients under 40 years (49.94 ±32.69 (Range12.50-120)) than patients aged above 40 years (60.54 ±28.07 (Range 13-120)). Due to the small sample size (15 (14.1%)), for the group of patients under 40, the T-test did not show a significant difference p= 0.10907.

4.3.1.2 Audiometric Configuration

During the data collection, we also registered the shape of audiometric configuration of VS patients with hearing loss and the shapes were significantly varied. The audiometric configurations that comprised the average thresholds used to define each category were described as sloping, rising or flat. The audiometric configuration was considered sloping

when the thresholds occurred at equal or successively higher levels from 250 and 8000 Hz >20dB. We determined that the configurations were rising when thresholds occurred at equal or successively lower levels from 250 to 8000 Hz. The difference between thresholds at 250 and 8000 Hz was always >20 dB and the configurations were flat when thresholds across the frequencies did not vary more than 20 dB from each other (e.g. see table 11).

Audiometric configuration	n	%	Size of VS mm	
			Average/±	Range
Sloping or hearing loss mostly in higher frequencies	61	63,5%	14.48 ±7.1	2-34
Rising or hearing loss in low frequencies	5	5,2%	17,4 ±18.2	7-50
Flat or pantonal hearing loss	24	25%	14,3 ±8.68	4-35
Other	6	6,3%	15.1 ±17.4	10-30
Total	96	100%		

Table 2. Type of audiometric configuration in a group of VS patients

The data plotted above shows that the majority of VS patients (63.5%) in the baseline stage showed NSHL with a slopping configuration, and 5.0% of the patients presented with a rising audiometric configuration. The flat or pantonal hearing loss was observed in 25% of the cases of VS. The frequency of other audiometric configurations, like the U-shaped/Basin-shaped, mountain-shaped, etc., registered in 6.3% of the VS patients.

Patients with sloping hearing loss included 25 (41%) with an intracanalicular VS, 24 (39.3%) with an intra-extracanalicular VS and 12 (19.6%) of the patients with an extracanalicular VS series. Patients with pantonal hearing loss included 11 (45.8%) of those with an intracanalicular VS, 4 (16%) with an extracanalicular VS and 9 (37.5%) with an intra-extracanalicular VS. Of the patients (5(5.2%)) with a rising audiometric configuration, 3 (4.9%) presented with an intracanalicular VS and 2 (3.2%) had an intra-extracanalicular VS.

4.3.1.2.1 The association between demographic and clinical data

In order to reveal the prevalence of hearing loss by age group and gender among the patients with a VS, we have conducted a comparative analysis between female and male patients as seen in Table 12.

Gender	Total number of patients	PTA/dB				
		Mean	Median	Minimum	Maximum	Std. Dev
Female	57	60,26	55,0	16,25	120,00	29,52
Male	49	57,10	52,50	3,75	120,00	28,50
Total	106	58,68	53,12	3,75	120,00	28,96

Table 3. Comparative data of hearing loss at diagnosis and gender of the patients

As we see from Table 13, the mean values of a PTA in both groups do not differ significantly. Moreover, applied statistical tests (t-Student) did not show a statistically significant difference between the two groups in terms of gender and hearing loss (p = 0.47).

In order to reveal if the value of PTA depends on the localization of a VS, we have compared the PTA in each type of localization. Graph 5 illustrates the mean and median values of a PTA in three different kinds of a localization where we can observe the difference in PTA between types of VS localizations.

The overall difference between the three types of localization groups were found using the ANOVA test, and the results were significantly different (p=0.014). According to Bonferroni, with multiple comparisons, there were statistical significant differences between intracanalicular and intra-extracanalicular types of localization (p=0.016).

Between the extracanalicular and intra-extracanalicular (p=0.750) and between the intracanalicular and extracanalicular (p=0.200) group of localization, there was no statistical significant difference (e.g. see table 13).

Localization of VS	N/%	PTA/dB		
		Mean	Median	St. Dev
Extracanalicular	25 (23,5)	61,7400	55,50	25,58
Intracanalicular	41 (38,67)	48,87	43,75	25,47
Intra-Extracanalicular	40 (37,73)	67,13	58,75	31,77

Table 4. The value of PTA regarding the localization of a VS

As we see from Table 13, the overall average PTA of an intracanalicular VS ≤50dB, while the overall average PTA of an extracanalicular and an intra-extracanalicular VS is ≥60dB.

4.3.1.3 Auditory Brainstem Responses (ABR)

Although the ABR is not considered as a gold standard diagnostic test for a VS, the test is usually performed before the MRI, especially when the patient presents with asymmetric hearing loss and tinnitus along with vestibular symptoms.

In our series, we found 43 (40.5%) VS cases with the ABR testing which was performed at the diagnostic stage. Among those tested, there were 25 (58.1%) females at the mean age of 51.17 (Range 69.73-24.75) with a mean PTA of 54.43 ±26.27 (Range 16.25-111.25)dB and a mean sized VS of 1.50 ±8.62 (Range 2-34mm). There were 18 (41.9%) males at the mean age of 58.33, the mean PTA of 60.60 ±31.63 (Range 12.50-120dB) and with a mean sized VS of 17.44 ±8.47 (Range 2-35mm).

The overall averages for both groups were 56.71 ±28.5 (Range 3.75-120dB) and the initial size of the VSs was 14.56 ±8.46 (2-35mm). In the group, 21 (48.8%) patients presented with an intracanalicular VS, 7 (16.2%) presented with an extracanalicular VS and 16 (37.2%) patients presented with an intra-extracaniclcluar VS.

In ABR testing, the morphology and latency of waves, including the interaural latency of wave V (IA5), were under our main focus.

4.3.1.3.1   Morphology

Among the 43 results, there were 20 (46.9%)   patients who presented with waveform morphology, in 8 (18.5%) cases of patients, the waveform morphology was abnormal and in 17 (39.5%) patients, the waveform morphology was absent. Patients who were absent of waveform morphology had more profound hearing loss, their average overall PTA was 70.1 ± 25.20 (Range 30-120)dB, and the size of their VS averaged 15.1 ±7.8 (4-35mm).

4.3.1.3.2   Waveform latencies

The average latency of waveforms I-V, I-III, III-V and the interaural difference of latency wave V are all presented in Table 14.

ABR waves	Latency (ms)			
	Average	**Minimal**	**Maximal**	**Std. Dev**
I-V	4,81	3,5	6,48	0,90
I-III	2,74	2,1	4,1	0,89
III-V	2,05	1,64	2,72	0,30
V - interaural	0,70	0,08	4,0	0,73

Table 5. The results of ABR waveform latencies

In the cases of 35 (81.3%) patients, the waveform I-V, I-III, III-V were all delayed, and in 36 (83.7%) patients, the interaural latency difference of wave V was pathologic. Seven (16.2%) patients (out of 43 VS patients) presented with completely normal ABRs while having a tumor with the average size of 10 ±8.99 (Range 2-32.5mm). We found abnormal ABRs in cases of intracanalicular and intra-extracanalicular types of VSs, p=0.001 (One Sample Kolmogorov-Smirnov Test).

4.3.1.3.3 Association between demographic and clinical data

Among 43 available ABR testing results, there were 21 female and 22 male patients and their average age was 55.6 years. We have compared the prevalence of females and males in respect to ABR testing results. At first, we checked the absolute latencies of I-V, I-III, III-V and we found that 83.7% of the patients have delayed latency. Among them 39.5% were female (out of 43 patients) and 44.1% were male patients. The detailed difference can be seen in Table 15.

Gender		Latency I-V		Latency I-III		Latency III-V	
		Normal	Pathologic	Normal	Pathologic	Normal	Pathologic
Female	N	4/43	17/43	3/43	18/43	11/43	10/43
	%	9,3%	39,5%	6,97%	41,8%	25,5%	23,2%
Male	N	3	19	4	18	7	17
	%	6,97%	44,1%	9,3%	41,8%	16,2%	39,5%
Total	N	7	36	7/43	36	18	25
	%	16,2%	83,7%	16,2%	83,7%	41,8%	58,1%

Table 6. The prevalence of abnormal ABR latencies regarding the gender of VS patients

As we see from Table 15, more than 80.0% of the patients showed a pathologic ABR in latencies I-V and I-III (83.7%) but in the cases with III-V waves, less pathologic results were found (58.1%). Apart from the latencies of I-V, I-III, III-V waves, we have separately performed comparisons of male to female ratios regarding ABR interaural latency of wave V (IT5), which can be seen in Table 16.

		IT5		Total
		Normal	Pathologic	
Gender	Male	5	16	21
	Female	2	20	22
Total		7	36	

Table 7. Female and male proportion and results of IT5

With the purpose of defining if there is any association, we have performed a comparative analysis of ABR results among three different variables: the IT5, the localization and the size of the tumor (e.g. see table 17).

Localization	N (%)	Size of the tumor	N	IT5	
				Normal	**Pathologic**
Extracanalicular	8 (18,6)	≤ 10	1	0	1
		11-20	3	0	3
		21-30	1	0	1
		> 30	3	0	3
Intracanalicular	17 (39,5%)	≤ 10	13	5	8
		11-20	4	0	4
		21-30	0		
		> 30	0		
Intra-extracanalicular	18 (41,9)	≤ 10	2	2	0
		11-20	8	0	8
		21-30	5	0	5
		> 30	3	0	3
Total	43		43	7	36
Percentage	100%		100%	16,3%	83,7%

Table 8. Tumor size by ABR Interval Latency Difference for wave V (IT5)

From Table 17, we can see the results of the ABR test in respect to the localization of the tumor, where we have found normal results in smaller tumors, both in intracanalicular and intra-extracanalicular locations. Thus, there are strong correlations between the size of the tumor and IT5 in the level of $p < 0.001$ (Chi- squared test).

4.3.1.4 Otoacoustic Emissions

We have found 28 (26.1%) available reports of DPOAE testing performed at the diagnostic stage. Among them there were 16 (59.2%) females and 11 (40.7%) males. The average overall age of this group was 56.30 (Range 24-81). The average size of PTA was 56.92 ±34.6 (Range 3.72-120)dB and the average size of the VS tumor was 15.57 ±8.6 (Range 2-35mm). In this group, there were 15 (14.1% out of 106) out of 28 patients who presented with OAE. In 13 (12.1%) patient cases, the OAE was absent (e.g. see table 18).

DPOAE	n	Gender		Localization of tumor		Pure Tone Average (dB)
		F(%)	M(%)	Intra-canalicular	Extracanalicular or Intr-extracanalicular	
Presents	15	8(53,6)	7(47%)	7 (47%)	8 (53,7%)	60,5
Absents	13	9(70%)	4(26,8%)	6 (46,1%)	7 (25%)	63,4
Total /%	28 (100%)	17 (61%)	11 (39,2%)	13 (46,5%)	15 (53,5%)	61,95

Table 9. Distribution of VS patients according to results of OAE

The 7 (6.5% out of 106) patients with the absence of an OAE presented with a VS more than 20mm, located extracanalicular or intra-extracanalicular, and their overall average PTA was 70.22 ±28.66 (Range 30-120)dB. In the cases which remained, 6 (5.6%) patients presented with intracanalicular VSs more than 10mm in size (Table 19). Due to the small sample size of patients, the statistical test regarding localization and size of VSs with OAE was not significant.

4.3.2 Vestibular and Balance Testing
4.3.2.1 Craneocorpography

In 68 (64.1%) cases, the patients were presented with a CCG test performed at the time of diagnosis. Out of the 68 cases, there were 39 (57.3%) female patients and 29 (39.7%) male patients. The average overall PTA of this group was 55.04 ±24.24 (Range 12.5-117.5) and average overall size of the VSs was 16.98 ±10.18 (Range 2-50mm) (e.g. see table 19).

CCG	Number of patients		Size of VS (mm)		Total
	Female	**Male**	**Mean/SD**	**Range**	**n (%)**
Type I	9 (23%)	10 (34%)	16,55 ±11,24	4-50	19 (27)
Type II	20 (51,2%)	12 (41%)	16 ±9,58	3-50	32 (47)
Type III	3 (7,6%)	5 (17%)	14,08 ±8,2	2-26	8 (11,7)
Type IV	7 (17,9%)	2 (6,8%)	22 ±12,14	8-35	9 (13,2)
Total	39 (100%)	29 (100%)	16,98 ±10,18	2-50	68 (100%)

Table 19. Results of CCG testing regarding the gender of the patients

As seen in Table 20 above, the average overall size of the VS in a Type IV CCG (corresponding to VS) is higher than a Type I (corresponding to normal CCG). Students who performed the t-test showed p=0.87183 due to a small sample size in a group of patients who presented with CCG IV. Likewise in PTA, the average PTA in the Type I group was 56.28 ±31.75 (Range 30-120). In Type IV 81.9 ±32.94 (Range 33.75-120), the p-value was not significant (p=0.96) due to the small sample sizes in the CCG Type IV group.

We also compared the clinical picture with the results of the CCG to determine whether there is any association between them (e.g. see table 20).

Clinical presentation	Number of patients in each type of CCG				Total n (%)
	Type I	Type II	Type III	Type IV	
Tinnitus	11	15	4	2	32 (47,0)
Vertigo	5	6	2	3	16 (23,5)
Imbalance	2	9	1	4	16 (23,5)
Dizziness	1	2	1	0	4 (5,8)
Total (n/%)	19 (27%)	32 (46%)	8 (11%)	9 (13%)	68 (100)

Table 10. Association of CCG with clinical picture of VS

As we see from the table above, the CCG Type IV corresponding to a VS was observed only in 9 (13.2%) cases.

Apart from the above-mentioned demographic and clinical association of a VS with CCG, we have analyzed the location of the tumor and its relationship with CCG. In the cases of extracanalicular location of a VS, there were 5 (4.71%) patients with Type I, 8 (7.5%) patients with Type II, 1 (0.94) patient with Type III and 4 (3.77%) patients with an extracanalicular VS registered Type IV CCG. In the cases of intracanalicular location of a VS, there were 8 (7.5%) patients with Type I, 13 (12.2%) patients with Type II, 2 (1.8%) patients with Type III, and in 2 (1.8%) patients with Type IV were registered with CCG.

The number of patients with a VS with an intra-extracanalicular location were 6 (5.6%) with Type II, 11(10.3%) patients with Type II, 5 (4.71%) patients with Type III and in 3 (2.8%) cases, the patients were registered with a Type IV CCG.

We did not find any significant association between localizations, size of VS and the CCG. Also there were no associations found between the CCG and the clinical presentations of a vestibular schwannoma.

4.3.2.2 Computerized Dynamic Posturography

The 60 (56.6%) patients presented with paper-based CDP results performed at the time of diagnosis. We have analyzed the data from the different conditions, and sensory analysis by gender and age within these groups. Values obtained are presented in tables and graphs. The overall results of CDP conditions can be seen in Table 21.

	Overall balance	Condition 5	Condition 6	VEST
Average	68,36	46,36	46,52	49,5
Median	70	46,6	48	48,5
Standard deviation	10.94	12,72	14,14	16,26
Maximum	86	79	79	149
Minimum	27	0	0	1

Table 11. Descriptive statistics of SOT for all 60 (56,6%) patients

We have compared the number of normal CDP results with the pathologic balance in different conditions of SOT. In the global balance cases, there are 38 (63.3%) patients who have had normal overall balance and in the cases of 22 (36.6%) patients, the overall balance was pathologic. In condition 5, there are 26 (43.3%) patients who presented with normal results and 32 (53.3%) patients who presented with pathologic results. In Condition 6, 32 (55.0%) patients are shown to have normal overall balance and 27 (45%) patients are shown to be pathologic.
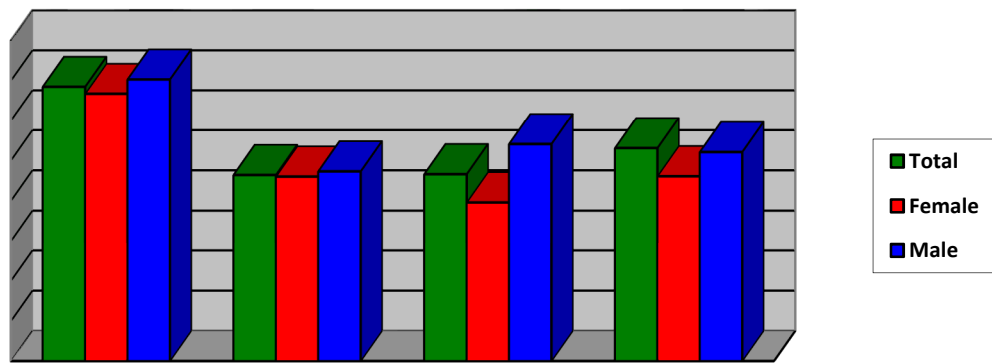
Figure 55. Graphical view of the average balance reached in the different conditions of SOT

Table 22 shows the existence of significant difference for the condition 6 and chart 5 also showing that percentage of balance slightly higher for males among the population.

The following Table 22 illustrates the comparative results of SOT in males and females.

	n	Overall balance/±	Condition 5 /±	Condition 6 /±	VEST /±
Female	31	66,53 ±10,43	44,81 ±19,47	39,84 ±21,39	51,52 ±29,1
Male	29	70,24 ±11,5	47,30 ±17,5	54,00 ±16,6	52,07 ±18,58

Table 12. Overall balance and CDP conditions regarding the gender of VS patients

By means of the t-Student, we have compared the female population with males and found significant difference in condition 6 (p= 0.005).

4.3.2.3 Caloric Testing

We have found 67 (63.2%) cases of a VS with available caloric testing. Among the cases, there were 36 (53.71%) females with the mean age of 56.91 (Range 24.16-58.55) years and 31 (46.2%) males with the mean age of 57.82 (Range 29.03-81.33) years.

The average overall PTA in the female group was 61.79 ±30.69 (Range16-120)dB and the size of their VSs was 14.82 ±10.36 (Range 2-50mm). Along with this group, a group of males presented with an average overall PTA of 58.64 ±28.39 (Range 3.75-120)dB and an average overall VS size of 16.60 ±8.46 (Range 2-35mm).

In general, we found 37 (55.2%) pathologic responses and 30 (44.8%) normal bithermal caloric responses. Among patients with pathologic responses, there were 4 (5.9%) patients with vestibular arreflexia. In a group with pathologic responses there were 23 (63.8%) females and 14 (46.4%) males. The overall percentage of normal results is the following: pathologic ratio was 44.8:55.2 with females (63.8%) being predominate over males (46.4%) . The results of the caloric tests for 67 patients can be seen in Table 23.

Vestibular testing with WNG	Hypofunction		Reflectivity		Total
	Normal	Pathologic	Normal	Pathologic	
Number of patients	30	37	29	34	67
Percentage	44,7	55,3	43,3	56,7	100

Table 23. Distribution of patients according to caloric testing results

In the female group, the average overall PTA (61.79 ±30.69) was slightly higher than those in males (58.64 ±28.39), but on the other hand, the males presented with a little bit higher overall size of VSs (16,60 ±8,46) than females (14,82 ±10,36).

The majority of patients (78.3%) who presented with abnormal caloric responses had intracanalicular or intra-extracanalicular VSs and their overall average PTA was 67,24 ±32.66 (Range 12.50-120)dB. The overall average size of the VSs was 16.82 ±10.02 (Range 4-50mm). Patients with normal caloric responses presented with a significantly lower average PTA (49.13 ±21.78 (3.75-88.78)dB) and (13.77 ±7.96 (2-32.50)) size of VS.

4.3.2.4   VEMPs

In the cases of VEMPs testing, we have 21 (19.8%) reports of testing performed at the time of diagnosis. Among the patients, there were 11 (52.38%) females and 10 (47.61%) males.

Results

The results of analysis showed that in the cases of 12 (57.14%) patients, the VEMPs was presented in lesion side and in the cases of nine (42.8%) patients, the VEMPs test was absent. Among the patients without VEMPs, one (4.7%) patient did not show a response on the VS tumor side.

Among patients who presented with a VEMPs response, there were 5 (23.8%) females and 6 males (28.7%). Among the patients with an absence of a VEMPs response, there were 6 (28.5%) female patients and 4 (19.0%) male patients. Also, we registered the Asymmetry Ratio (AR) between the two ears, which indicates the difference between right or left VEMPs. The average asymmetry for all 12 (57.1%) patients who presented with a response to the VEMPs stimuli was 33.94% (±24.0) with the maximum being 87.0% and the minimum being 6.2%. In the Asymmetry ratio of VEMPs in patients who presented with VEMPs, there are 6 (28.5%) patients out of 21 (100.0%) whose test showed normal.

We performed a comparative analysis to establish if there were some associations between VEMPs and other tests and we found no clear association between the results of VEMPs and the localization of a VS (Table 24).

Gender	VEMPs Present					VEMPs Absent					Total
	n	PTA/ SD	Localization			n	PTA/ SD	Localization			
			Int	Ext	Int-Ext			Int	Ext	Int-Ext	
Female	6	42,2 ±15,9	2	0	4	5	60,55 ±4,5	3	0	2	11
Male	6	45,2 ±18,56	4	1	1	4	44,8 ±21,3	2	1	1	10
Total	12	41,5 ±15,9	6	1	5	9	55,5 ±33,76	5	1	3	21
%	57,1		28,5	4,76	23,8	42,8		23,8	4,76	14,2	100

Table 13. Association between VEMPs, PTA regarding the localization of VS

From the information in Table 24, we can see that there is no relationship between the VEMPs and the localization of a VS. Perhaps it is due to our small sample size of patients who have undergone the VEMPs testing.

4.3.3   Imaging Tests

4.3.3.1   MRI

The results of the MRI analysis scans which determined the initial size of the VS in 106 (99.0%) patients was performed at the time of diagnosis and is presented in the following Table 25.

Gender	Total number of patients	Size of the tumor/mm				
		Mean	Median	Minimum	Maximum	Std. Dev
Female	57	14,96	12,00	2,00	50,00	10,16
Male	49	17,37	17,00	2,00	45,00	9,05
Total	106	16,08	15,00	2,00	50,00	9,69

Table 14. The size of tumor regarding the gender of the patient

We have observed that the mean size of the tumor is a little bit bigger in the cases of males 17.37 (±9.05) than in the cases of females 14.96 (±10.16). Particularly, this difference was more pronounced in patients ≤ 40 years old (21.7 ±12.21 (6-50mm)) and this difference was negatively correlated in older patients. Although the increased the age the tumor was a determinant of size, statistical tests (t-Student) didn't show any significant difference in the size of the tumor between the two genders.
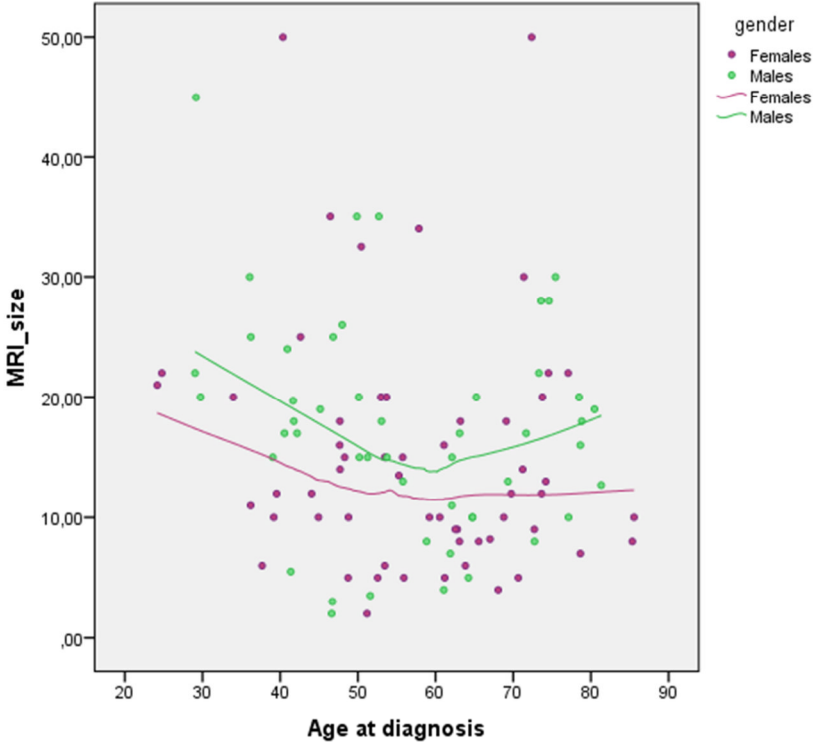
Figure 55. Shows the initial size of the VSs in regard to the age of the patients

The above graph shows the relationship between age and the size of the tumor at the time of diagnosis. Although the plotted samples are disperse, we can see a slight difference in males in presenting with a relatively larger VS.

4.4 Treatment

4.4.1 Wait-and-watch

The 67 (63.2%) patients were under a wait-and-watch scan. Among them, there were 36 (53.2%) females and 31 (46.3%) males. The average age of patients in this group were 59.21 ±14.35 (Range 24-85) and the average size of the VSs were 12.68 ±6.76 (Range 2-35). The overall average PTA and size of the VS for the wait-and-watch group is presented in the following table:

	Average / ±	Range
PTA	57,30 ±28,53	12-120
MRI	12,68 ±6,76	2-35

Table 15. The overall average PTA and size of VS in wait-and-watch group

The distribution of the patients regarding localization was the following: out of 67 (100.0%) patients, 35 (52.2%) presented with intracanalicular VSs, 10 (14.9%) patients presented with extracanalicular VSs, and 22 (32.8) patients presented with intra-extracanalicular VSs. Thus, the intracanalicular localization was a more frequent localization among patients in the wait-and-watch group and it dominated over extracanalicular and intra-extracanalicular types of VS localization.

4.4.2 Radiosurgery

At the diagnostic stage, there were 27 (25.5%) patients directed to GK Radiosurgery. Among them there were 15 (55.67%) females and 12 (44.4%) males. The average age of patients in this group was 56.82 ±14.30 (Range 24.75-78.48). The overall average PTA and size of the VS is presented in following table.

	Average / ±	Range
PTA	59.80 ±26,86	16,25-120
MRI	16,13 ±7,56	5-30

Table 16. The overall average PTA and size of VS in the GK Radiosurgery group

We have compared the size of tumors between females and males, which was slightly higher in females 14,86 ±8,06 than males 17,72 ±6,88 (p=0.064). The localization of a VS among the GK Radiosurgery group was the following: intracanalicular tumors 7 (25.9%), extracanalicular tumors 9 (33.3%), and intra-extracanalicular tumors were in 11 (40.74%) of the cases.

4.4.3 Conventional neurosurgery

In the group of patients under conventional neurosurgery, initially, there were 12 (11.32%) patients, including 6 (50.0%) females and 6 (50.0%) males. The average age of patients in this group was 43.78 ±9.28 (Range 29.16 – 57.85) years. The overall PTA and size of the VS is presented in the following table:

	Average / ±	**Range**
PTA	66.40 ±35.84	25.50-120
MRI	30.04 ±11.37	8-50

Table 17. The overall average PTA and size of VS in the Conventional neurosurgery group

Out of 12 patients, 5 (41.6%) presented with extracanalicular VSs and 7 (58.3%) patients presented with an intra-extracanalicular VS.

4.4.4 Association between the wait-and-watch and radiosurgery treatment groups

As we see from the table above, the stated results of the data of patients in three different groups slightly differs. The patients in the conventional neurosurgery group are younger than the wait-and-watch and GK radiosurgery group p=0.03 (ANOVA). The average age of patients in radiosurgery and the wait-and-watch group show no significant difference (p = 0.19) (t-Student). We do not find significant differences between genders in the three treatment groups. The overall average PTA in the wait-and-watch and GK radiosurgery groups show no significant difference.

As a main point of our objective, we compared only the wait-and-watch and HK radiosurgery groups. The overall average size and PTA in the watch-and-wait and GK radiosurgery treatment groups are presented in the following table below:

	Treat. groups	Mean ±	95% CI	
			Lower	**Upper**
Age (y)	Wait-and-watch	59,21 ±14,35	55,71	62,71
	Radiosurgery	56,82 ±14,30	51,17	62,48
PTA (dB)	Wait-and-watch	57,30 ±28,53	50,34	64,26
	Radiosurgery	59,80 ±26,86	49,18	70,34
MRI (mm)	Wait-and-watch	12,68 ±6,76	11,42	15,35
	Radiosurgery	16,13 ±7,56	13,14	19,12

Table 29. Comparative characteristics of age, PTA, and size of VS among wait-and-watch and GK radiosurgery groups

We found a significant statistical difference between the size of the tumor ($p = 0.002$; 95.0% CI of difference: -4.5602 <-2.75< -0.9398; two sided: 0.004) in the wait-and-watch and GK radiosurgery groups, but we did not find a statistical difference in PTA between the two groups ($p= 0.33$). The dot plot illustrates the comparative view of the overall average PTA and size of the tumor in three treatment groups (e.g. see fig. 6). The dashed line shows the average level (PTA and size of VS) for the three groups.
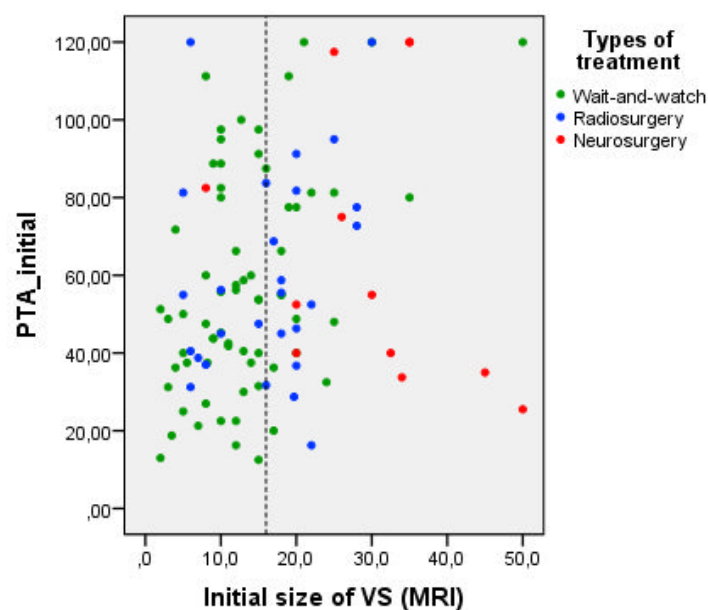
Figure 56. The value of MRI and PTA in three treatment groups

175

Also, the majority of patients (52.2%) in the wait-and-watch group presented with an intracanalicular VS. Although, there is a poor relationship between the two measurements (R-squared = 0.079), the majority of patients under the wait-and-watch control group presents tumors smaller than 15mm.

The initial average size of tumors in each group of treatment and the differences can be seen in the following graph (e.g. see fig 57).
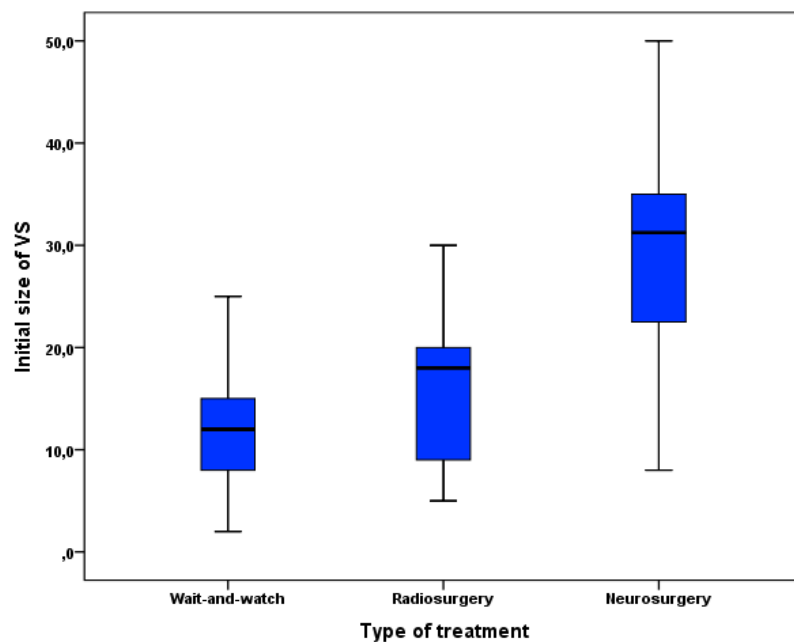
Figure 57. The average initial size of VS in 3 different treatment groups (p<0,001)

In order to find the differences for general comparison, we have used the two step ANOVA methods.

First of all, we performed a global comparison of the groups (all groups were not equal) and we have found that the differences between the groups were significant at the level of $p < 0.001$ (one-way ANOVA).

The mean size of the VS in the wait-and-watch group (12.68 ±6.76) was smaller than the size of the VS in the radiosurgery (16.13 ±7.56) group. This difference is statistically significant at the level of p= 0.014. The mean size of the VS in the neurosurgery group

(30.04 ±11.37) is much more significant than in both the wait-and-watch and radiosurgery groups (p < 0.001) (Bonferroni test).

4.5 Complications of treatment

By the last follow-up, overall, there were 42 (39.6%) patients who underwent GK Radiosurgery and 16 (15.1%) patients who were treated with Neurosurgery and 48 (45.2%) were still under the wait-and-watch control. The complications of a VS after Conventional Neurosurgery was obvious; therefore, we have exclusively analyzed the complications of GK Radiosurgery. According to the patient records and test results after first review (after one month of GK Radiosurgery), there were 61.90% (26/42) who did not present with any post-radiosurgery complications. However 38.1% (16/42) of the patients presented with either type of complications. Among them, the 11.09% (5/42) of patients presented with facial paresis, 2.3% (1/42) had facial palsy, 6.9% (3/42) became completely deaf, 2.3% (1/42) suffered significant hearing loss (more than 10dB), and 4.76% of the patients (2/42) complained of vertigo, which was not observed before the GK Radiosurgery. There were 4.76% (2/42) who complained of increased tinnitus after GK Radiosurgery. Also one (2.3%) patient complained of a permanent holocraneal headache after one week of GK Radiosurgery and later presented with atrophy of the cerebellar hemisphere in the revised MRI. In addition to the main complications, all the above-mentioned patients presented with headaches in varying intensities.

4.6 Follow up

As we mentioned before, after diagnosis and initial treatment, patients were under follow-up control. The first follow-up review after diagnosis, or baseline, was in six months and then one year, then three years and finally, five years, according to the follow-up stages. In our surveillance, we analyzed the data of patients for each stage of follow-up. In the last follow-up year, there were 6 (5.6%) patients who were lost before follow up. Including one patient from the neurosurgery group who died because of postoperative complications and severe postoperative infection. Two (1.8%) patients were lost before follow-up due to being in advanced age and 3 (2.8%) patients were relatively recently diagnosed and did not present data for the fifth year.

The overall average follow-up time for the three groups was 56.52 ±10.79 (Range 25.02-71.74) months. In Table 38, the follow-up times for each group are presented separately.

Treatment groups	Mean (±SD)	95% CI		Range
		Lower Bound	Upper Bound	
Wait-and-watch	55,30 ±11,92	52,39	58,20	46,19
GK Radiosurgery	58,60 ±9,22	54,95	62,25	35,57
Neurosurgery	58,70 ±5,7	55,06	62,34	18,64
Total	56,52 ±10,79	54,21	58,56	46,72

Table 18. Duration of overall follow up times in different treatment groups

Our photos show the initial diagnostic tests and establishing of a diagnosis of a VS. Usually, within the first 6 months, patients receive planned treatment and would be under post-treatment follow-up. But sometimes, for example, after one year of being under the wait-and-watch strategy, due to other factors (enlargement of the tumor, worsening of the clinical picture or a patient's desire) the initial treatment (wait-and-watch) is changed to radiosurgery, conventional surgery and/or from radiosurgery to conventional neurosurgery. The majority of these cases in our study are considered as a risk group. Therefore, we focused on the interval between diagnosis and treatment.

During the five years of follow-up there were 20 (18.86%) out 106 (100.0%) patients who had more than a six months interval from diagnosis to treatment (average 27.32 ±17.48 (Range 10.85-69.90) months) and we found changes from initial treatment. The average age of patients in this group was 54.61 ±13.27 (Range 39.05-74.20) including 8 (40.0%) female patients and 11 (55.0%) male patients.

The 12 (60.0%) out of 20 (100.0%) patients changed their treatment options because of tumor enlargement and worsening of the clinical picture. Among them, the five (25.0%) patients passed from wait-and-watch to conventional surgery and 8 (40.0%) patients passed from wait-and-watch to GK radiosurgery. The five (25.0%) patients passed from wait-and-watch to radiosurgery because of worsening of the clinical picture while the size of the VS was steady. Three (15.0%) patients remained within the first and third years of follow up and changed their treatment options by their own desires while having stable clinical pictures and tumor size in the follow-up frame. The dynamics of follow-up of the above-mentioned 20 patients is presented in Figure 58.
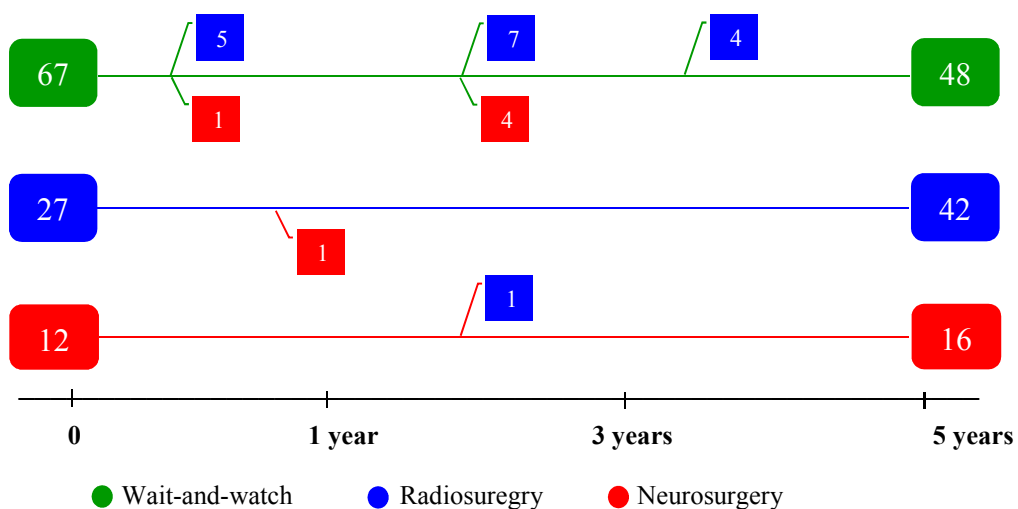
Figure 58. The dynamics of follow up of 106 VS patients

As we can see in the above figure, there is one (0.94%) patient within the first year from the radiosurgery group and passed on to the neurosurgery group. This patient was a 48 year old male with the initial size of his VS being 34mm, PTA was 75dB along with having tinnitus and the absence of an ABR response to click stimuli. In the beginning, he was under wait-and-watch control, but within the first year, he presented with tumor growth

(+35, 5mm), with a stable initial clinical picture and he was directed to conventional neurosurgery. The conventional neurosurgery was complicated with a CSF leak, facial palsy and complete hearing loss on the lesion side. In the postoperative review (third and sixth months), the clinical picture was stable and in MRI there was a 3mm mass compatible with a postoperative scar. However, after one year of postoperative review, the patient complained of the worsening of his tinnitus and presented vestibular symptoms. In the MRI, we detected the tumor growth, which measured 16mm, and the patient was directed to GK radiosurgery. In the last two years of post-radiosurgery follow-up, the VS remained steady (16mm) and the patient still occasionally feels the vestibular symptoms along with tinnitus.

As we mentioned before, due to the above-mentioned changes in each follow-up stages, we had a different number of patients in treatment groups; therefore, statistically, in addition to the final treatment approach (As-treated), we have also used the initial treatment approach (intention-to-treat), which allowed us to catch the risk groups.
We have exclusively compared the wait-and-watch and radiosurgery groups.

During the overall follow up period, there are a total of 42 (39.6%) patients who underwent GK Radiosurgery ("As-treated" analysis). After one month, all of them were reviewed in the Outpatient Unit of the Otolaryngology Department of CHUS. Among them there were 27 (64.2%) patients who do not show any complications related with GK Radiosurgery; however, there were 15 (35.7%) patients who presented with either type of complication. Among them, one (2.3%) had facial palsy, five (11.9%) had facial paresis, two (4.7) experienced deafness, three (4.7%) had hearing loss (worsening of hearing more than 15 dB), four (9.5%) had tinnitus, two (4.7) experienced vertigo, and one (2.3%) patient presented with atrophic changes of the cerebellar hemisphere.

4.6.1   Size of the tumor
4.6.1.1   Watch-and-wait group

The mean tumor size at presentation in the wait-and-watch group was 12.68 ±6.76mm. Among the 67 who had a VS, 11.9 (8/67) patients exhibited shrinkage, 58.2% (39/67) were stable, with no growth over the follow-up course, and 28.3% (19/67) of the VSs grew.

Among the 19 growing tumors, there were 13 (68.4%) males and 6 (31.57%) females and the average growth rate was 0.51mm per year.

The overall VS growth rate for the wait-and-watch group was 0.12mm per year (range 0-3). Among the patients with a tumor growth, there were 7.46% (5/67) of patients who eventually went to conventional neurosurgery, 17.9% (12/67) went to GK radiosurgery and one patient, due to minimal growth, preferred to remain under the wait-and-watch control. The size of the VS measured in each follow-up period and the initial overall average sizes of the VS in each follow-up period is presented in Table 31.

Follow up time	n	Average size of VS ±	95% CI	
			Lower Bound	**Upper Bound**
Initial	67	12,68 ±6,76	10,87	14,37
6 months	67	13,20 ±7,79	11,16	15,23
1 year	67	12,80 ±6,72	11,01	14,49
3 year	67	12,33 ±6,08	10,64	13,74
5 year	62	12,12 ±6,13	10,55	13,69

Table 19. The variation of tumor size of VS in a group of patients under wait-and-watch control

As we see from the above table, the average size of the VS slightly differs over the follow-up years. The changes are especially more pronounced in the sixth month follow-up after initial diagnosis, which in our case, corresponds to the treatment stage. However, with a Repeated Measures ANOVA with a Greenhouse-Geisser (p=0.52) and Huynh and Feld (p=0.52) correction, shows no difference was found between each measure (F=0.67). Even with the Bonferroni, the multiple comparisons were not significant between the average VS sizes. The difference between the means and the medians can be seen in the following box plot illustration (e.g. see fig. 59).
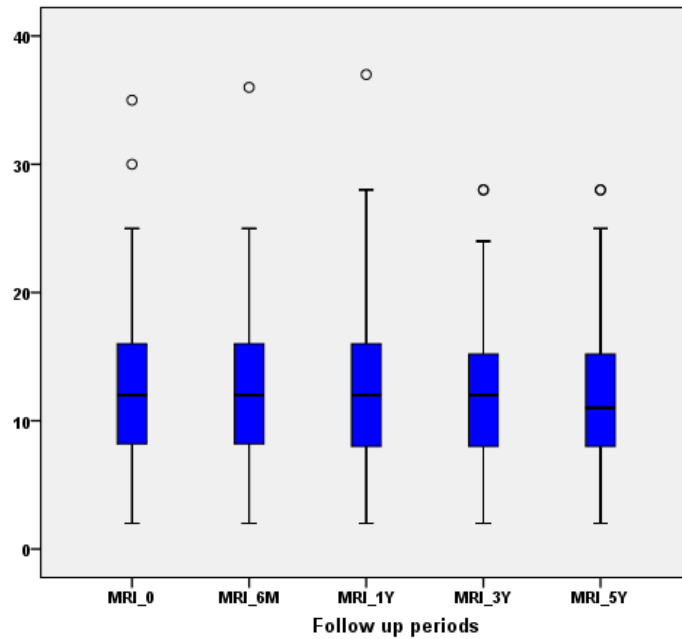
Figure 59. The evolution of VS size over the follow-up stages in a group of patients under the wait-and-watch control

The box plot shows the third year follow-up results of the size of the tumor going down, and in the fifth year, the average size of the VS became smaller than at initial examination. There are some scattered cases in the wait-and-watch group as seen in the box plot.

4.6.1.2   Radiosurgery group

In the GK radiosurgery group, 66.0% (14/21) ("Intention-to-treat" statistical approach) of the patients exhibited a VS shrinkage, 33.0% (7/21) were stable and 4.76% (1/21) of the patients presented with growth of the VS even after GK radiosurgery. The overall average size of the VS and its relative changes is presented in Table 32.

Follow up time	n	Average size of VS ±	95% CI	
			Lower Bound	**Upper Bound**
Initial	67	16,13 ±7,56	13,14	19,12
6 months	67	15,81 ±7,82	12,72	18,90
1 year	67	15,74 ±8,05	12,55	18,92
3 year	67	14,46 ±7,43	11,52	17,40
5 year	62	14,05 ±7,41	11,12	16,98

Table 20. The average size of the tumor over follow up years in a group of patients under radiosurgery

A Repeated Measures ANOVA with a Greenhouse-Geisser (p=0.05) and Huynh and Feld (p=0.05) correction determined that the overall average size of the VS differed statistically significantly between time points (F=7,316). The graphical illustration of difference between the averages of a VS in each follow up stage can be seen (e.g. see fig. 60).
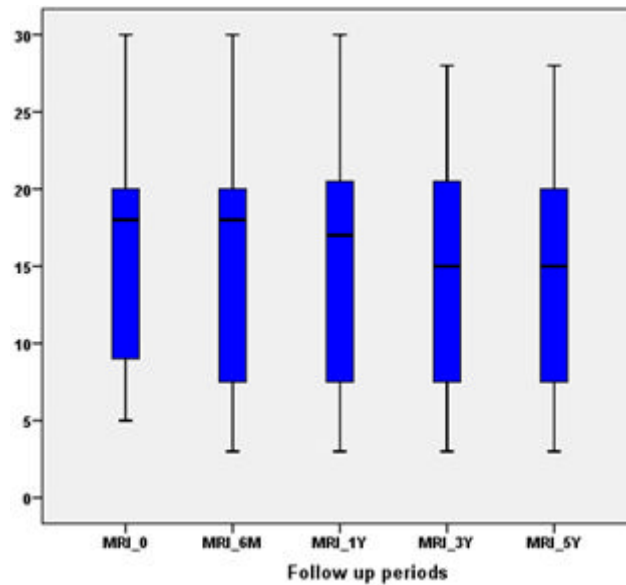
Figure 60. Chart showing variations in tumor size in the follow-up years in a group of patients under GK radiosurgery

From the figure above, we can observe that starting from the third year, there is a visible change in tumor size. Therefore, as repeated measures ANOVA with a Greenhouse-Geisser and Huynh and Feld was significant, we have performed another test (Bonferroni post-hoc test) in order to know where exactly those differences occurred. In the Bonferroni post-hoc test, we found it to be significant in the levels of baseline and the fifth year (p=0.034), and between the second and fifth years (p=0.05) of follow up.

4.6.1.3 Statistical difference in size of tumor in radiosurgery and the wait-and-watch group

The comparative study of tumor sizes between the wait-and-watch and radiosurgery groups show that the course of tumor size in the two groups is different. The comparative graphical illustration of VS sizes in the two groups presented (e.g. see fig. 61).
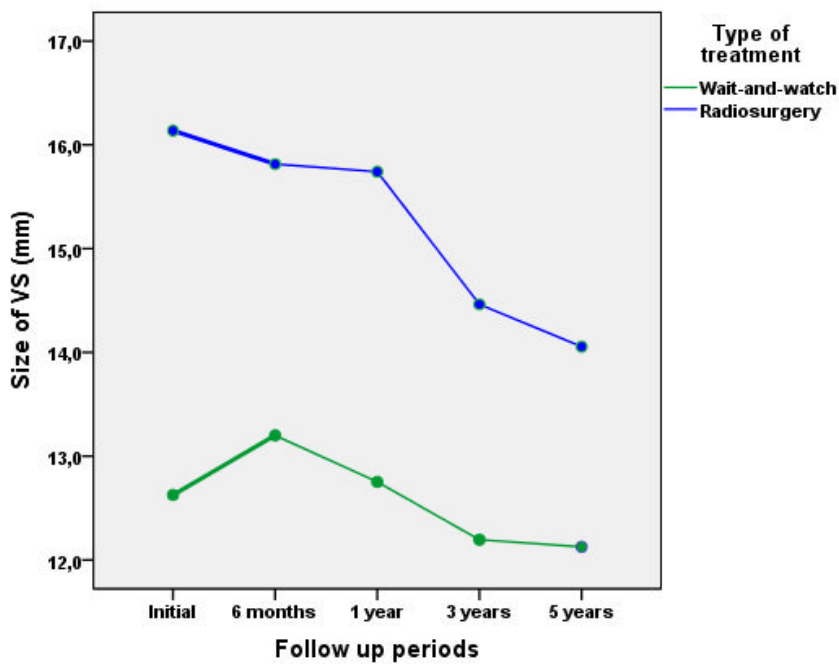
Figure 61. Chart showing variations in tumor size over the follow-up years in the wait-and-watch and radiosurgery groups

As we see from above-stated graphical illustration, the initial thick projection line between the initial diagnosis and sixth months in both groups indicates the tumor evolution. In the wait-and-watch cases, the tumor slightly enlarges, while in the GK radiosurgery group, the tumor undergoes shrinkage. After one year, unlike the wait-and-watch group, in the radiosurgery group, the shrinkage of the VSs was more pronounced. The shrinkage could reflect the results of the applied Gamma radiation to the tumor tissue. On other hand, in wait-and-watch group, the curve line descends, which means that during the initial periods, some patients passed into the radiosurgery and/or neurosurgery groups due to tumor growth.

4.6.2 Auditory function (PTA)

4.6.2.1 Haring results in the wait-and-watch group

In the group of patients under the wait-and-watch control, the initial PTA average was 57.30 ±28.53. At the diagnostic stage, there were 32 out of 67 patients who presented the overall average PTA ≤ 50dB, in six-months, one-year, three and five-years and the information was retained 100.0%, 75.0%, 59.3% and 59.3% respectively.

The overall average PTA in the follow up periods are presented in the following table (e.g. see table 33):

Follow up time	Average PTA ±	95% CI	
		Lower Bound	Upper Bound
Initial	57,30 ±28,53	50,34	64,26
6 months	59,17 ±28,21	52,29	66,06
1 year	61,91 ±28,50	54,96	68,86
3 year	68,41 ±31,19	60,80	76,02
5 year	71,38 ±30,31	62,45	77,98

Table 21. Variations in the overall average PTA in the follow-up years of the wait-and-watch group
(Intention-to-treat cohort)

A repeated measures ANOVA with a Greenhouse-Geisser correction determined that the mean PTA differed statistically significantly between time points ($F = 21.96$. $P < 0.001$). The changes in PTA are illustrated with lines (e.g. see fig. 62).
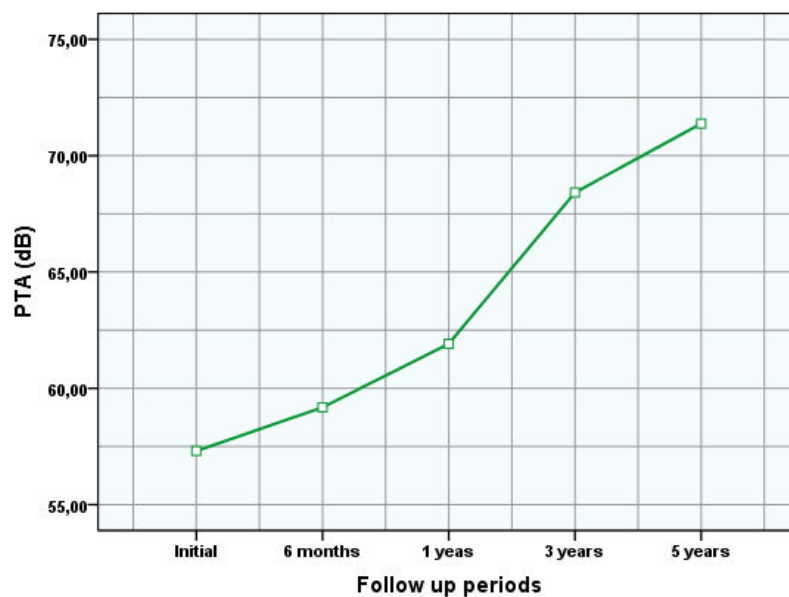
Figure 62. A chart showing the evolution of the PTA overall average in the follow-up years of patients under
the wait-and-watch control group

Post hoc tests using the Bonferroni correction revealed that the mean PTA from the initial diagnosis to after one year of follow up (57.30 ±28.53dB vs. 59.17 ±28.21dB, respectively), was slightly different, but not statistically significant $p = 0.061$. However, time points between the initial exam presenting a VS and all other (six months, one year, three years and five years) time points was statistically and significantly different

(p <0.001). The difference between the second time point (6 months) and all other time points was statistically and significantly different (p <0.015). We did not find significant associations in terms of audiometric configurations of the initial exam and other follow-up points.

4.6.2.2 Hearing results in GK Radiosurgery group

The overall average initial PTA for the radiosurgery group was 59.80 ±26.86. After each year, the hearing loss gradually increased. At the diagnostic stage, there are 20 out of 42 patients who presented the overall average PTA ≤ 50dB (useful hearing), after six months, one year, three years and five years, the average was 75.0%, 60.0%, 50.0% and 35.0%, respectively (As-treated cohort). Also, in the diagnostic stage, there were 30.9% (13/42) of patients with flat/pantonal audiometric configuration, but at the end of the last follow-up study, there were 50.0% (21/42) versus patients who presented flat audiometric configurations p<0.0001(t-test). The comparative analyzes of the average in the follow-up years is presented in the following Table 34.

Follow up time	n	Average PTA ±	95% CI	
			Lower Bound	Upper Bound
Initial	27	59.80 ±26.86	49.18	70.43
6 months	27	69.18 ±26.28	58.78	79.58
1 year	27	74.71 ±24.42	86.04	84.37
3 year	27	78.96 ±24.95	69.09	88.83
5 year	27	81.58 ±23.66	72.22	90.94

Table 22. Variations of the PTA average over the follow-up years in a group of patients under GKR

As we see from table above, the average PTA in the GK Radiosurgery group over the follow up times changes in a more pronounced way.

The graphical illustration of the overall average PTA can be seen (e.g. see fig. 13).
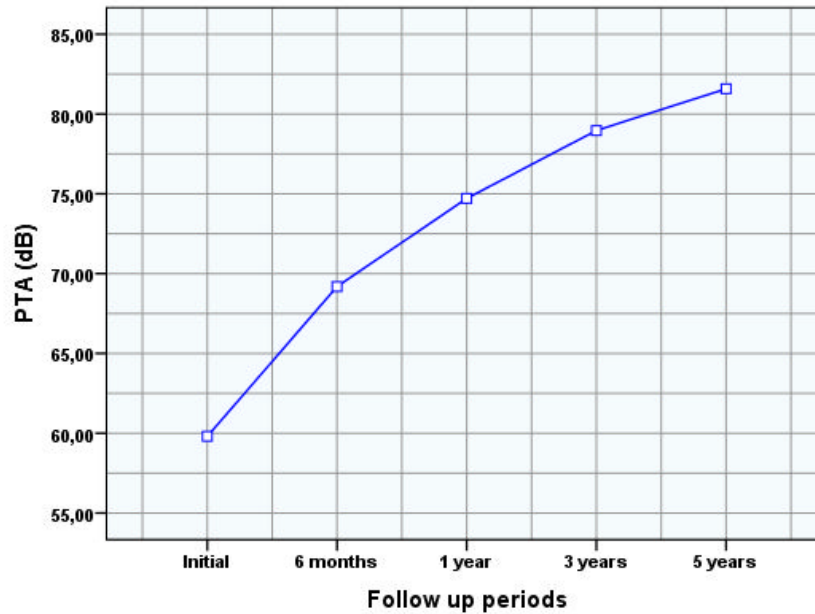
Figure 63. The evolution of a PTA overall average in the follow-up years of patients who underwent GK Radiosurgery

Figure 13 shows that the mean value of the PTA changes in each observation period. Repeated Measures ANOVA detected that in six months after initial diagnosis, there is no significant (p=0.19) change in the average PTA, but following after one year, the difference of the PTA between the initial diagnosis was significant (p=0.013). In the same way, in the third and fifth years after initial diagnosis, the hearing deterioration was more expressed and the difference between each follow-up stage was statistically and significantly different (p<0.001). Also the Bonferroni multiple comparison revealed that there are more statistically and significantly differences between other follow-up levels, including the six months versus the fifth year p< 0.000 and the third year versus the fifth year p= 0.038.

4.6.2.3   Association of auditory functions in the radiosurgery and follow-up group.

Over the years, in both groups, the overall average PTA for each patient all that increases, but the intensity of the increase in both groups are different.

We found that the PTA, at the initial point in both groups, does not differ significantly (p= 0.21). However, if we compare both groups in each of the follow-up levels, we can see minimal differences between the mean PTA of two groups. For instance, the difference in

the initial diagnosis and the six months time points is clear and this difference is statistically and significantly different p=0.005 (Repeated Measures ANOVA). Following difference between the initial point and one year is also statistically and significantly different p=0.002 (Table 35).

Follow up periods	PTA (dB)		
	Wait-and-watch	**Radiosurgery**	**Difference**
Initial	57,307	59,807	-2,5
6 months	59,179	69,185	-10,006
1 year	61,914	74,713	-12,79
3 years	68,414	78,963	-10,54
5 years	71,38	81,583	-10,20

Table 23. The rate of changes of the average PTA and/or hearing deterioration over the follow-up years in the wait-and-watch and radiosurgery groups

According to multivariate test (Repeated Measures ANOVA), the PTA is statistically and significantly different between the subjects in the two groups (Sphericity Assumed) p=0.028. The level at which the differences are located between groups can be seen (e.g. see fig. 13).
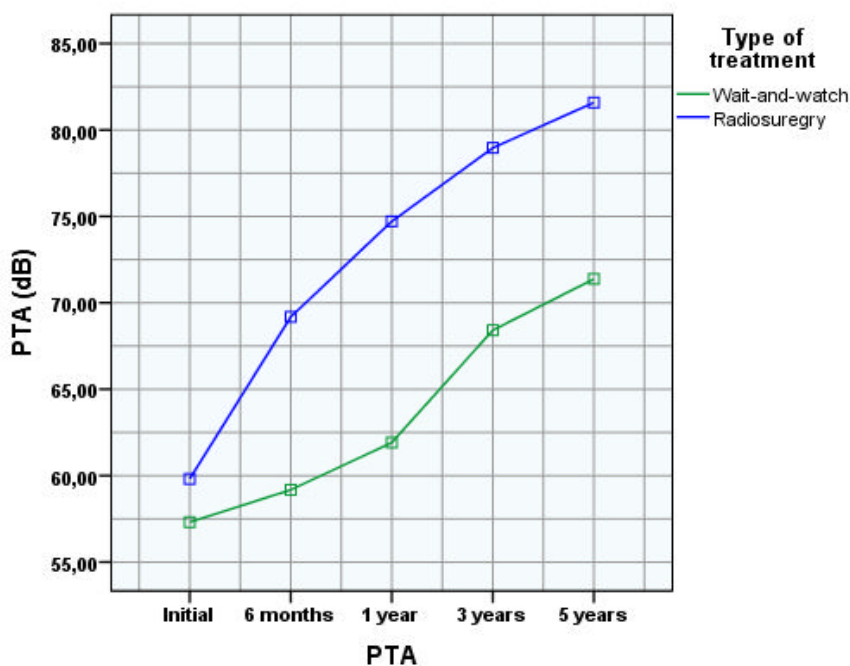
Figure 64. Image of the comparison of the mean PTA over the follow-up years between the patients under the wait-and-watch and radiosurgery groups

The plotted graph above shows the two groups after the initial diagnosis and shows the lines being directed far apart. The test indicated that there is a significant time effect. In other words, the wait-and-watch and radiosurgery groups do change over time. Both groups increase over time, but the radiosurgery group shows a greater increase in the mean PTA over time. Moreover, the interaction of time and group is significant, because the groups do not have parallel lines that increase over the time periods. However, the lines are more or less stable after the fourth and fifth years. Seemingly, the GK Radiosurgery does negatively affect hearing. If we compare the mean PTA of groups at the initial time point (Repeated Measures Contrast – Simple Comparison) and following each time point, we can see the difference between the means to be only borderline ($p=0.07$), but not statistically significantly ($p>0.05$) different (Bonferroni multiple comparison).

The difference in hearing preservation over the follow-up periods between the wait-and-watch and GK radiosurgery groups is presented in the following table below:

Intention-to-treat cohort	n	Patients with PTA≤50dB				
		Baseline	6M	1Y	3Y	5Y
Wait-and-watch	67	32 (100%)	32 (100%)	24 (75%)	19 (59,3%)	19 59,3%)
Radiosurgery	21	13 (100%)	8 (61,5%)	7 (53,8%)	6 (46,1%)	3 (39,0%)
As-treated cohort	**n**	**Baseline**	**6M**	**1Y**	**3Y**	**5Y**
Wait-and-watch	48	24 (100%)	22 (91,6%)	20 (83,3%)	17 (70,8%)	15 62,1%)
Radiosurgery	42	20 (100%)	15 (75%)	12 (60%)	10 (50%)	7 (35%)

Table 24. Outcome results of useful hearing preservation for "Intention-to-treat" and "As-treated cohort"

From the table above, we can see that the rate of useful hearing in the cases of the GK radiosurgery group is affected more than the group of patients under the wait-and-watch control. However, in general, the statistical differences between the overall average PTA in the initial and last follow-up points of both groups are statistically significantly different $p<0.001$(two tailed t-test).

4.6.2.4 Hearing deterioration and tumor growth

In the period of follow-up, we have revealed that the rate of tumor growth and hearing deterioration both in the wait-and-watch and GK radiosurgery groups were different. In the cases of the wait-and-watch group, the overall mean hearing loss for all follow-up years is 7.93dB, but in the cases of the GK radiosurgery group it is 15.1dB. Nevertheless, this difference is statistically not significant (p=0.070). The differences could be due to the following factors: the first important factor is the difference in group size, but there are also large differences in the standard deviations between the two groups, especially in the last few time points. That could be minimizing the differences in the means. Also the wait-and-watch group is becoming more variable as time progresses while the GK radiosurgery group becoming less variable. Table 37 shows the average hearing loss and tumor growth in two treatment groups and compares the outcome results for "Intention-to-treat" and "As-treated" statistical approaches.

Intention-to-treat cohort		Mean ±				
		Baseline	**6M**	**1Y**	**3Y**	**5Y**
PTA (dB)	Wait-and-watch	57,30 ±28,53	59,17 ±28,21	61,91 ±28,50	68,41 ±31,19	71,38 ±30,31
	Radiosurgery	59,80 ±26,86	69,18 ±26,28	74,71 ±24,42	78,96 ±24,95	81,58 ±23,66
Size of the VS (mm)	Wait-and-watch	12,68 ±6,76	13,20 ±7,79	12,80 ±6,72	12,33 ±6,06	12,12 ±6,13
	Radiosurgery	16,13 ±7,56	15,81 ±7,82	15,74 ±8,05	14,46 ±7,43	14,05 ±7,41
As-treated cohort						
PTA (dB)	Wait-and-watch	57,70 ±27,85	59,43 ±27,15	61,55 ±27,69	64,86 ±28,85	64,55 ±26,26
	Radiosurgery	55,82 ±25,34	62,94 ±26,39	68,04 ±25,73	74,33 ±27,73	78,44 ±27,41
Size of the VS (mm)	Wait-and-watch	11,25 ±5,23	11,35 ±5,09	11,39 ±5,08	11,55 ±5,10	11,24 ±4,81
	Radiosurgery	15,72 ±7,23	15,71 ±7,26	16,0 ±7,59	15,45 ±6,9	15,14 ±7,09

Table 25. Outcome results of PTA and Size of the VS for "Intention-to-treat" and "As-treated cohort"

As we see from table above, both statistical approaches show that the mean size of the VS tumor in both groups undergoes shrinkage. In the cases of the "Intention-to-treat" approach, patients are expected to remain in the same group regardless of applied

treatment, and on the other hand, the tumor shrinks as a result of applied treatment. Similarly, for patients in the "As-treated" approach, the mean size of the tumor shrinks over the follow-up points as an effect of applied treatment. Observing the patients under the wait-and-watch and GK radiosurgery groups via the "Intention-to-treat" statistical approach and the interval of time between diagnosis and treatment, enabled us to reveal the risk group. Detecting the risk group is also important for the estimation of the two treatment options. Figure 14 illustrates the rate of "survival" for "wait-and-watch" group.
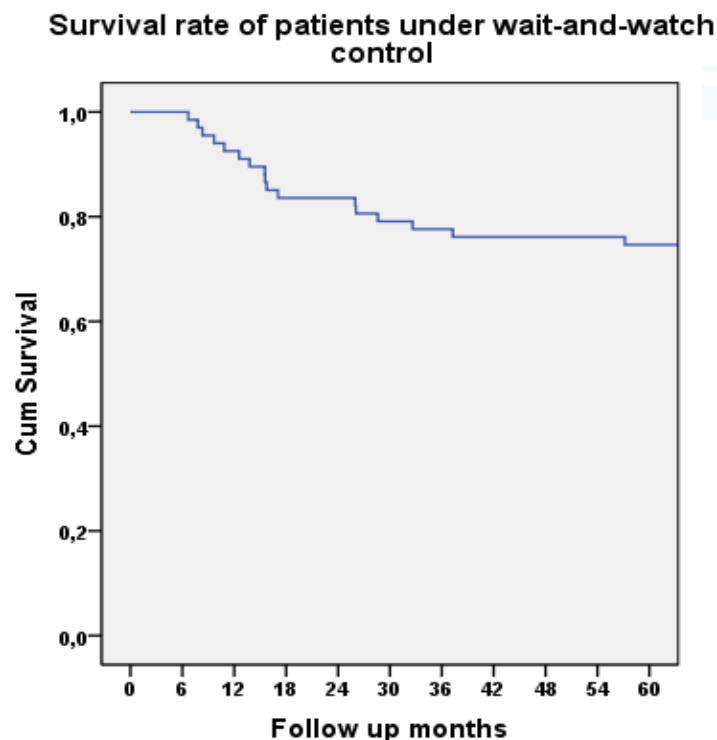
Figure 65. The survival rate of the wait-and-watch approach (Kaplan-Meir)

As we mentioned before, during the five years of follow up there are 20 (29.8%) out of 94 (100.0%) patients had more than a six month interval from diagnosis to treatment (average 27.32 ±17.48 (Range 10.85-69.90) months) and we found the tumors were changed from the time of initial treatment. The average age of these patients was 54.61 ±13.27 (Range 39.05-74.20) including eight (40.0%) female patients and eleven (55.0%) male patients.

The overall difference in the tumor size between the initial and last follow-up exam was 2.95 ±1.68 (range 1-6mm), with the average growth between each follow-up period being 0.98 ±0.57mm. The average hearing loss between the initial exam and the last follow-up exam was 7.05 ±39.11 (range 0-110)dB. The 45.0% (9/20) of patients in this group initially presented with useful hearing (PTA≥50), after one year the number of those who could hear dropped to 6 (30.0%). After five years, 5 (25.0%) of them retained useful hearing.

According to the ANOVA paired t-test, there are significant differences between the initial PTA and the PTA after one year ($p<0.001$), and between the initial size of the tumor and after one year $p=0.001$. The 17 (85.0%) patients initially had an abnormal ABR and absent DPOAE responses.

4.7 Results of exploration of VS patient due to NF2

As we stated before, we had one male patient with a bilateral VS which has been diagnosed in November 2005 at the age of 36.

The primary symptoms of this patient were hearing loss, tinnitus, imbalance and holocraneal headaches. The audiometry at diagnosis showed SNHL in the right ear (PTA 51,25) and complete hearing loss in the left ear (PTA 120dB). The MRI shoved multiple intracranial meningiomas and pure extracanalicular VSs in both ears with the maximal size of 11mm in the right and 20mm in the left side. In February 2006, the patient underwent a bilateral GK Radiosurgery with a 12Gy single dose, since the VS tumor was steady in size. However, in the control review performed in June 2010, the patient presented tinnitus and worsening vestibular symptoms with a long with left peripheral facial palsy. Also the MRI revealed an enlargement of the VS size towards the internal acoustic canal. Subsequently, a patient is directed to the Neurosurgery unit. In March 2013, the patient was operated on with the retrosigmoid approach. In the postoperative review in the ENT department, the patient presented a left-sided hemiatrophy of the tongue and a left-sided hypoglossal palsy with a palsy of tensor veli palatine.

Discussion

5   Discussion

5.1   Population characteristics and epidemiological considerations of VS

5.1.1   Sex distribution

According to traditional opinions, VS is more common in females than in males, with the ratio being around 2:1[236] and 1:1.4.[237-242] In our series, there is also a slight sex difference at presentation with 57 (53.8%) females versus 49 (46.2%) males out of 106 VS patients. But other studies with a larger sample size suggest a slight tendency towards a female bias, but one study found a less significant bias than that suggested traditionally. In a series of 1000 surgically managed tumors, Samii (Germany, 1997) describes a sex distribution of 54.0% female and 46.0% male patients. Bakkouri (France, 2009) found a 53:47% Female:Male ratio in conservatively managed patients. Jennifer, et al., (2005) studied the epidemiology of a VS regarding age, gender, race, year and region and found the incidence of VSs similar among males and females and higher in whites than in nonwhites.[247] In spite of many authors claiming to have found a slight tendency toward the female bias, including Gal and his colleagues (USA, 2010), who found the VS tumor to be equally distributed across gender and tumor laterality.[280] But they found a significant tendency towards having a VS in the Caucasian (84.0%) race.

5.1.2   Age at presentation

As stated in the results section, the average age of our patients at presentation was 57.0 (range 24-86). Including the cases of females 57.51 (range 24-86) and in the cases of males 56.21 (range 24-85). Despite the fact that onset in the third decade is rare,[236-240] there are other studies reporting the VS being diagnosed between the ages 30 and 68.[246] In our series, we observed only 4 (3.0%) patients who presented with a VS in their third decade of age and the majority of patients were distributed over the 5th - 7th decades.

In cases of Jennifer, et al., (2005) the incidence of a VS is lowest among the 0- to 19-year age group, and highest among the 45- to 64-year age group.[247] Gal and his colleagues (USA, 2010) studied 1,621 VS patients, and in their series, the mean age of patients with a VS was 51.3 years. The cases of a VS in pediatric patients is rare, and can deform part of

NF2.[236-247] It has been suggested that younger patients may be less sensitive to cochleovestibular dysfunction because of greater reserves of baseline functions. Some authors found that younger patients often presented with large tumors but with signs and symptoms that were less severe than those of older patients.[279] Also, the young patients tolerate more tumor growth because of a greater neurological effect.

5.2   Clinical characteristics

5.2.1   Symptoms at presentation

In general, the primary signs of a VS can be otologic, vestibular, neurologic and neurosurgical. The most common presenting otologic symptoms of a VS are considered to be hearing loss.[243-246] In our series, also, there are 68 (64.1%) patients who complained of hearing loss as a presenting symptom of VS. Most literature reviewed is in agreement that tinnitus is the second most common presenting symptom of a VS.[240-246] In our series, there were 24 (22.6%) patients who presented with a VS as a first sign, and 43 (40.5%) patients who presented with tinnitus and with the other otologic or vestibular symptoms. Although, all 24 patients presented with tinnitus as a first sign, with a diagnostic PTA, patients presented with hearing loss in either level. Martin (Birmingham, 2013) has investigated 730 patients with a VS, and among them in 7.0% of the cases, patients were found with tinnitus as a presenting symptom, and in 58.0% of patients, tinnitus was an accompanying symptom. In our series, there is only one patient (0.9%) who presented with tinnitus as a sole-reported complaint. Bakkouri (France, 2009) found that 4.0% of the patients with a VS showed the symptom of tinnitus alone.

5.2.2   Side of lesion

According to reviewed literature, in more than 90.0% of cases, the tumor is unilateral, affecting the right and the left sides with equal frequency.[248-249] In our series, a total of 55 (51.9%) patients presented with a right-sided VS and 51 (48.1%) patients presented with a left-sided VS. We did not find a statistical correlation in terms of frequency of affection in the right or the left ear. Edwards CG, et al., investigated 160 patients with a VS and in their

their series, VS tumor location was more commonly on the right side (59 percent), more so than on the left side (41 percent).[250] A couple of other authors (Christensen, *et al.,* 2004 and Takebayashi T., *et al.,* 2006) also conducted research about the prevalence of a VS in the right or left ear in long-time mobile phone users, and they didn't find any significant difference in either the right or the left side.[251-252]

5.2.3   Localization of VS

The location of a VS is usually reflected in the clinical picture; therefore, there is always a clinical, scientific and statistical interest associated with the localization of a VS. In our series, we have found an intracanalicular VS in the cases of 41 (38.7%) patients. We found 40 (37.7%) intra-extracanalicular tumors, and 25 (23.6) extracanalicular VSs in the patients. From the literature, we found only a few articles describing the rate or percentage of VS localization. Kwan, et al., (2004) analyzed 54 VS patients, and they found 22 (40.0%) patients with a pure intracanalicular VS and 32 (59.2%) patients with an intra-extracanalicular VS. They did not find VS cases presenting a pure extracanalicular localization.[253]   Also, Haapaniemi (2000) and his colleagues found that 22.0% of the cases were mainly an intracanalicular tumor and 78.0% of the cases were an extracanalicular tumor. They did not clarify as to whether the cases were a pure intra- or extracanalicular localization.[254] Godefroy WP (2009), and his colleagues, conservatively observed 70 patients, and in their cases found 30 (43.0%) intracanalicular tumors and 40 (57.0%) extrameatal tumors. But they also did not clarify as to whether the VS cases were an intra- or extracanalicular localization.[255]

5.3   Exploration
5.3.1   Audiometric assessment
5.3.1.1   Pure Tone Audiometry

The audiometric assessment of VS patients at diagnostic stage is very important for the further management in follow up stages.   In our series at diagnostic stage there are 96(90,5%)patients presented hearing loss with the overall average PTA 58,8dB. Among

them there were 51(53,1%) females with the mean PTA of 64,93dB and 45(46,8%) males with mean PTA of 60,96dB. We didn't find any association between PTA and gender of patients. Hajioff (Canada, 2007) and his colleagues observed 72 cases of VS with the duration of 10 years, and their series the baseline average overall PTA was 43.8 ± 17.5 and they didn't mention about age or gender prevalence, but they found prevalence regarding the localization of VS.[257] Hajioff described the average overall PTA for wait-and-watch groups only. Woodson and his colleagues (USA, 2010) studied pre and post-treatment PTA (500, 1,000, 2,000, and 3,000 Hz pure-tone thresholds) of 156 VS patients and in their series the mean pretreatment PTA was 29 ± 13 dB[259]. But their baseline average overall PTA much more differs than ours. In the literatures there are few articles describing baseline average overall PTA for all VS patients before dividing them to treatment groups. Walsh and his colleagues (Canada, 2000) retrospectively observed 72 VS patients and in their cohort the baseline PTA was 49.4 dB[258] which is also close to our baseline findings.

5.3.1.2 Audiometric configuration

Several authors described and classified the configuration of the pure tone audiogram in their studies of VS, but very few authors described the prevalence of a VS associated with each type of configuration.[260-261] In our series, at the diagnostic stage, there are 63.5% of patients who showed SNHL with a slopping audiometric configuration. The following audiometric configurations were registered: 5.0% rising, 25.0% flat or pantonal and 9.3% of cases of other (U-shaped/Basin-shaped, mountain-shaped etc.) audiometric configurations. In the follow-up stage, the radiosurgery group presented interesting results regarding the audiometric shape. Suzuki and his colleagues (Japan, 2010) performed a retrospective study of 500 patients with asymmetric SNHL, and among them, they found 2.6% (13/500) of patients with a VS.[261] According to them, the pure tone audiogram configuration associated with the highest prevalence of VS was the basin-shaped ("U" shapes) loss, followed by a flat loss, total deafness, high-frequency sloping, and lastly, a high-frequency steep. They suppose that compression neuropathy or a conduction block of the cochlear nerve leads to a basin-shaped hearing loss.[262] Although the main limitation of their work was a small sample size, which made their work statistically insignificant.

5.3.1.3 Auditory Brainstem Responses (ABR)

As mentioned before, in our series, we had 43 (40.5%) cases with an available ABR test performed at the time of diagnosis. Among the 43 patients, we found 36 (83.7%) cases with a pathologic ABR, and in 7 (16.2%) patients, the ABR results were completely normal, regardless of whether the patient had a hearing loss and VS. In our series, we found IA5 to be more sensitive for a VS.

There are enough controversial articles in the literature regarding the diagnostic value of ABR for a VS. Some authors consider that there is no place for an ABR in the modern management of a VS[263-264] . Some studies, with large sample sizes, show credible information about the utility of ABR testing**.**

Koors and his colleagues (2013) studied the role of ABR testing in the diagnosis of VS patients.[263] They analyzed 43 publications (1978-2009) which included 3,314 patients. According to their results, the pooled sensitivity for ABR detection of vestibular schwannomas was 93.4% (95% CI 92.6–94.3, P = 0.0000). For tumors that were less than 1 cm, sensitivity was 85.8%. For tumors greater than 1 cm, the pooled sensitivity was 95.6%. Unlike our results, the sensitivity of the ABR to detect extracanalicular tumors was higher than that for detecting intracanalicular tumors, but according to the authors, their pooled data was not statistically valid[263].

Chien Shih and her colleagues (2009) described 30 cases of a VS with the average tumor size of 2.48 ±1.31 cm. In their series they found 100% sensitivity of ABR[265] which seemed to us a little bit unreliable. Although, they believe the main limitations of their study are that it was retrospective and included a relatively small number of patients.

5.3.1.4 Otoacoustic Emissions

In spite of hearing loss in a VS, it is an example of a retro-cochlear SNHL. The OAEs could seem rather useless and not significant in an attempt to compare a VS with OAEs, which conversely represent an investigative tool of the cochlea[266].

In our series, from 28 (26.1%) available reports of DPOAE testing, there are 15 (53.7) patients who presented with OAE compatible and with hearing function. In the cases of 13 (12.1%) patients, the OAE was absent due to profound hearing loss. We found a relationship between tumor size and OAE, but due to the small sample size and the statistical test regarding localization, the size of a VS with OAE was not significant. Although, apart from the direct compressive effect of a VS tumor to the hearing nerves, there are many factors which interfere with the results of an OAE[267]. The VS tumor, although located outside the cochlea, may influence hair cell activity in a more or less significant measure; consequently, hearing loss induced by a VS will be somewhat influenced by cochlear function[266-267].

Ferri GG and his colleagues (Italy, 2009) studied the cochlear function in 183 patients with a unilateral VS[266]. They also recorded OAE by means of DPOAE. In their series, with an OAE present, the absent ratio was 80.9%:25.1%. Interestingly, they divided abnormal OAE into two patterns, cochlear and retro-cochlear patterns. According to authors, SNHL, due to a VS, can be of sensory and/or neural origin and they recommend DPOAEs as a complementary auditory test. Kagoya and his colleagues (Japan, 2013) studied cochlear function in 196 patients with a VS by DPOAEs[268]. They found DPOAEs to be predictive of a cochlear schwannoma, with a 75.0% sensitivity and an 87.0% specificity. Retro-cochlear hearing loss was detected in 5 patients and it was also predictive of a cochlear schwannoma which showed a 25.0% sensitivity and a 97.4% specificity.

5.3.2   Vestibular Testing
5.3.2.1   Craneocorpography

As we know the VS by its localization and nature may cause peripheral as well as central vestibular symptoms. But almost always the central vestibular compensation almost always takes place by means of neuronal plasticity mainly within the region of the vestibular nuclei and also in the brain stem vestibular commissures.[269]

Our group, as mentioned before, has found 69 (65.0%) available CCG tests with a difference in the results of the male and female patients, and it is as follows: There were 29

(39.7%) male patients and 39 (57.3%) female patients. The average overall PTA was 55.04 ±24.24 (Range 12.5-117.5) and the average overall size of the VS was 16.98 ±10.18 (Range 2-50mm). Patients with a CCG Type IV, corresponding to a VS, presented a relatively larger tumor size (22 ±12.14) than those patients who presented a CCG Type I (16.55 ±11.24), corresponding to a normal CCG.

There are only a few publications devoted to the role of CCG in the diagnosis of a VS. Gomez and his colleagues (Spain 2000) studied the CCG in 21 VS patients, but the study was performed in post-operative VS patients, which has not presented much diagnostic value.[269]

Apart from Gomez, in the same way Claussen (by whom the CCG initially was described) and his colleagues (Germany, 1989) also studied 20 post-operative VS patients[270]. They concluded that, like other vestibular tests, the CCG in addition does not cover the whole range of vestibular pathologies[270-271]. Due to their different locations in the IAC, the superior and inferior vestibular nerves and the cochlear nerves all may give rise to various symptoms[270]. Moreover, it is clear that the CCG would not be helpful in cases where a VS is attached to the cochlear nerve or in cases where the vestibular lesion has been compensated by the higher centers.

5.3.2.2   Computerized Dynamic Posturography

Although, the CDP does not provide localizing or lateralizing information, it does provide functional information regarding how well VS patients can use their balance and an indication of the importance of a patient's entire balance disturbance. CDP may be helpful in the decision making process for choosing the appropriate type of management.

The 60 (56.6%) patients, who were analyzed in regard to balance in different conditions of SOT, show that 38 (63.3%) had normal overall balance, and in the case of 22 (36.6%) patients, the overall balance was pathologic. Following, we noticed Conditions 5 and 6 of SOT. There were 26 (43.3%) patients who presented with normal results and 32 (53.3%) patients who presented pathologic results. In the cases with Condition 6, there were 32

(55.0%) normal results and 27 (45.0%) patients who presented with pathologic results. We also performed a comparative analysis between the genders and found a significant difference in Condition 6 (p= 0.005), VEST (p= 0.93), and in the overall balance (p= 0.19).

Gouveris and his colleagues (Germany, 2007) studied CDP in 216 VS patients with the mean age of 54 years. According to their results, they found a significant difference in the distribution of Condition 5 and 6 between VS patients with and without vestibular symptoms[272].

In our case, we did not find a clear correlation in the results of a CDP among patients with and without vestibular symptoms. Nevertheless, in our series, we have found a significant difference in Condition 6 between males and females among the VS patients. Authors concluded, although patients with symptoms present a lower Condition 5 and 6 than patients without symptoms, the results are not sufficient for reliable discrimination for all patients[272].

5.3.2.3 Caloric Testing

According to the medical literature reviewed for our work, we assumed that caloric tests are frequently altered ones, showing vestibular hyporreflexia or arreflexia[273].

In our group, we found 67 (63.2%) available caloric tests. Among the patients, there were 36 (53.71%) females with the mean age of 56.91 (Range 24.16-58.55) and 31 (46.2%) males with the mean age of 57.82 (Range 29.03-81.33) years.

We found 37 (55.2%) pathologic and 30 (44.8%) normal bithermal caloric responses. The overall percentage of normal:pathologic ratio was 44.8:55.2 with the higher number of patients being predominately female (63.8%) over males (46.4%). In the female group, the average overall PTA (61.79 ±30.69) was slightly higher than those in males (58.64 ±28.39), but in the other hand, males presented a little bit higher overall size of a VS (16.60 ±8.46) than females (14.82 ±10.36). Nevertheless, we did not find a clear

correlation or influence of PTA, size and localization of a VS related to the results of caloric testing.

Diallo and his colleagues (Senegal, 2006) studied the diagnostic value of caloric testing in 100 VS patients. In their series, they found 61.0% normal and 11.0% abnormal caloric responses. In the cases of 28% of the patients, they could not analyze the caloric response.[274] Some authors believe the caloric tests are the most frequently altered ones (77.0%) among other vestibular tests showing vestibular hyporreflexia or arreflexia[273].

Iwasaki S. and his colleagues (Japan, 2005) performed an interesting study to investigate clinical features of diseases showing abnormal VEMP responses with normal caloric test responses. They studied 811 patients with balance problems who had undergone both caloric response and VEMP testing. In the results, they found 40 (5.0%) (out 811 patients) to have abnormal VEMP responses with normal caloric test responses. Among these patients there were 8 VS patients[275].

An analogic study was conducted by Wang WQ and his colleagues (China, 2000) and they also aimed at summarizing the outcome of neurootologic examination in the diagnosis of 13 VS patients. In their cases, 5 patients tested normal in the caloric test, but all were abnormal in the visual-vestibular optokinetic response and in 90.9% of the cases, the ABR were positive[276]. Another group of authors from Japan performed caloric testing in 78 VS patients and in their series the 63 (80.8%) patients showed no caloric responses and the remaining 15 (19.2%) patients showed normal caloric responses[277]. So far, there is no fully comprehensive vestibular or audiologic test meeting the current diagnostic interests of a VS.

5.3.2.4 Vestibular Evoked Myogenic Potentials

We had 21 (19.8%) VEMPs tests available. Including 11 (52.38%) females and 10 (47.61%) males. In 12 (57.14%) patients, the VEMPs were presented on the VS side, and in cases of nine (42.8%) patients, the VEMPs were absent in the pathologic ear. Among the patients with absent of VEMPs, there is one (4.7%) patient who showed no click VEMP

response on the VS side. In the group of patients who presented a response, there were 5 (23.8%) females and 6 males (28.7%). Following in a group of patients with an absence of VEMPs response, there were 6 (28.5%) females and 4 (19.0%) males. The average AR for all 12 (57.1%) normal VEMPs stimuli was 33.94 ±24.0% (Range 87-6.2%). In the overall result there were 6 (28.5%) patients (out of 21) who presented with a normal AR and a normal VEMP.

Ushio and his colleagues (Japan, 2009) performed a comparative study of VEMPs and caloric testing in 78 VS patients with the mean age of 50.4 ± 12.8 years. They found an abnormal click VEMP in 46 (59.0%) patients. In eight (10.3%) cases, they found normal responses on both sides and the following 24 patients (30.8%) showed a no click-VEMP response on both sides[277]. In their series, the specificity of VEMP was 52.7%. In our series, the specificity of VEMPs was a little bit lower (42.8%) than their series. The main reason for the relatively low specificity of VEMPs and caloric testing is explained in many comparative studies. For instance, unlike auditory brainstem response, which could be specific for retrocochlear lesions such as a VS, abnormal VEMP and caloric test results are not specific for retrolabyrinthine lesions[277-278].

5.3.3   Imaging test
5.3.3.1   MRI

The overall average size of a VS at the diagnostic stage for the 106 patients was 16.08 ±9.69 (2-50mm). The males show a little bit bigger overall average size 17.37 ±9.05 of a VS than females 14.96 ±10.16. Particularly, this difference was more pronounced in patients ≤40 years (21.7 ±12.21 (6-50mm). Although, due to the difference in sample size, the realized statistical test (t-Student) didn't show a significant difference between the two genders. Although this slight difference was not significant, it has been confirmed by the other large sample-sized studies. For instance, Harun and his colleagues[279] (USA, 2012) performed a retrospective study in 1,296 patients diagnosed with a unilateral VS. In their study, the male subjects had significantly larger tumors than female subjects at presentation (18.23 versus 16.81mm, p = 0.031); interestingly, in their cases, this difference was also particularly pronounced in patients younger than 40 years.

With respect to age, we found that increasing age was negatively correlated with tumor size and positively correlated with hearing loss, but did not predict the presence of dizziness.

In our series, we found a difference between tumor localization and PTA. The overall average PTA in intracanalicular localization was (48.87 ±25.47) different than both an extracanalicular and an intra-extracanalicular localization.

Unlike our studies, Massick and his colleagues (USA, 2000) studied the influence of VS size and location to the hearing function in the cases of 21 VS patients and they did not find significant differences in the tumor characteristics and audiometric function[281]. Moreover, they conducted their study in VS patients under the wait-and-watch policy. The larger the sample size, the more likely the findings will be significant; therefore, taking into account their small sample size perhaps we may not be able to precisely estimate their results. In the literature, we did not find any article discussing the tumor characteristics in a VS patient before applying either type of modern management.

5.4   Treatment

After establishment of a VS diagnosis, patients have had several options for managing their tumor. The most popular types of treatment modalities include the wait-and-watch or conservative management, Gamma Knife Radiosurgery and Conventional Neurosurgery. During the last few decades, the election of treatment modality by the patient is gaining more popularity. But in some other cases, unfortunately, evidence suggests that a predictor of treatment choice is the discipline of the attending physician[283]. This may be attributed partly to the limited evidence-based guidelines for treating a VS[282.] In our series, applied treatment modality, as usual, depended on the following conditions: tumor size, associated symptoms and signs, patient age, patient health, and patient preference.
.

As we mentioned before, our cohort included the 67 (63.2%) patients under the wait-and-watch scan. Of the 67 patients, there were 36 (53.2%) females and 31 (46.3%) males. The average age of the patients in this group were 59.21 ±14.35 (Range 24-85), the average

size of the VS was 12.68 ±6.76 (Range 2-35) and the overall average PTA was 57.30 ±28.5 (12.50-120).

In the Radiosurgery group, there were 27 (25.5%) patients who were directed to GK Radiosurgery. Among them, there were 15 (55.67%) females and 12 (44.4%) males. The average age of patients in this group was 56.82 ±14.30 (Range 24.75-78.48). In following the results of the overall average PTA in the radiosurgery group, we found that they did not differ significantly from the wait-and-watch group. The averages were 56.31 ±29.16 (3.75-120)dB, but the overall average sizes of the VS slightly differs (15.72 ±7.19 (Range 2-30mm). Following, the ratio of the intracanalicular, extracanalicular and intra-extracanalicular VS was 26.1%:30.95%:44.85% respectively.

In the group of patients under conventional neurosurgery initially, there were 12 (11.32%) patients, including 6 (50%) females and 6 (50%) males. The average age of patients in this group were 43.78 ±9.28 (Range 29.16 – 57.85) years, which was younger than both of the above-mentioned treatment groups. The overall average size of the tumor in this group (30.04 ±11.37mm and PTA 66.40 ±35.84dB) was significantly higher than that of both of the above-mentioned groups.

Since the era of both Cushing and Dandy in the early 20th century, almost all patients with a newly diagnosed VS have undergone attempts at surgical removal of their tumors. Although outcomes in the era of microsurgery greatly improved the quality of life of patients after surgery, the earlier diagnosis of these tumors prompted a comprehensive evaluation of less invasive management strategies[284]. But there are still evidences of serious perioperative, postoperative and long term complications of VS microsurgery.

Sarna and his colleagues (Italy, 2004) performed a retrospective study of 707 VS patients and made a review of the complications other than those related to the facial nerve and hearing, encountered in vestibular schwannoma surgery[285]. According to them, the only preoperative complication in the cases of 707 patients was followings: abdominal subcutaneous hematoma (site of fat harvest) which occurred in 23 patients (3.2%). Cerebrospinal fluid leak was present in 20 patients (2.8%), 15 of whom needed revision surgery. Other complications included VI cranial nerve dysfunction in 12 cases (1.68%),

subdural hematoma in 3 cases (0.4%), CPA hematoma in 4 cases (0.6%), cerebellar edema in 2 cases (0.28%), brainstem hematoma in 1 case (0.14%), transitory aphasia in 1 case (0.14%), and lower cranial nerve dysfunction in 1 case (0.14%). Even mortality occurred in one case (0.14%).

5.5 Follow up

In the last decade due to no clinical parameters identified to correlate with VS growth the growth of a VS is objectified by performing a consecutive MRI[286]. Therefore, the wait-and-watch policy has gained popularity as an alternative or prelude to conventional neurosurgery and radiosurgery. This can be justified, as growth is known to be extremely variable with most VS remaining stable or showing minimal growth for many years.

As we mentioned before, in follow-up, our main focus was on the wait-and-watch and radiosurgery patients. The overall average follow-up for the wait-and-watch group was 55.30 ±11.92 (Range 25.02-71.21) months, and for GK Radiosurgery it was 58.80 ±9.22 (36.16-71.74).

The most reviewed literature to current work[255,257-258,281,287-289] described follow up study of VS with conservative approach has an average 52,68 ±13,82 (Range 43,2-80) months follow up times and their average number of patients in both groups included in the study was 79,28 ±87,64 (Range 21-273). The majority of the above-mentioned authors in either stage of follow-up faced the problem of lost cases[255, 257-258,281, 288].

5.5.1 Auditory function

5.5.1.1 Wait-and-Watch group

In the literature there are only a few publications regarding hearing loss or audiovestibular symptoms after wait-and-watch management of VSs[255]. The initial overall average PTA in our wait-and-watch group was 57.30 ±28.53dB, and the initial number of patients was 30 (44.77%) out of 67 patients with useful hearing (PTA≤ 50 dB). In the first 6 months, after initial diagnosis, there was no significant change (p=0.38) observed in the overall average PTA. But after one year of initial diagnosis, the difference in PTA between the initial point is significant (p=0.001) and in this stage, there were 28 (93.3%) out of 30 (100.0%) patients who had useful hearing. In the third and fifth years after initial diagnosis, the hearing deterioration was more significant (p<0.001) and in this stage, there were 21 (70.0%):17 (56.6%) patients who had useful hearing, accordingly. In the wait-and-watch group, we did not find a direct relationship between tumor growth and hearing loss. Also, in this group, the overall average hearing loss in the first, third and fifth years was 4.6:11.10:14.07 dB, accordingly.

Pennings and his colleagues (Canada, 2011) [289] reviewed 47 unilateral intracanalicular VS and evaluated hearing function in the follow up period. The mean follow-up was 3.6 years. In their series all patients showed hearing degradation during follow-up. The mean pure tone average at the first audiogram was 37.5 dB, which diminished to 50.9 dB at the time of the last audiogram. Despite the documentation of both tumor progression and hearing deterioration in many patients, the authors continued to recommend observation rather than intervention.

Godefroy and his colleagues (Netherlands, 2009) studied 70 VS patients who underwent the wait-and-watch management. In their series, useful hearing was maintained in 57.0% of patients after almost 4 years of follow-up[255]. Their results were very close to ours and they also did not find a relationship between hearing loss and tumor growth.

There are some other authors also reported the evolution of PTA in VS patients under the wait-and-watch control. In the series of Walsh and his colleagues (Canada, 2000) the

hearing loss was observed in 50.0% to 67.0% of cases after conservative treatment, regardless of tumor regression[258].

In the series of Hafioff and his colleagues[257] the audiometric follow-up in 40 patients at 80 months showed that most patients had significant hearing loss even in the absence of measurable tumor growth. In their case the overall average hearing loss within 80 months was 36dB. Also they found hearing loss to be worse in the presence of measurable tumor growth.

According to Massick and his colleagues[281] (USA, 2000) the auditory pathways have a level of reserve when injured. When this reserve is expended, any increase in tumor volume results in progressive deterioration in audiometric function. The initial overall average PTA in their series was 34.71 ±20.8dB, and after 5 years of follow-up, this average changed to 53.90 ±31.11dB. Within the five years, the group lost 19.2dB. They revealed significant correlations of changes in tumor volume with changes in the pure-tone average ($p < 0.0001$). Although the hearing loss is significant, the number of patients included in the study is probably important for rightly estimating presented results of given work..

Breivik and his colleague (2013, Norway)[287] comparatively studied two treatment options wait-and-watch and radiosurgery in 237 unilateral VS patients with the mean follow up time of 55 month. They found that within the follow up time the useful hearing was lost in 76,0% of 71 (100,0%) wait-and-watch patients, which is significantly higher than our observation.

Régis and his colleagues (France, 2010) also studied two treatment options, wait-and-watch and radiosurgery, in 47 unilateral intracanalicular VSs with the mean follow-up time of 43.8 ±40 months. In their group, at 3, 4, and 5 years, the useful hearing preservation rates were 75.0%, 52.0%, and 41.0% in the wait-and-watch group. Wait-and-watch management failed in 35 patients (74.0%) due to tumor growth or worsening of hearing[288].

In our follow-up group, there are 30 (62.5%) out 48 (100.0%) patients who presented with an intracanalicular tumor with the initial average PTA of 49.18 ±23.45 (Range 16.25-

97.50)dB. After 5 years, there were 17 (61.5%) patients who presented with useful hearing with an overall average PTA ≤ 50dB.

Author, year (Ref. n)	Patients (n)	Follow up (months)	Tumor growth rate	Hearing preservation rate	Additional treatment needed
Breivik 2013 (287)	124	55	NR	24%	50,8%
Pennings 2011 (289)	47	43,2	17%	74%	17%
Régis 2010 (288)	47	43,8	77%	41%	74%
Godefroy 2009 (255)	70	43	36%	57%	39%
Sughrue 2010 (138)[m]	34 (982)	26–52	NR	54%	16%
Hajioff 2008 (257)	72	121	77,7%	NR	35%
Massick 2000 (281)	21	45,6	66%	66,6%	NR
Walsh 2000 (258)	25	43,8	32%	43%	12%

*NR not reported, [m] - meta-analyses

Table 26. Summary of the recent series of VSs managed with the wait-and-watch strategy

5.5.1.2 Radiosurgery group

GK Radiosurgery has often been cited as a safe and effective treatment for small and medium sized VSs[288,290] But sometimes this safety and effectiveness may be questioned due to the lack of comparison with the natural course of other studies.

According to our follow-up results, the initial and final PTA average were significantly different (p<0.001). At the diagnostic stage, there were 20 (41.6%) patients who presented useful hearing (PTA ≤ 50dB), and the rate of useful hearing preservation in six months, one, three and five years were at 75.0%, 60.0%, 50.0%, and 35.0% respectively. Also, in diagnostic stage, there were 30.9% (13/42) (As-treated cohort) patients who presented the flat audiometric configuration, but at the end of the last follow-up study, there were 50.0% (21/42) VS patients who presented with a flat audiometric configuration p<0.0001. We have observed statistically significantly different hearing degradation in all patients who underwent GK radiosurgery, and the overall average PTA at the follow-up points were also

statistically significantly different (initial vs. one year p=0.01, initial vs. third and five years p<0.001). Of the 42 patients treated with GK radiosurgery, one (2.3%) patient failed to complete the radiosurgery as a result of tumor growth after the GK radiosurgery. The patient was then directed to Neurosurgery.

Hearing preservation is an important and critical issue for patients with VS undergoing GKS. The literature to the topic contains controversies, and a large number of individual results have been reported, but to date there have been few efforts to aggregate this research to achieve statistical power[291].

Unlike our studies, some GK Radiologists, in their studies, reported the useful hearing preservation to be 61.0% to 80.0% in the third and five years after GK radiosuregry[284].
But the results of large meta-analysis performed by Yang and his colleagues (USA, 2010) are close to our results[291]. Yang and his colleagues performed a systematic literature review of the results of GKS hearing preservation which included 45 articles from 4,234 patients who provided the data. The mean follow-up was 44 months. Overall, the hearing preservation rate was 61.0% with a dose of 13 Gy or lower, and 50.4% at more than 13 Gy. They concluded that neither patient age nor tumor volume correlated with hearing preservation and an overall hearing preservation rate of approximately 51.0% can be expected approaching 3-4 years after radiosurgical treatment. The analysis reveals that patients treated with < or = 13 Gy were more likely to have preserved hearing than patients receiving larger doses of radiation.

In the series of Régis and his collagues[288] in the GK radiosurgery group, 66.0% (31/34) had useful hearing at the time of diagnosis. Only 21 (68.0%) preserved useful hearing and 10 (32.0%) lost useful hearing during follow-up. Authors confirmed that tumor control and functional hearing preservation rates were higher in patients who underwent early GK radiosurgery, which in their series was 88.0%, 79.0%, and 60.0% at 1, 2, and 5 years, respectively.

According to Kondziolka and his colleagues[284] in a longer-term assessment of hearing at a median of 6 years the hearing was preserved in 71.0% of patients, serviceable hearing was

confirmed in 74.0% of patients, and any testable hearing was present in 95.0% of patients. For intracanalicular tumors, these rates were 84.0%, 92.0%, and 100.0%, respectively. The summary of results from anological studies of some authors are presented in Table 39.

Author, year (Ref. n)	Pts (n)	Follow up mean (months)	Tumor control rate	Hearing preservation rate	Additional treatment needed
Arthurs 2011 (282)[m]	(84) 1,850	72	91–95%	60%	3,9%
Régis 2010 (288)	34	43,8	3%	64%	3%
Yang 2010 (291)[m]	45 (4,234)	44,4	NR	51%	NR
Yang 2009 (179)[m]	74 (5,825)	41	94%	57 (=2,083)	NR
Paek 2005 (293)	25	45	0%	52%.	0%
Carlson 2012 (294)	44	111,6	NR	23%	NR
Yamakami 2003 (183)[m]	9 (1,475)	46	92,6%	66%	4,2%

* NR –not reported, [m] -Meta-analysis.
Table 39. Summary of recent series of VSs managed with GK Radiosurgery

Timmers and his colleagues (USA, 2011) performed a prospective study in 100 patients treated with GK radiosurgery. Eight patients needed additional treatment after a mean follow-up period of 38 months. One patient experienced a temporary facial nerve deficit. In their series, based on the measurements of the largest extrameatal diameter, the tumor size decreased or remained stable in 94.0% of the patients.

Some other authors reported the negative effects of GK radiosurgery to overall hearing, and they believe the reason for the hearing deterioration after GK radiosurgery in patients with vestibular schwannoma has not been documented clearly. However, there are several hypothetical causes of hearing deterioration proposed in the literature. One of those causes could be the direct radiation of the brainstem, which is believed to be a significant prognostic factor for hearing deterioration after GK SRS. Interestingly, the cochlear nucleus may be one of the other sensitive structures to be damaged by radiotherapy[293].

5.5.2 Size of the tumor

5.5.2.1 Wait-and-watch group

During the overall observational period, the VSs seemed to be non-growing in a majority of cases (70.2%). However, as we mentioned before, there are 29.8% (20/94) patients who presented the tumor growth. Among them 28.3% (19/67) of the patients were under the wait-and-watch strategy.

Like many authors we also did observe the tumor shrinkage after GK Radiosuregry[287-288], however, unlike some other authors we did not observe the protective effect of GK Radiosurgery on hearing[287,290-291].

Rosenberg and his colleagues (2000, USA)[295] conducted a retrospective study of 80 patients with unilateral vestibular schwnnoma who had conservative treatment with the average duration of 57,6 months by serial imaging studies. In their series, the overall growth rate, with conservative treatment, was 0.91mm per year, and in 42.0% of the cases, they found the VS to be non-growing or regressing in size. According to them, neither auditory nor vestibular testing was a reliable measure for determining tumor growth. The percentage of non-growing tumors in their series was a little bit smaller than ours. However, other authors stated the percentage of non-growing tumors to be higher. For instance, in the series of Godefroy [255] the percentage of non-growing tumors in conservatively managed patients was 63.0% (44/70), and the percentage of patients who required treatment was 39.0% (27/70). Following Régis and his colleagues (2010, France)[288] found the percentage (ratio) of growing and nongrowing VSs to be 74:26.

Another study based on a review of 47 patients with unilateral intracanalicular schwannomas was performed by Pennings and his colleagues[289] to evaluate hearing function during a period of observation. The mean follow-up was 43,2 months. Nineteen patients (40.0%) had tumor growth greater than 2mm (8 patients underwent treatment), 24 (51.0%) had stable tumors, and 4 (9.0%) had slight tumor regression. All patients showed hearing degradation during the follow-up stages. In spite of the documentation of both tumor progression and hearing deterioration in many patients, the authors continued to recommend observation rather than intervention.

5.5.2.2 Radiosurgery group

According to more recent studies conducted by Breivik and his colleagues (2013, Norway) the GK Radiosurgery reduces the tumor growth rate and prevents the new treatment about tenfold[287]. According to the long-term results of GK Radiosurgery for VSs the tumor control rate varies from 93.0% to 100.0% after radiosurgery[288,292,296-297].

In our series, a total of 42 patients (As-treated cohort) underwent GK Radiosurgery and among them, only one (2.8%) patient presented the tumor growths after they were treated with GK Radiosurgery. In 26.1 % (11/42) of cases, we have observed negative growth after GK Radiosurgery and in all other cases, the tumor remained steady.

Kondziolka and his collagues[290] studied 5 to 10 year outcomes in 162 patients with a VS who had undergone radiosurgery. In this study, a long-term 98.0% tumor control rate was reported. In another study performed by the same authors in 157 patients, there was a decrease in tumor size in 114 patients (73.0%), no change in 40 patients (25.5%), and an increase in 3 patients who later underwent resection (1.9%). In their series, only 2.0% of patients required tumor resection after radiosurgery.

Kim and his colleagues (2007, Korea)[298] observed 59 post-radio surgery patients with the duration of at least 5 years, and in their series, the tumor control rate was 97.0%. They also classified the patterns of change in tumor volume into three categories. Transient increases in tumor volume were detected in 29.0% of the patients, and the maximum transient increase in tumor volume was identified at 6 to 30 months after GK Radiosurgery. The report stated that the hearing was preserved in 4 of the 12 patients who had serviceable hearing prior to treatment. They concluded that the tumor control after GK Radiosurgery depends on the dosage of radiation, and they believe that with an average of 12 Gy, the tumor control would be between 86.0% and 98.0%.

Some studies have reported about malignant transformation of VS after performed GK Radiosurgery[299], has been performed, but in our series, we did not observe cases of a VS transforming into a malignant tumor. According to certain authors, after fractionated

external-beam radiation therapy, the risk of malignant transmission may be as high as 2.0%, as has been reported many years after such radiation therapy for pituitary tumors[300].

Delayed oncogenesis following radiosurgery is rare because the target and regional tissue volume irradiated are small. The procedure results in a single radiation exposure, and the high central dose more than likely leads to cell death rather than cell transmutation[290].

5.6 Case of NF2

The NF2 is a less frequent among VS patients and its low incidence contributes to the difficulty in obtaining an accurate diagnosis[301]. Although the NF2 is less frequent but it causes dramatic clinical outcomes[281,301]. Patients with NF2 are routinely treated and controlled by neurosurgeons since they usually have a VS as well as meningiomas in other parts of the CNS. However, due to the importance of periodic monitoring of hearing and vestibular functions, patients with NF2 should be controlled by otolaryngologists as well. In the last few years, the hearing rehabilitation for NF2 patients by means of auditory brainstem implantation (ABI) is gaining more popularity because an ABI after tumor removal is a safe procedure and is the best means of hearing rehabilitation if the cochlear nerve is not preserved.

5.7 Final considerations

Over the past few years, the wait-and-watch strategy in the management of VSs is increasingly adopted as an initial treatment option for a VS. As shown in previous reports, our study shows that a wait-and-watch strategy serves as a screening tool for the management of VSs because there aren't any effective criteria to consider GK Radiosurgery or Conventional Neurosurgery at the diagnostic stage.

Wait-and-watch management does not seem to worsen the patient's overall quality of life over time and useful hearing is preserved in wait-and-watch control much better than GK Radiosurgery. Thus, in our group, patients with non-growing small tumors and with a

stable clinical picture were prospectively continued in follow-up under the wait-and-watch plan.

We have observed the hearing loss to be more pronounced in case of GK Radiosurgery, and by comparing with other similar studies, we were brought to the conclusion that the radiation dose is perhaps the most important contributing factor. Nevertheless, no definite guideline for determining the appropriate radiation dose for GK SRS has been established. At times, it appears to be that there are other issues related with a patient's individual resistance to radiation; however, a satisfactory hearing preservation and tumor control rate could not be achieved using a low radiation dose.

Our study demonstrates that a trial of the wait-and-watch approach is reasonable in the majority of selected patients with a small-sized VS and outcomes are not adversely affected in those patients who ultimately failed in the wait-and-watch management.

5.8   Our guidelines on clinical management of a VS – protocol of treatment

Choosing the treatment option for a VS continues to be a challenging issue for more than 100 years because of their benign nature and potentially significant surgical morbidity and mortality related to the complex anatomy of the CPA. However, in recent years, development of new diagnostic modalities such as the CT, the MRI and the auditory evoke potentials has resulted in the drastic decrease in the average size of a VS at diagnosis. Using the serial MRI also enables the control of non-growing VSs, thereby warning of possible complications of Conventional Neurosurgery and/or Radiosurgery.

The following Table 31 presents the main factors for consideration of treatment options for a VS.

217

	Factors Influencing to the treatment	Treatment options		
		Wait-and-watch	Radiosurgery	Neurosurgery
Tumor size	≥20mm		+	++
	10-15	+	+	
	≤10	++	+	
Age	≥60	+	+	+
	45-60	+	++	+
	≤45		+	+
Tumor localization	Intracanalicular	+	++	+
	Extracanalicular	++	++	+++
	Intra-Extracanalicular	+	++	++
PTA≥50dB	Yes	++	+	
	Not	+	++	+

Table 27. The plus signs show factors which influence VS treatment options

There are also some other important factors which may influence the decision of either treatment options and one of those factors could be the clinical presentation. Although the predictive value was limited, the symptoms of vertigo, facial paralysis and hearing loss may be the indicators which predict tumor growth.

5.9   Limitations of this study

Although this research was carefully prepared, we are still aware of its limitations and shortcomings.

First of all, not all VS's were histologically confirmed because many patients were diagnosed with an MRI; therefore, it is possible that our sample included individuals with other diagnoses such as meningioma or facial nerve schwannoma.

Second, due to the fact that our study was retrospective in almost all cases, the size of the tumor was considered according to the maximal diameter. In our awareness nowadays in many centers, volumetric measurement becomes more popular and the measurement of a

tumor by its volume gives more reliable information for comparing the tumor size in the follow-up periods.

Third, not all patients may have reported all relevant symptoms because there are differences in the willingness to report certain symptoms or differences in provider interviews. Also, our study did not include some important information, in our opinion. Tests like the Speech Recognition Test (SRT) and the results of the stapedial reflex (SR) may have made our study more reliable. The SRT is especially important for the comparison of hearing preservation rates with other analogic works used, like the Gardner-Robertson Classification; however, the works used for this scale does not include frequencies higher than 2000 Hz.

In addition, in the last follow-up time, we lost some patients. Also, over each follow-up time, some patients in our series changed treatment options which complicated comparing groups in follow-up points. Therefore we used "Intention-to-treat" and "As-treated statistical approaches".

Conclusions

6   Conclusions

The *first* conclusion in our series is that the vestibular schwannoma affects both genders equally at all ages, and its peak incidence is in the sixth decades of life.

Secon, in our patients, the percentage of affection of the intra- and extracanalicular components of vestibulococlear nerve is similar.

Third, the most common presenting symptom at the time of diagnosis is the hearing loss. Fourthly, the usual type of hearing loss we meet in our patients is the sensorineural high-frequency hearing loss with the sloping audiometric configuration.

The *fifth* conclusion is that the severity of audiometric alteration is related with the localization of the vestibular schwannoma and the hearing is more affected in intracanalicular tumors than extracanalicular tumors.

Sixth, the instrumental tests for vestibular functions tend to show abnormal results in those patients who presented with vestibular symptoms at the diagnostic stage and the tests are usually normal in those patients who do not present with vestibular symptoms at the time of diagnosis.

Seventh, in small tumors, the two compared therapeutic approaches (wait-and-watch and GK Radiosurgery) are effective in controlling the growth of the vestibular schwannomas.

Eighth, in those patients who underwent GK Radiosurgery, the hearing deterioration observed during follow-up is higher than those included in the wait-and-watch group.

Ninth, in patients who underwent GK Radiosuregry, over the follow-up years, show tumor shrinkage more that those patients included in the wait-and-watch group.

Tenth, the complications experienced as a result of GK Radiosurgery were not significant.

Conclusions

Eleventh, in patients with a small vestibular schwannoma, the wait-and-watch protocol is a correct therapeutic approach which does not worsen the medium-term prognosis.

Twelfth and finally, we consider the wait-and-watch therapeutic approach to be a "screening tool" for vestibular schwannomas in the early stages after diagnosis.

Bibliography

7   Bibliography

1. Spickler E, Govila L. The Vestibulocochlear nerve. Seminars in Ultrasound, CT and MRI 2003; Volume 23, Issue 3: 218-237.

2. Kim HS, Kim DI, Chung IH, Lee WS, Kim K. Topographic relationship of the Facial and Vestibulocochlear Nerves in the Suparachnoid Space and Internal Auditory Canal. Am J Neuroradiol 1998; 19:1155-1161.

3. Rubinstein D, Sandberg E, Cajade-Law A. Anatomy of the Facial and Vestibulocochlear Nerves in the Internal Auditory Canal. Am JNeuroradiol 1996; 17:1099–1105.

4. Cummings Ch, Lee Harker, Krause Ch, Richardson M, Schuller D, Krause CH. Otolaryngology Head & Neck surgery 1998; Third edition.

5. Daniels DL, Schenck JF, Foster T, Hart H, Pech P, Haughton VM. Surface-coil magnetic resonance imaging of the internal auditory canal. Am J Neuroradiol 1985;6:487–490.

6. Casselman J, Kuhweide R, Deimling M, Ampe W, Dehaene I and Meeus L. Constructive interference in steady state-3DFT MR imaging of the inner ear and cerebellopontine angle. AJNR Am J Neuroradiol 1993;14:47–57.

7. Rasmussen A. Studies of the VIIIth cranial nerve of man. Laryngoscope 1940;50:67–83.

8. Sato H, Sando I, Takahashi H. Three-dimensional anatomy of human Scarpa's ganglion. Laryngoscope 1992;102:1056–1063.

9. Silverstein H. Cochlear and vestibular gross and histologic anatomy (as seen from postauricular approach). Otolaryngol Head Neck Surg 1984:92;207–221.

10. Heil P, Neubauer H. Temporal Integration of Sound Pressure Determines Thresholds of Auditory-Nerve Fibers. J. Neurosci 2001, 21(18):7404–7415.

11. Bailey B, Johnson J, Newlands Sh. Anatomy and Physiology of Hearing. Head and Neck Surgery - otolaryngology. Fourth Edition 2006, 1893-1903.

12. Popper A, Fay R. The Mammalian auditory pathway: Neurophysiology. Springer Handbook of Auditory Research 1992, p39.

13. Stevens S, Warshofsk F. Excerpt from "Sound and Hearing"., Time-Life Books 1965, p54.

14. Dau T, Hohmann V, Kollmeier B. Psychophysics, physiology and models of hearing. World scientific Ltd 1999, 4-12.

15. Jahn A, Santos-Sacchi J. Physiology of the Ear. Second edition. 2001,196-291.

16. Schubert M, Minor L. Vestibulo-ocular Physiology Underlying Vestibular Hypofunction. Phys Ther. 2004; 84:373–385.

17. Goldberg JM. Fernandez C. Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey, I: resting discharge and response to constant angular accelerations. J Neurophysiol. 1971;34:635–660.

18. Lysakowski A, Minor LB, Fernández C, Goldberg JM. Physiological identification of morphologically distinct afferent classes innervating the cristae ampullares of the squirrel monkey. J Neurophysiol. 1995; 73: 1270–1281.

19. Minor L. Physiological principles of vestibular function on earth and in space. Otolaryngol Head Neck Surg. 1998; 118:S5–S15.

20. Green GD. Regional variations in the visual acuity for interference fringes on the retina. J Physiol. 1970; 207:351–356.

21. Rhoton A, Tedeschi H. Microsurgical anatomy of acoustic neuroma. Neurosurgery Clinics of North America Volume 19, Issue 2, 2008:145-174.

22. Sandifort E: Observations anatomicopathologicae. 1777. Lugduni Balvarorum. (Generic reference) 116-120.

23. Charabi S. Acoustic Neuroma/Vestibular Schwannoma. In Vivo and in Vitro Growth Models. A Clinical and Experimental Study. Acta Otolaryngol (Stockh) 1997;530: 6-27.

24. Akard W, Tubbs RS, Seymour ZA, Hitselberger WE, Cohen-Gadol AA. Evolution of techniques for the resection of vestibular schwannomas: from saving life to saving function. J Neurosurg 2009:110:642–647.

25. Cruveilhier J. Anatomie pathologique du corps humain, ou Descriptions, avec

figures lithographiées et coloriées, des diverses alterations morbides dont le corps humain est susceptible. Paris: Bailiére, 1829–1842, Vol 2; Liv 32, Pl 2, 19–24; Liv 38, Pl 5, 1–4.

26. Machinis TG, Fountas KN, Dimopoulos V, Robinson JS. History of acoustic neurinoma surgery. Neurosurg Focus 2005. 18(4): e9.

27. Cushing H: Tumours of the Nervus Acusticus and the Syndrome of the Cerebellopontine Angle. Philadelphia: wb Saunders 1917,183-242.

28. Tooth HH. The treatments of tumours of the brain and the indications for operation. Trans 17th Intl Con Med Lond 7. 1913: 203–299.

29. Dandy W. An operation for the total extirpation of tumours in the cerebello-pontine angle. A preliminary report. Bull Johns Hopkins Hosp 1922, 33:344–345.

30. Koerbel A, Gharabaghi A, Safavi-abbasi S, Tatagiba M, Samii M. Evolution of vestibular schwannoma surgery: the long journey to current success. Neurosurg Focus 2005, 18 (4):e10.

31. Dandy W. Ventriculography following the injection of air into the central ventricles. Ann Surg 1918, 68:5–11.

32. Foote RL, Coffey RJ, Swanson JW, Harner SG, Beatty CW, Kline RW, Stevens LN, Hu TC. Stereotactic radiosurgery using the gamma knife for acoustic neuromas. International Journal of Radiation Oncology, Biology, Physics 1995, 32(4):1153-60.

33. Preston D, Ron E, Yonehara Sh, Kobuke T, Fujii H, Kishikawa M. Tumours of the nervous system and pituitary gland associated with atomic bomb radiation exposure. J Natl Cancer Inst. 2002; 94:1555-1563.

34. Karlan MS, Basek M, Potter GB.Intracochlear neurilemoma. Arch Otolaryngol 1972; 96:573-575.

35. Herwadker A, Vokurka EA, Evans DG, Ramsden RT, Jackson A. Size and growth rate of sporadic vestibular schwannoma: predictive value of information available at presentation. Otol Neurotol 2005; 26:86-92.

36. Edwards CG. Exposure to loud noise and risk of acoustic neuroma. PhD dissertation. Med.School of the Ohio State University 2007, 7-10.

37. Thomasen Per Caye, Baandrup Lone, Jacobsen Grete Krag, Thomsen Jens, Stangerup Steven-Eric. Immunohistochemical Demonstration of Vascular Endothelial Growth Factor in Vestibular Schwannomas Correlates to Tumour Growth Rate. Laryngoscope 2003, 113:2129–2134.

38. Ho S, Kveton J. Acoustic neuroma: Assessment and management. Otolaryngologic Clinics of North America V35: N2: 2002, 393-404.

39. Stonecypher MS, ChaudhuryAR, Byer SJ, Carroll SL. MS: Neuregulin growth factors and their ErbB receptors form a potential signaling network for schwannoma tumourigenesis. J Neuropathol Exp Neurol 2006; 65:162-175.

40. Eldridge R, Parry D. Vestibular schwannoma (acoustic neuroma) consensus development conference. Neurosurgery 1992, 30:962-964.

41. Daniels RL, Swallow C, Shelton C, Davidson HC, Krejci CS and Harnsberger HR. Causes of unilateral sensorineural hearing loss screened by high-resolution fast spin echo magnetic resonance imaging: review of 1070 consecutive cases. Am. J. otol 21: 2000, 173-180.

42. Stangerup SE, Caye-Thomasen P, Tos M, Thomsen J. The natural history of vestibular schwannoma. Otol Neurotol 2006; 27:547-552.

43. Adelman S. Identification of acoustic neuroma in noise-exposed workers. Scand Audiol 1983; 12: 247-250.

44. Komatsuzaki A, Tsunoda A. Nerve origin of the acoustic neuroma. J Laryngol Otol 2001; 115(5):376-379.

45. Hain T. Acoustic Neuroma. Dizziness-and-balance.com (25.06.2011).

46. ¿Cuántos habitantes tiene España? www.sergas.es (04.08.2011).

47. Valvassori G and Shannon M. Natural history of VSs. Skull Base Surgery, V1:N3, 1991. 165-167.

48. Kim L, Klopfenstein J, Porter R, Syms M. Acoustic neuroma: Symptoms and

diagnosis. Barrow quarterly. Vol 20 No.4.2004. 7-13.

49. Chaimoff M, Nageris BI, Sulkes J, Spitzer T, Kalmanowitz M. Sudden hearing loss as a presenting symptom of acoustic neuroma. AMJ otolaryngol 20,1999: 157-160.

50. Jackler RK, Pitts LH. Acoustic Neuroma. Neurosurg Clin NA 1990:199-223.

51. Fortnum H, O'Neill C, Taylor R, Lenthall R, Nikolopoulos T, Lightfoot G, O'Donoghue G, Mason S, Baguley D, Jones H, Mulvaney C. The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost effectiveness and natural history. Health Technol Assess 2009;13:iii-iv, ix-xi, 1-154.

52. Suzuki M, Hashimoto S, Kano S, Okitsu T. Prevalence of Acoustic Neuroma Associated With Each Configuration of Pure Tone Audiogram in Patients With Asymmetric Sensorineural Hearing Loss. Ann Otol Rhinol Laryngol. 2010, 119(9):615-618.

53. Stangerup S, Tos M, Caye-Thomasen P, Tos T, Klokker M, Thomsen J. Increasing annual incidence of vestibular schwannoma and age at diagnosis. J Laryngol Otol 2004, 118:622-627.

54. Pedriali IVG, Kozlowski L. Auditory Brainstem Response on the Detection of the Acoustic Neuroma. International Archives of Otorhinolaryngology 2005;9(1):1.

55. Selesnick S, Jackler R, Pittis L. The changing clinical presentation of acoustic tumours in the MRI era. The Laryngoscope 1993, 103: 431–436.

56. Laurikainen E, Johansson R, Varpula R. Audiovestibular findings and location of an acoustic neuroma. Eur Arch Otorhinolaryngol 2000, 257 :237–241.

57. Chaimoff M, Nageris BI, Sulkes J, Spitzer T, Kalmanowitz M Sudden hearing loss as a presenting symptom of acoustic neuroma. Am J Otolaryngol 1999, 20:157-160.

58. Naessens BF, Gordts F, Clement PA, Buisseret T. Reevaluation of the ABR in the diagnosis of CPA tumours in the MRI-era. Acta Otorhinolaryngol Belg 1996, 50:99–102.

59. Nadol JB, Diamond PF, Thornton AR. Correlation of hearing loss and radiologic

dimensions of vestibular schwannomas (VSs). Am J Otol 1996, 17:312–316.

60. Bush ML, Jones RO, Shinn JB. Auditory brainstem response threshold differences in patients with vestibular schwannoma: a new diagnostic index. Ear, Nose and Throat Journal 01.08.2008 online (1).

61. Dowley AC. Whitehouse WP, Mason SM, Cope Y, Grant J, Gibbin KP.Auditory neuropathy: unexpectedly common in a screened newborn population. Dev Med Child Neurol. 2009;51(8):642-646.

62. Berlin C. Assessment of cochlear function with distortion products of otoacoustic emissions in acoustic neuroma. HNO. 1996 Dec;44(12):677-684.

63. Liberman, M. C., Gao, J., He, D. Z., Wu, X., Jia, S., & Zuo J. Prestin is required for electromotility of the outer hair cell and for the cochlear amplifier. Nature 2002;419, 300-304.

64. Decker N. Otoacoustic emissions. Seminars in Hearing 1992; 13 (1).

65. Hall JW. Handbook of Otoacoustic Emissions. San Diego, Calif: Singular Publishing 1999;439-451.

66. Robinette M, Glattke MR. Otoacoustic Emissions: Clinical Applications. NY: Thieme Medical Publishers; 1997; 63-82.

67. Brownell WE. Outer hair cell electromotility and otoacoustic emissions. *Ear & Hearing*, 1990;11(2), 82–92.

68. Ceranic BJ, Prasher DK, Luxon LM. Presence of tinnitus indicated by variable spontaneous otoacoustic emissions. *Audiol Neurootol*, 1998;3(5),332-44.

69. Perez M, Delgado RE, Ozdamar O. Design of a clinically viable pneumatic system for the acquisition of pressure compensated otoacoustic emissions. Conf Proc IEEE Eng Med Biol Soc. 2011,7699-7702.

70. Gorga M, Neely S, Ohlrich B, Hoover B, Redner J, Peters J. From laboratory to clinic: A large scale study of distortion product otoacoustic emissions in ears with normal hearing and ears with hearing loss. Ear & Hearing, 18; 1997, 440-455.

71. Kharkheli ESh, Shurygina LS, Davitashvili OZ, Tushishvili MA, Chibalashvili

Bibliography

NIu, Korteweg MP, Kevanishvili ZSh. Acoustic neuroma diagnosis. Georgian Med News. 2011 Mar;(192):21-28.

72. Althen H, Wittekindt A, Gaese B, Kössl M, Abel C. Effect of contralateral pure tone stimulation on distortion emissions suggests a frequency specific functioning of the efferent cochlear control. J Neurophysiol. 2012.,400-452.

73. Reyes SA. Salvi RJ, Burkard RF, Coad ML, Wack DS, Galantowicz PJ, Lockwood AH. Brain imaging of the effects of lidocaine on tinnitus. Hearing Research 2002, 171(1-2), 43-50.

74. Cope TE, Baguley DM, Moore BC. Tinnitus loudness in quiet and noise after resection of vestibular schwannoma. Otol Neurotol. 2011;32(3):488-496.

75. Shehata WE, Brownell WE, Dieler R. Effects of salicylate on shape, electromotility and membrane characteristics of isolated outer hair cells from guinea pig cochlea. Acta Oto-laryngologica 1991, 111 (3), 707-718.

76. Shera CA. Mechanisms of mammalian otoacoustic emission and their implications for the clinical utility of otoacoustic emissions. Ear and hearing 2004; 25 (2):86-97.

77. Shiomi Y: Tsuji, J., Naito, Y., Fujiki, N., & Yamamoto. Characteristics of DPOAE audiogram in tinnitus patients. Hearing Research 1997, 108, 83-88.

78. Stach B, Clifton Park. Comprehensive dictionary of audiology illustrated 2nd Ed. New York: Thomson Delmar Learning 2003; 100-110.

79. Starr A. Cochlear receptor (microphonic and summating potentials, otoacoustic emissions, and auditory pathway (auditory brain stems potentials) activity in auditory neuropathy. Ear & Hearing 2001, 11(3), 215-230.

80. Cunningham RF. Otoacoustic Emissions: Beyond Newborn Hearing Screening ebekah., Still University, Arizona School of Health Sciences http://www.audiologyonline.com (14/3/2011)

81. Stavroulaki P, Vossinakis IC, Dinopoulou D, Doudounakis S, Adamopoulos G, Apostolopoulos N. Otoacoustic emissions for monitoring aminoglycoside-induced ototoxicity in children with cystic fibrosis. Arch Otolaryngol Head Neck Surg 2002, 128,150-155.

82. Swabey MA. Using otoacoustic emissions as a biometric. Proceedings of the First International Conference on Biometric Authentication (ICBA 2004), Hong Kong2004, 600-606.

83. Mihajloski T, Lachowska M, Bennett CL, Ozdamar O. Hearing level equalized otoacoustic emissions acquired by swept-tones: Intensity characteristics. Conf Proc IEEE Eng Med Biol Soc. 2011; 2011:818-821

84. Deltenre P, Mansbach AL, Bozet C, Christiaens, F., Barthelemy P. Auditory neuropathy with preserved cochlear microphonic and secondary loss of otoacoustic emissions. Audiology, 1999; 38 (4),187-195.

85. Gorga MP, Stelmachowicz, PG, Barlow SM, Brookhouser PE. From laboratory to clinic: A large scale study of distortion product otoacoustic emissions in ears with normal hearing and ears with hearing loss. Ear & Hearing1997;18, 440-455.

86. Xu J, Liu C, Guo L, Lian N, Liu B. Spontaneous otoacoustic emissions and efferent control of cochleaHandbook of otoacoustic emissions. New York: Singular Publishing Group Thomson Learning. 2000, Zhonghua Er Bi Yan Hou Ke Za Zhi, 2001;36(6):436-440.

87. LePage EL. A model for cochlear origin of subjective tinnitus: Excitatory drift in the operating point of inner hair cells. In: J. Vernon & A. Møller (Eds.), Mechanisms of tinnitus. Boston: Allyn and Bacon. 1995;115-148.

88. Hesse G, Laubert A. Acoustic neurinoma with preserved inner ear function. Interesting audiologic constellation of findings. HNO. 2002;50(1):59-61.

89. Rosanowski F, Hoppe U, Pröschel U, Eysholdt U. Chronic tinnitus in children and adolescents. HNO, 45(11), 927-932.

90. Cacace AT, Lovely TJ, Winter DF, Parnes SM, McFarland DJ. Auditory perceptual and visual-spatial characteristics of gaze-evoked tinnitus. Audiology 1994;33(5):291-303.

91. Shera CA, Guinan JJ. Evoked otoacoustic emissions arise by two fundamentally different mechanisms: a taxonomy for mammalian OAEs. J Acoust Soc Am. 1999;105(2 Pt 1):782-798.

92. Shiomi Y: Characteristics of DPOAE audiogram in tinnitus patients. Hearing Research 108, 1997; 83-88.

93. Quaranta A, Zini C, Gandolfi A, Piazza F, De Thomasis G, Frisina A, Mercante G,Quaranta N, Scaringi A, Uccelli M. Acoustic neuroma: clinical-functional finding, results and surgical complication. Acta Otorhinolaryngol Ital 2001 Oct;21(5 Suppl 68):1-20.

94. Singh G, Tatke M. Rosenthal fibers and eosinophilic granular bodies in an acoustic schwannoma. Indian J Pathol Microbiol. 2011;54(3):629-631.

95. Friedman RA, Berliner KI, Bassim M, Ursick J, Slattery WH, Schwartz MS, Brackmann DE. A paradigm shift in salvage surgery for radiated vestibular schwannoma. Otol Neurotol. 2011;32(8):1322-1328.

96. van Huffelen WM, Mateijsen NJ, Wit HP. Classification of patients with Meniere's disease using otoacoustic emissions. Audiology & Neuro-Otology 1998, 3, 419-430.

97. Burch-Sims PG, Ochs MT. The anatomic and physiologic bases of otoacoustic emissions. The Hearing Journal, 1992;45(11):9-l0.

98. Probst R, Lonsbury-Martin BL, Martin GK. A review of otoacoustic emissions. J Acoust Soc Am 1991;89:2027-2067.

99. Wang Y, Jiang HY, Guan C, Jiang XJ, Kazuo I, Zhou HW. Gait instability in patients with small acoustic neuroma. Chin Med J (Engl). 2011;124(11):1735-1738.

100. Vailleau B, Qu'hen C, Vidal PP, de Waele C. Probing residual vestibular function with galvanic stimulation in vestibular loss patients. Otol Neurotol. 2011 Jul;32(5):863-781.

101. Zappia JJ: Rethinking the use of auditory brainstem response in acoustic neuroma screening. Laryngoscope. Oct 1997;107(10):1388-1392.

102. Chandrasekhar SS, Brackmann DE, Devgan KK. Utility of auditory brainstem response audiometry in diagnosis of VSs. Am J Otol. Jan 1995;16(1):63-67.

103. Gordon ML, Cohen NL. Efficacy of auditory brainstem response as a screening test for small VSs. Am J Otol. Mar 1995;16(2):136-139.

*104.*Schmidt RJ, Sataloff RT, Newman J, Spiegel JR, Myers DL The sensitivity of auditory brainstem response testing for the diagnosis of VSs. Arch Otolaryngol Head Neck Surg. Jan 2001;127(1):19-22.

105.Cueva RA. Auditory brainstem response versus magnetic resonance imaging for the evaluation of asymmetric sensorineural hearing loss. Laryngoscope. Oct 2004;114(10):1686-1692.

106.Kehrle HM, Granjeiro RC, Sampaio ALL, Bezerra R, Almeida VF, Oliveira CA Comparison of auditory brainstem response results in normal-hearing patients with and without tinnitus. Arch Otolaryngol Head Neck Surg. Jun 2008;134(6):647-651.

107.de Sousa LC, Colli BO, Piza MR, da Costa SS, Ferez M, Lavrador M. Auditory brainstem response: prognostic value in patients with a score of 3 on the Glasgow Coma Scale. Otol Neurotol. 2007;28(3):426-428.

108. McDonald R. Acoustic neuroma: what the evidence says about evaluation and treatment. J Fam Pract. 2011 Jun;60(6):E1-4.

109.Don M, Masuda A, Nelson R, Brackmann D. Successful detection of small acoustic tumours using the stacked derived-band auditory brain stem response amplitude. Am J Otol. Sep 1997;18(5):608-21;682-685.

110. Doyle KJ. Is there still a role for auditory brainstem response audiometry in the diagnosis of acoustic neuroma? Arch Otolaryngol Head Neck Surg. Feb 1999;125(2):232-234.

111.Kakigi A, Nakatani H, Takeda T. Electrocochleographic and pure-tone audiometric findings in contralateral ear of unilateral acoustic neurioma. ORL J Otorhinolaryngol Relat Spec. 2010; 71, 1:78-84.

112. Jack Katz, Larry Medwetsky, Robert Burkard, Linda Hood Handbook of Clinical Audiology. Baltimore, Md: Lippincott Williams & Wilkins; 1994;200-220.

113. Kileny PR, Niparko JK, Shepard NT, Kemink JL. Neurophysiologic intraoperative monitoring: I. Auditory function. Am J Otol. Dec 1988;9 Suppl:17-24.

114. Lieu JE, Champion G. Prediction of auditory brainstem reflex screening referrals in high-risk infants. Laryngoscope. Feb 2006;116(2):261-267.

115. Markand ON: Brainstem auditory evoked potentials. *J Clin Neurophysiol*. May

1994; 11(3):319-42.

116. National Institutes of Health. Acoustic Neuroma. *NIH Consens Statement*. 1991;9 (4):1-24.

117. Simon MV. Neurophysiologic intraoperative monitoring of the vestibulocochlear nerve. J Clin Neurophysiol. 2011 Dec; 28(6):566-581.

118. Wilson DF. Talbot JM, Mills L. The sensitivity of auditory brainstem response testing in small VSs. Laryngoscope. 1992 Sep; 102(9):961-964.

119. Josey AF, Glasscock ME III, Musiek FE. Correlation of ABR and medical imaging in patients with cerebellopontine angle tumours. Am J Otol. 1988;9(suppl):12-16.

120. Selesnik SH, Jackler RK. Atypical hearing loss in acoustic neuroma patients. Laryngoscope. 1993; 103:437-441.

121. Dornhoffer JL, Helms J, Hoehmann DH. Presentation and diagnosis of small acoustic tumours. Otolaryngol Head Neck Surg. 1994; 111:232-235.

122. Schmidt RJ, Sataloff RT, Newman J, Spiegel JR, Myers DL. The Sensitivity of Auditory Brainstem Response Testing for the Diagnosis of VSs. Arch Otolaryngol Head Neck Surg. 2001;127: 19-22;

123. Black FO, Angel CR, Pesznecker SC, Gianna C. "Outcome analysis of individualized vestibular rehabilitation protocols." American J Otology 2000; 21:543-551.

124. Calder JH, Jacobson GP "Acquired bilateral peripheral vestibular system impairment: rehabilitative options and potential outcomes." J American Academy Audiology 2000; 11:514-521.

125. Shepard NT, Telian SA. Practical Management of the Balance Disorder Patient. Singular Publishing Group, Inc., San Diego1996, p221.

126. Rose D, Clark S. "Can the control of bodily orientation be significantly improved in a group of older adults with a history of falls?" *JAGS* 2000; 48:275-282.

127. Stewart MG, Chen AY, Wyatt R, Favrot S, Beinart S, Coker NJ, Jenkins HA. Cost-effectiveness of the diagnostic evaluation of vertigo. *The Laryngoscope*. 1999;108:600-605.

128. Gianoli G, McWilliams S, Soileau J & Belafsky P. Posturographic performance in patients with the potential for secondary gain. Otolaryng Head Neck Surg 2000;

122:11-18.

129. Fortnum H, C O'Neill, R Taylor, R Lenthall, T Nikolopoulos, G Lightfoot, C Mulvaney. The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost-effectiveness and natural history. Health Technology Assessment 2009; Vol. 13: No. 18;

130. Curtin DH, Hirsch WL Jr: Imaging of VSs. Neurosurg Clin N Am 19, 2008. 175–205.

131. Glasscock ME, Levine SC, McKennan KX. The changing characteristics of acoustic neuroma patients over the last 10 years. Laryngoscope 1987;97:1164–1167.

132. Gentry LR, Gentry LR, Jacoby CG, Turski PA, Houston LW, Strother CM, Sackett JF. Cerebellopontine angle-perromastoid mass lesions. Comparative study of diagnosis with MR imaging and CT. Radiology 1987; 162:513.

133. Sheps SB, Schechter MT. The assessment of diagnostic tests. JAMA 1984; 252:2418-2422.

134. Newton JR, Shakeel M, Flatman S, Beattie C, Bhasker R. Magnetic resonance imaging screening in acoustic neuroma. American Journal of Otolaryngology–Head and Neck Medicine and Surgery 31 (2010) 217–220.

135. Weissman JL. Hearing loss. Radiology 1996; 199: 593-611.

136. Jackler RK. Cost-effective screening for acoustic neuroma with unenhanced MR; a clinician's perspective. Am J Neuroradiol 1996; 17:1226-1228.

137. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, Lugt Aam. Incidental findings on brain MRI in the general population. N Engl J Med 2007;357:1821–1828.

138. Sughrue ME, Yang I, Aranda D, Rutkowski MJ, Fang S, Cheung SW, Parsa AT. The natural history of untreated sporadic vestibular shwannomas: a comprehensive review of hearing outcomes. J Neurosurg 2010;112:163–167.

139. Flickinger JC, Kondziolka D, Niranjan A, Lunsford LD. Results of acoustic neuroma radiosurgery: an analysis of 5 years' experience using current methods. J Neurosurg 2001; 94:1–6.

140. Slattery WH, Brackmann DE, Hitselberger W. Middle fossa approach for hearing preservation with VSs. Am J Otol 1997;18:596–601.

141. Meyer TA, Canty PA, Wilkinson EP, Hansen MR, Rubinstein JT, Gantz BJ. Small VSs: surgical outcomes versus observation or radiation. Otol Neurotol

2006;27:380–392.

142. Glasscock 3rd ME, Pappas DG Jr, Manolidis S, Von Doersten PG, Jackson CG, Storper IS. Management of acoustic neuroma in the elderly population. Am J Otol 1997; 18: 236-242.

143. Levo H, Pyykkö I, Blomstedt G. Non-surgical treatment of vestibular schwannoma patients. Acta Otolaryngol [Suppl] (Stockh) 529:56–58.

144. Valvassori GE, Guzman M. Growth rate of VSs. Am J. Otol.1989; 10:174-176.

145. Thomsen J, Tos M. Acoustic neuroma: clinicalaspects, audiovestibular assessment, diagnostic delay, and growth rate. Am J Otol 1990:11: 12-19.

146. Bederson JB, von Ammon K, Wichmann WW, Yasargil MG. Conservative treatment of patients with acoustic tumours. Neurosurgery 1991 May; 28(5):646–651.

147. Sterkers O, Badreldine M, Martin N, Viala P, Sterkers JM. Slow versus rapid growing VSs. In: Tos M, Thomsen J (eds) Proceedings of the First International Conference on Acoustic Neuroma. Kugler Pub, Amsterdam New York, pp 145-147 1992.

148. Ogawa K, Kanzaki J, Yamamoto M, Ikeda S, Shiobara R. The growth rate of VSs. Acta Otolaryngol [Suppl] (Stockh) 1991; 487:157-163.

149. Nedzelski JM, Nedzelski JM, Schessel DA, Peiderer A, Kassell EE, Rowed DW. The natural history of growth of VSs and its role in non operative management. In: Tos M, Thomsen J (eds) Proceedings of the First International Conference on Acoustic Neuroma. Kugler Pub, Amsterdam New York 1992,149-158.

150. Charabi Samih. Acoustic neuroma (vestibularschwannoma): growth and surgical and nonsurgical consequences of the wait and see policy. Otolaryngol Head Neck Surg 1995; 113:5-14.

151. Woods CI, Glasscock M.E, Jackson Gary, Matar Salim. Followed acoustic tumours. In:Tos M, Thomsen J(eds) Proceedings of the First International Conference on Acoustic Neuroma. Kugler Pub1992, Amsterdam New York, 159-163.

152. Noren G, Greitz D. The natural history of acoustic neurinomas. In:TosM, ThomsenJ (eds) Proceedings of the First International Conference on Acoustic Neuroma. Kugler Pub 1992, Amsterdam NewYork, 191-192.

153. Rosenberg SI, Silverstein H, Gordon M A, Flanzer JM, Willcox TO, Silverstein J. A comparison of growth rates of VSs: nonsurgical patients vs. subtotal resection.

Otolaryngol Head Neck Surg 1993; 109:482-487.

154. Strasnik B, Glasscock ME 3rd, Haynes D, McMenomey SO, Minor LB. The natural history of untreated VSs. Laryngoscope 1994;104:1115-1119.

155. Modugno GC, Pirodda A, Ferri GG, Fioravanti A, Calbucci F, Pezzi A, Ceroni AR, Pirodda E. Small VSs: Monitoring the Growth Rate by MRI. Acta Neurochir (Vienna) 1999. 14.141: 1063-1067.

156. Lassaletta L, Gavilán J. An update on the treatment of vestibular schwannoma. Acta Otorrinolaringol Esp. 2009;60(2):131-140.

157. Alfonso C, Castro A, Gavilán J. Calidad de vida tras la cirugía del schwannoma vestibular. Acta Otorrinolaringol. Esp. 2007; 58:61-65.

158. Naguib MB, Saleh E, Aristegui M, Mazzoni A, Sanna M. Decision making in acoustic neuroma management: the only hearing ear. Skull base surgery. 1994; 4(1): 32–36.

159. Das Kaushik, Murali R, Lindstrom JC, Couldwell TW. Symptomatic Subdural Hygroma and Temporal Lobe Edema After Translabyrinthine Removal of Acoustic Neuroma. Case report, Skull Base. 2001; 11(2): 137–142

160. Kondziolka D, Flinckinger JC. Long-term outcomes after radiosurgery for VSs. N Engl J Med 1998; 339: 1426-1433.

161. Whittaker CK, Luetje CM Vestibular schwannomas. J Neurosurg 1992;76:897–900.

162. Briggs RJ, Luxford WM, Atkins JS: Translabyrinthine removal of large VSs. Neurosurgery. 1994; 34: 785–90; discussion 790–791.

163. Koos WT, DayJD, Matula Cetal. Neurotopographic considerations in the microsurgical treatment of small acoustic neurinomas. Neurosurg 1998; 88:506–512.

164. Baschnagel AM, Chen PY, Bojrab D, Pieper D, Kartush J, Didyuk O, Hearing preservation in patients with vestibular schwannoma treated with Gamma Knife surgery. J Neurosurg. 2013 Mar;118(3):571-8. doi: 10.3171/2012.10.JNS12880. Epub 2012 Dec 7.

165. Gjuric M, Wigand ME, Wolf SR. Enlarged middle fossa vestibular schwannoma surgery: experience with 735 cases. Otol Neurotol 2001; 22:223–230; discussion 230–231.

166. Chen DA. Acoustic neuroma in private neurotology practice: trends in demographics and practice patterns. Laryngoscope 2007;117 (11):2003–2012.

167. Jackler RK, Pitts LH: Selection of surgical approach to acoustic neuroma: 1992. Neurosurg Clin N Am 2008;19 (2):217–238.

168. Schmerber S, Vasdev A, Chahine K, Tournaire R, Bing F. Long-term control of vestibular schwannoma after a translabyrinthine complete removal. Neurosurgery 2005;57(4):693-698.

169. Silk PS, Lane JI, Driscoll CL. Surgical Approaches to Vestibular Schwannomas: What the Radiologist Needs to Know. November 2009 RadioGraphics, 29, 1955-1970.

170. Haynes BM. Surgical approaches and complications in the removal of vestibular schwannomas. Otolaryngol Clin North Am 2007; 40(3):589–609.

171. Ryzenman JM, Pensak ML, Tew JM. Headache: a quality of life analysis in a cohort of 1,657 patients undergoing acoustic neuroma surgery results from the Acoustic Neuroma Association. Laryngoscope 2005;115(4):703–711.

172. Falcioni M, Taibah A. Cerebrospinal fluid leak after retrosigmoid excision of vestibular schwannomas. Otol Neurotol 2008;29(3): 384–386.

173. Falcioni M: Mangus Brannon D, Rivas Alejandro, Yoo Mi Jin, Alvarez JoAnn, Wanna George B, Haynes David S, Bennett Marc L. Management of Cerebrospinal Fluid Leaks After Vestibular Schwannoma Surgery. Otol & Neurol, December 2011 - Volume 32 - Issue 9; 1525–1529.

174. Kameda K, Shono T, Hashiguchi K, Yoshida F, Sasaki T. Effect of tumour removal on tinnitus in patients with vestibular schwannoma. J Neurosurg. 2010 Jan;112(1):152-157.

175. Schmerber S, Palombi O, Boubagra K, 5 Charachon R, Chirossel JP, Gay E. Long-term control of vestibular schwannoma after a translabyrinthine complete removal. Neurosurgery 2005; 57(4):693-698.

176. Brors D, Schafers M, Bodmer D, Draf W, Kahle G, Schick B. Postoperative magnetic resonance imaging findings after transtemporal and translabyrinthine vestibular schwannoma resection. Laryngoscope 2003;113(3):420–426.

177. Shelton C. Unilateral acoustic tumours: how often do they recur after translabyrinthine removal. Laryngoscope 1995;105(9 pt 1):958–966.

178. Larson TL: Understanding the posttreatment imaging appearance of the internal auditory canal and the cerebellopontine angle. Semin Ultrasound CT MR 2003;24(3):133–146.

179. Yang I, Sughrue ME, Han SJ, Fang S, Aranda D, Cheung SW, Pitts LH, Parsa AT.

Facial nerve preservation after vestibular schwannoma Gamma Knife radiosurgery. Journal of neuro-oncology. 2009;93(1):41-48.

180. Kondziolka D, Mathieu D, Lunsford LD, Martin JJ, Madhok R, Niranjan A, Flickinger JC. Radiosurgery as Definitive Management for Intracranial Meningiomas. Neurosurgery. 2008;62(1):53.

181. Lee JY, Niranjan A, McInerney J, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery providing long-term tumour control of cavernous sinus meningiomas. Journal of neurosurgery. 2002;97(1):65-72.

182. Myrseth E, Pedersen PH, Moller P, Lund-Johansen M. Treatment of vestibular schwannomas. Why, when and how? Acta Neurochir (Wien) 2007, 149:647-660.

183. Yamakami I, Uchino Y, Kobayashi E, Yamaura A. Conservative management, gamma-knife radiosurgery, and microsurgery for acoustic neurinomas: a systematic review of outcome and risk of three therapeutic options. Neurol Res 2003, 25:682-690.

184. Flickinger JC, Kondziolka D, Niranjan A, Maitz A, Voynov G, Lunsford LD: Acoustic neuroma radiosurgery with marginal tumour doses of 12 to 13 Gy. Int J Radiat Oncol Biol Phys 2004, 60:225-230.

185. Karpinos M, Teh BS, Zeck O, Carpenter LS, Phan C, Mai WY, Lu HH, Chiu JK, Butler EB, Gormley WB, Woo SY. Treatment of acoustic neuroma: stereotactic radiosurgery vs. microsurgery. Int J Radiat Oncol Biol Phys 2002, 54:1410-1421.

186. Kaylie DM, Horgan MJ, Delashaw JB, McMenomey SO. A meta-analysis comparing outcomes of microsurgery and gamma knife radiosurgery. Laryngoscope 2000, 110:1850-1856.

187. Linskey ME. Hearing preservation in vestibular schwannoma stereotactic radiosurgery: what really matters? J Neurosurg 2008, 109(Suppl):129-136.

188. Flickinger JC, Kondziolka D, Pollock BE, Lunsford LD. Evolution in technique for vestibular schwannoma radiosurgery and effect on outcome. Int J Radiat Oncol Biol Phys 1996, 36:275-280.

189. Hansen MR, Clark JJ, Gantz BJ, et al. Effects of ErbB2 signaling on the response of vestibular schwannoma cells to gamma-irradiation. Laryngoscope. Jun 2008; 118 (6):1023-1030.

190. Lim YJ, Choi SK. Gamma Knife Radiosurgery for Vestibular Schwannomas. J Korean Neurosurg Soc 2007 (42)159-167.

191. Mitsuoka H, Arai H, Tsunoda A, Okuda O, Sato K, Makita J. Microanatomy of the

cerebellopontine angle and internal auditory canal: study with new magnetic resonance imaging technique using three-dimensional fast spin echo. Neurosurgery 1999;(44)561-566.

192. Pitts LH, Jackler RK. Treatment of VSs [editorial; comment]. N Engl J Med. Nov 12 1998; 339(20):1471-1473.

193. Lunsford LD, Flickinger J, Coffey RJ. Stereotactic gamma knife radiosurgery. Initial. North American experience in 207 patients. Arch Neurol. Feb 1990; 47(2):169-175.

194. Seker Askin, Kilic Turker. Atlas of anatomical dissections: The Cerebellopontine angle. Marmara University, Turkey,
http://nsa.marmara.edu.tr/anatomy/6/Serebellopontin-Aci.

195. Lanman TH, Brackmann DE, Hitselberger WE, et al. Report of 190 consecutive cases of large acoustic tumours (vestibular schwannoma) removed via the translabyrinthine approach. J Neurosurg. Apr 1999;90(4):617-623.

196. Arthurs BJ, Lamoreaux WT, Giddings NA, Fairbanks RK, Mackay AR, Demakas JJ, Cooke BS, Lee CM. Gamma Knife radiosurgery for vestibular schwannoma: case report and review of the literature. World Journal of Surgical Oncology 2009, **7**:100/1477-7819-7-100.

197. Smouha EE, Yoo M, Mohr K. Conservative management of acoustic neuroma: a meta-analysis and proposed treatment algorithm. Laryngoscope 2005, 115:450-454;

198. Claussen CF: Clinical Study of Human Equilibrium by Electronystagmography and Other Allied Tests, Popular Prakashan, Bombay 1978, 180-205.

199. Kirtane MV. Standardization in electronystagmography. Ind. J. Otolaryngol 1979; 31: 126-132.

200. Cevette MJ, Puetz B, Marion MS, Wertz ML, Muenter MD. Aphysiologic performance on dynamic posturography. Otolaryngol Head Neck Surg. 1995; 112:676-688.

201. Rey-Martínez J, Rama-López J, Pérez-Fernández N. Exploración posturográfica de pacientes simuladores. Acta Otorrinolaringol Esp. 2007; 58:202-207.

202. Ronda JM. Asociación entre síntomas elínicos Y Resultados de la Posturografía Computarizada Dinámica. Acta Otorrinolaringol Esp 2002; 53: 252-255.

203. Mehra YN. Eletronystagmography: A study of caloric tests in normal subjects. J Laryngol Otol 1964; 78:520-529.

204. Riesco-MacClure JS. Caloric tests: methods and interpretation. Ann Otol Rhinol

Laryngol 1964; 73:829-837.

205. Hulshof JH, Hilders CGJM, Baarsma EA. Vestibular investigation in acoustic neuroma. Acta Otolaryngol (Stockh) 1989; 108: 38-44.

206. Katsarkas A, Smith H, Galiana H. Caloric and rotational testing: merits, pitfalls and myths. ORL Nova 2001; 11:59-67.

207. Kirtane MV, Medikeri SB, Merchant SN, Desai M, Bhanage B. Electronystagmography findings in VSs. J Postgrad Med 1985;31:128-133.

208. Shiffman FD, Dancer J, Rothballer AB, Berrett A, Baum S. The diagnosis and evaluation of VSs. Otolaryngol. Clin. North. Amer1973, 6:189-198.

209. Linthicum FH, Khalessi MH, Churchill D. Electronystagmographic caloric bithermal vestibular tests (ENG) Results in acoustic tumour cases. In, "Acoustic Tumours", Vol. I. Editors: W. F. House and C. H. Luetje, University Park Press, Baltimore, 1979, 237-240.

210. Pietkiewicz P, Pepaś R, Sułkowski WJ, Zielińska-Bliźniewska H, Olszewski J. Electronystagmography versus videonystagmography in diagnosis of vertigo. Int J Occup Med Environ Health. 2012 Mar;25(1):59-65

211. Welgampola MS, Colebatch JG. Vestibulocollic reflexes: normal values and the effect of age. Clin Neurophysiol. 2001; 112:1971-1979.

212. Renato Cal1, Fayez Bahmad Jr. Vestibular evoked myogenic potentias: an overview. Braz J Otorhinolaryngol 2009; 75(3):456-62.

213. Jongkees LB, Maas JP, Philipszoon AJ. Clinical nystagmography. A detailed study of electronystagmography in 341 patients with vertigo. Pract Otorhinolaryng. 1962;24:65-93.

214. Schwab B, M. Durisin, and G. Kontorinis. Investigation of Balance Function Using Dynamic Posturography under Electrical-Acoustic Stimulation in Cochlear Implant Recipients. Hindawi Publishing Corporation International Journal of Otolaryngology V2010, p7.

215. Dejardin S. The clinical investigation of static and dynamic balance. Clinique Saint-Luc, Bouge, Belgium, B-ENT, 2008, 4, Suppl. 8, 29-36.

216. Said J, Izita A, González AL, Tovar E. Comparative Results of Craniocorpography and the Test of Balance in Tinnitus and Vertigo Patients. International Tinnitus Journal, 2006.Vol. 12, No. 2, 179–184.

217. Claussen CF. Modernas Técnica Topodiagnósticas y Terapéuticas. Berlin: Springer-Verlag, 1988:8–13.

218.Claussen CF, Claussen E. A computer analysis of typical CCG patterns in 1021 neurootological patients. Acta Otolaringol Suppl (Stockh) 1989;468:235–238.

219.Rosmaninho JC. The Medical Audiological Evaluation of Tinnitus Patients. International Tinnitus Journal, 1999.Vol. 5, No. J, 53-56.

220. Claussen CF. Zahl der Schwindelpatienten nimmt ständig zu. Therapie Woche, 1990; 40:1365-1368.

221.Clinton J, Hdeib Alia, Suk Ian, Francis HW, Michael J. Reduction of cerebrospinal fluid rhinorrhea after vestibular schwannoma surgery by reconstruction of the drilled acoustic porus with hydroxyapatite bone cement. JNS 2007 / Vol. 107 / No. 2. 347-351.

222.Jeffrey WB, Rowed WD, Nedzelski JM, Chen JM. Cerebrospinal fluid leak after acoustic neuroma surgery: influence of tumour size and surgical approach on incidence and response to treatment. February 2001 / Vol. 94 / No. 2 /217-223.

223.Magliulo G, Sepe C, Varacalli S, Fusconi M. Cerebrospinal fluid leak management following cerebellopontine angle surgery. J Otolaryngol. 1998; 27(5):258-262.

224.Diaz Anadon A, Lassaletta L, Roda JM, Gavilán J. Fístulas de LCR tras la cirugía de tumoures del ángulo pontocerebeloso y su relación con el índice de masa corporal; Published in Acta Otorrinolaringol Esp.2009; Vol.60.N 05.318-24.

225.Burak Sade, Gérard Mohr, Jean-Jacques J. Vascular complications of vestibular schwannoma surgery: a comparison of the suboccipital retrosigmoid and translabyrinthine approaches. JNS 2006.Vol. 105 / No.2. 200-204.

226. Brennan JW, Rowed DW, Nedzelski JM, Chen JM. Cerebrospinal fluid leak after acoustic neuroma surgery: influence of tumour size and surgical approach on incidence and response to treatment. JNS 2001; 94:217-233.

227.Levo H, Blomstedt G, Pyykkö I. Tinnitus and Vestibular Schwannoma Surgery. Acta Oto-laryngologica, 2000, Vol. 120, No.543, 28-29.

228.Raftopoulos C, Abu Serieh B, Duprez T, Docquier MA, Guérit JM. Microsurgical results with large vestibular schwannomas with preservation of facial and cochlear nerve function as primary aim. Acta Neurochir 2005; 147:697-706.

229.Régis J, Roche PH. Modern Management of Acoustic Neuroma. Prog Neurol Surg. Basel, Karger 2008, Vol. 21,136-141.

230.Pollock BE, Lunsford LD, Kondziolka D, Sekula R, Subach BR,Foote RL. Vestibular schwannoma management. Part II. Failed radiosurgery and the role of delayed microsurgery. 1998, J Neurosurg 89, 949-955.

231. Hwang SK, Park K, Lee DH, Park SH, Park J and Hwang JH. Gamma Knife Radiosurgery. Handbook. Gamma Knife Radiosurgery for the Vestibular Schwannomas, Technical Considerations and Hydrocephalus as a Complication. 2011. 59-69.

232. Pirouzmand F, Tator CH, Rutka J. Management of hydrocephalus associated with vestibular schwannoma and other cerebellopontine angle tumors. Neurosurgery 1995;48:1246–12153.

233. Atlas MD, Perez de Tagle JR, Cook JA, et al. Evolution of the management of hydrocephalus associated with acoustic neuroma. Laryngoscope 1996;106:204–206

234. Cauleya K.A, Ratkovitsa B,S.P. Braffa, Linella G. Communicating Hydrocephalus after Gamma Knife Radiosurgery for Vestibular Schwannoma: An MR Imaging Study. AJNR 2009. 992-994.

235. Balasubramaniam A, Shannon P, Hodaie M, Laperriere N, Michaels H, Guha A. Glioblastoma multiforme after stereotactic radiotherapy for acoustic neuroma: case report and review of the literature. *Neuro Oncol*. Oct 2007;9(4):447-453.

236. Zülch, K.J., Brain tumours: their biology and pathology. 3rd ed. Berlin 1986.

237. Avan M.S, Qureshi H.U, Sheikh A.A, Ali M.M. Vestibular Schwannomas: Clinical Presentation, Management and Outcome. JPMA 02., Pakistan 2002.

238. Martin, Thomas Peter Cutlack, MD thesis, University of Birmingham, 2013.

239. Wiegand, D.A. Oiemann, Ri, Fickel. V. Surgical treatment of acoustic neuroma (vestibular schwaiinoma) in the United States Report from the Acoustic Neuroma Registry. Lanrngoscope, 1996:106(1 Pt I): 58-66.

240. Roland, P.S., Glassock, M E. Acoustic Neuroma. In: Paparella, M M., Shumrick, D.A., Gluckman, iL., et al. eds. Otolaryngology (Vol II).3rd ed, Philadelphia, W.B. Saunders Company, 199 1. 1775-1 787.

241. Tew. J.M., Sawaya. R.. Pensak. M.L. Neurosurgery of the Head and Neck In: Paparella, MM.. Shumrick, D.A., Gluckman, J.L., et at eds. Otolaryngology (Vol IV). 3rd ed. Philadelphia. W.B. Saunders Company, 1991;2983-3031.

242. Eisenberg, M.B., Catalano. P.J., Post, K.L) Manangement of Acoustic Scliwannomas In: Tindall, G.T., Cooper. P.R., Barrow, DL. eds. The Practice of Neurosurgery (Vol 1). Baltimore, Williams and Wilkins, 1996; 995-1004.

243. Samii M, Matthies C. Management of 1000 vestibular schwannomas (acoustic neuromas): surgical management and results with an emphasis on complications and how to avoid them. Neurosurgery. 1997 Jan;40(1):11-21; discussion 21-3.

244. Bakkouri WE, Kania RE, Guichard JP, Lot G, Herman P, Huy PT. Conservative management of 386 cases of unilateral vestibular schwannoma: tumor growth and consequences for treatment. J Neurosurg. 2009 Apr;110(4):662-9. doi: 10.3171/2007.5.16836.

245. Preston-Martin S, Thomas DC, Wright WE, Henderson BE. Noise trauma in the aetiology of acoustic neuromas in men in Los Angeles County, 1978-1985. Br J Cancer 1989;59:783-786.

246. Edwards CG. Exposure to Loud noise and Risk of Acoustic Neuroma. PhD Dissertation, The Ohio State University 2007.

247. Jennifer M. Propp, Bridget J. McCarthy, Faith G. Davis, Susan Preston-Martin Descriptive epidemiology of vestibular schwannomas. J Neuro Oncology, 2005.

248. Sam Eljamel. Problem Based Neurosurgery, Chapter 7. January 24, 2011.

249. Schu¨z J, Steding-Jessen M, Hansen S, Stangerup S, Thomasen P, Poulsen A. Long-Term Mobile Phone Use and the Risk of Vestibular Schwannoma: A Danish Nationwide Cohort Study.

250. Edwards CG, Schwartzbaum JA, Lo¨nn S, Ahlbom A, Feychting M. Exposure to Loud Noise and Risk of Acoustic Neuroma. Am J Epidemiol 2006;163:327–333.

251. Christensen HC, Schüz J, Kosteljanetz M, Skovgaard H, Thomsen J. Johansen C. Cellular Telephone Use and Risk of Acoustic Neuroma Am. J. Epidemiol. (2004) 159 (3);277-283.

252. Takebayashi T, S Akiba, Kikuchi Y, Taki M, Wake K, Watanabe S. Mobile phone use and acoustic neuroma risk in Japan *Occup Environ Med* 2006;63:802-807 doi:10.1136/oem.2006.028308.

253. Kwan TL, Tang KW, Pak KKT, Cheung JYL. Screening for vestibular schwannoma by magnetic resonance imaging: analysis of 1821 patients. Hong Kong Med J Vol 10 No 1 February 2004.

254. Haapaniemi J, Laurikainen E, Miettinen S, Varpula M. Cochleovestibular symptoms related to the site of vestibular schwannoma. Acta Otolaryngol Suppl. 2000;543:14-6.

255. Godefroy WP, Kaptein AA, Vogel JJ, van der Mey AG. Conservative treatment of vestibular schwannoma: a follow-up study on clinical and quality-of-life outcome. Otol Neurotol. 2009 Oct;30(7):968-74.

256. American Association of Otolaryngology Head and Neck Surgery Committee on hearing and equilibrium guidelines for the evaluation of hearing preservation in

acoustic neuroma (vestibular schwannoma). Otolaryngol Head Neck Surg 1995;113:179Y80.

257. Hajioff D, Raut VV, Walsh RM, Bath AP, Bance ML, Guha A, Tator CH, Rutka JA. Conservative management of vestibular schwannomas: third review of a 10-year prospective study. Clinical Otolaryngology, 2008. 33, 255–264.

258. Walsh RM, Bath AP, Bance ML, Keller A, Rutka JA. Consequences to Hearing During the Conservative Management of Vestibular Schwannomas. Laryngoscope 110: February 2000, 250-255.

259. Woodson EA, Dempewolf RD, Gubbels SP, Porter AT, Oleson JJ. Hansen RH, Gantz BJ. Long-Term Hearing Preservation After Microsurgical Excision of Vestibular Schwannoma. Otol Neurotol. 2010 September; 31(7): 1144–1152.

260. Fortnum H. O'Neill C. Taylor TR, et al. The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost effectiveness and natural history. Health Technol Assess 2009;13:iii-iv. ix-xi, 1-154.

261. Suzuki M, Hashimoto S, Kano S, Okitsu T. Prevalence of Acoustic Neuroma Associated With Each Configuration of Pure Tone Audiogram in Patients With Asymmetric Sensorineural Hearing Loss. Annals of Otology 2010. Rhinology & Laryngology 119(9):615-618.

262. Day AS, Wang CT, Chen CN, Young YH. Correlating the cochleovestibular deficits with tumor size of acoustic neuroma. Acta Otolaryngol 2008. 128 (7): 756-60.

263. Koors PD, Thacker LR, Coelho DH. ABR in the diagnosis of vestibular schwannomas: A meta-analysis. Am J Otolaryngol 2013. May-Jun;34(3):195-204.

264. Cueva, RA. "Clinical thresholds for when to test for retrocochlear lesions: pro." Arch Otolaryngol Head Neck Surg. 2010 Jul;136(7):725-727.

265. Shih C, Tseng FY, Yeh TH, JenHsu C, Chen YSh, Ipsilateral and contralateral acoustic brainstem response abnormalities in patients with vestibular schwannoma Otol. Head& Neck Surgery (2009) 141, 695-700.

266. Ferri GG, Modugno GC, Calbucci F, Ceroni AR, Pirodda A. Hearing loss in vestibular schwannomas: analysis of cochlear function by means of distortion-product otoacoustic emissions. ANL -1228. 2009; p5.

267. Perlman HB, Kimura R, Fernandez C. Experiments on temporary obstruction of the internal auditory artery. Laryngoscope 1959;69:591–613.

268. Kagoya R, Shinogami M, Kohno M, Yamasoba T Distortion-product otoacoustic emission tests evaluate cochlear function and differentiate cochlear and vestibular schwannoma. Otolaryngol Head Neck Surg. 2013 Feb;148(2):267-71.

269. Gomez D, Fierek O, Madrazo J, O´Connor C, Galera H. Diagnosis and documentation of central nervous system dysfunctions with craniocorpography after surgical removal of acoustic neurinomas. Otolaryngol Head Neck Surg April 2000 vol. 122;4:592-595.

270. Claussen CF, Helms J, Patil NP, Schneider D. Vestibulospinal testing using cranio-corpo-graphy in patients suffering fromacoustic neuroma. Acta Otolaryngol Suppl. 1989;468:239-41.

271. Serafini F, Caovilla HH, Ganança MM. Digital Craniocorpography and Peripheral Vestibular Diseases. Int Tinnitus J. 2008;14(1):34-36.

272. Gouveris H, Stripf T, Victor A, Mann W. Dynamic posturography findings predict balance status in vestibular schwannoma patients. Otol Neurotol. 2007 Apr ;28(3):372-5.

273. Hernández M, Rodrigo F, García M, Sampériz M, Ajuria E, García O. The role of video-nystagmography in the diagnosis of acoustic neuroma. Acta Otorrinolaringologica Espanola 2003, 54(6):413-416.

274. Diallo BK, Franco-Vidal V, Vasili D, Négrevergne M, Darrouzet P, Diouf R, Darrouzet V. The neurotologic evaluation of vestibular schwannomas. Results of audiological and vestibulartesting in 100 consecutive cases. Rev Laryngol Otol Rhinol (Bord). 2006;127(4):203-9.

275. Iwasaki S, Takai Y, Ito K, Murofushi T. Abnormal vestibular evoked myogenic potentials in the presence of normal caloric responses. Otol Neurotol. 2005 Nov; 26(6):1196-9.

276. Wang WQ, Wu LW. Neurootologic study of acoustic neuroma. Journal of Clinical Otolaryngology; 2000 Apr;14(4):149-51.

277. Ushio M, Iwasaki S, Murofushi T, Sugasawa K, Chihara Y, Fujimoto C. The diagnostic value of vestibular-evoked myogenic potential in patients with vestibular schwannoma. Clin Neurophysiol. 2009 Jun;120(6):1149-53.

278. Murofushi T, Takegoshi H, Ohki M, Ozeki H. Galvanic-evoked myogenic responses in patients with an absence of click-evoked vestibulo-collic reflexes. Clin Neurophysiol 2002;113:305–9.

279. Harun A, Agrawal Y, Tan M, Niparko JK, Francis HW. Sex and age associations

with vestibular schwannoma size and presenting symptoms. Otol Neurotol. 2012 Dec;33(9):1604-10.

280. Gal TJ, Shinn J, Huang B. Current epidemiology and management trends in acoustic neuroma. Otolaryngol Head Neck Surg. 2010 May;142(5):677-81.

281. Massick DD, Welling DB, Dodson EE, Scholfield M, Nagaraja HN, Schmalbrock P; Chakeres DW. Tumor Growth and Audiometric Change in Vestibular Schwannomas Managed Conservatively. The Laryngoscope, November 2000. Volume 110, Issue 11;1843–1849.

282. Arthurs BJ, Fairbanks RK, Demakas JJ, Lamoreaux WT, Giddings NA, Mackay AR, Cooke BS. A review of treatment modalities for vestibular schwannoma. Neurosurg Rev 2011. 34:265–279.

283. Pogodzinski MS, Harner SG, Link MJ. Patient choice in treatment of vestibular schwannoma. Otolaryngol Head Neck Surg 2004.130:611–616.

284. Kondziolka D, Mousavi SH, Kano H, Flickinger JC, Lunsford LD. The newly diagnosed vestibular schwannoma: radiosurgery, resection, or observation? Neurosurg Focus 33 (3):E8, 2012;1-9.

285. Sanna M, Taibah A, Russo A, Falcioni M, Agarwal M. Perioperative complications in acoustic neuroma (vestibular schwannoma)surgery. Otol Neurotol. 2004 May;25(3):379-86.

286. Langenberg R, de Bondt BJ, Nelemans PJ, Baumert BG, Stokroos RJ. Follow-up assessment of vestibular schwannomas: volume quantification versus two-dimensional measurements. Neuroradiology (2008) 51:517–524.

287. Breivik CN, Nilsen RM, Myrseth E, Pedersen PH, Varughese JK, Chaudhry AA, Lund-Johansen M. Conservative Management or Gamma Knife Radiosurgery for Vestibular Schwannoma: Tumor Growth, Symptoms, and Quality of Life. Neurosurgery. 2013 Jul;73(1):48-57.

288. Régis J, Carron R, Park MC, Soumare O, Delsanti C, Thomassin JM, Roche PH. Wait-and-see strategy compared with proactive Gamma Knife surgery in patients with intracanalicular vestibular schwannomas. J Neurosurg. 2010 Dec;113 Suppl:105-11.

289. Pennings RJ, Morris DP, Clarke L, Allen S, Walling S, Bance ML: Natural history of hearing deterioration in intracanalicular vestibular schwannoma. Neurosurgery 2011;68:68–77.

290. Kondziolka D, Lunsford LD, Flickinger JC: Gamma knife radiosurgery for

vestibular schwannomas. Neurosurg Clin N Am 2000,11:651–658.

291. Yang I, Sughrue ME, Han SJ, Aranda D, Pitts LH, Cheung SW, et al: A comprehensive analysis of hearingpreservation after radiosurgery for vestibular schwannoma. Clinical article. J Neurosurg 112, 2010:851–859.

292. Timmer FC, Hanssens PE, van Haren AE, van Overbeeke JJ, Mulder JJ, Cremers CW. Follow-up after gamma knife radiosurgery for vestibular schwannomas: volumetric and axial control rates. Laryngoscope. 2011 Jul;121(7):1359-66.

293. Paek SH, Chung HT, Jeong SS, Park CK, Kim CY, Kim JE, Jung HW. Hearing preservation after gamma knife stereotactic radiosurgery of vestibular schwannoma. Cancer. 2005 Aug 1;104(3):580-90.

294. Carlson ML, Jacob JT, Pollock BE, Neff BA, Tombers NM, Driscoll CL, Long-term hearing outcomes following stereotactic radiosurgery for vestibular schwannoma: patterns of hearingloss and variables influencing audiometric decline. J Neurosurg. 2013 Mar;118(3):579-87.

295. Rosenberg SI. Natural history of acoustic neuromas. Laryngoscope. 2000 Apr;110(4):497-508.

296. Chung WY, Liu KD, Shiau CY, Wu HM, Wang LW, Guo WY, et al: Gamma knife surgery for vestibular schwannoma: 10- year experience of 195 cases. J Neurosurg 102 Suppl: 2005;87–96.

297. Flickinger JC, Kondziolka D, Niranjan A, Maitz A, Voynov G, Lunsford LD: Acoustic neuroma radiosurgery with marginal tumor doses of 12 to 13 Gy. Int J Radiat Oncol Biol Phys 2004. 60: 225–230.

298. Kim KM, Park ChK, Chung HT, Paek SH, Jung HW, Kim DG. Long-term Outcomes of Gamma Knife Stereotactic Radiosurgery of Vestibular Schwannomas. J Korean Neurosurg Soc 2007, 42: 286-292.

299. Tanbouzi Husseini S, Piccirillo E, Taibah A, Paties CT, Rizzoli R, Sanna M: Malignancy in vestibular schwannoma after stereotactic radiotherapy: a case report and review of the literature. Laryngoscope 2011,121:923–928.

300. Niranjan A, Kondziolka D, Lunsford LD: Neoplastic transformation after radiosurgery or radiotherapy: risk and realities. Otolaryngol Clin North Am 2009, 42:717–729.

301. Chen Sh, Liu Ch, Liu B, Yi Ch, Wang Zh, Romg Y. Schwannomatosis: a new member of neurofibromatosis family. Chinese Med. J. 2013;126(14):2656-2660.