A new concept called “Polyganglionitis Episodica (PGE)” was proposed by Dr Kedar Adour, chairman of the Cranial Nerve Research Clinic of the Kaiser Permanente Group in San Francisco, when he addressed otolaryngologists and neurologists in Bloemfontein, South Africa, on April 29, 1997. This new concept (syndrome) comprises a group of conditions with the same etiological mechanism, i.e. reactivation of viruses in the ganglia of cranial and/or spinal nerves.

Dr Adour stated: I am here today to imply that herpes simplex is the great masquerader of our generation and the most frequent cause of acute cranial polyganglionitis. We used the term polyneuritis in the past, but have now changed to polyganglionitis, because with this term we can explain all the signs and symptoms which occur. The disease is primarily in the ganglion, followed by a neuritis. The mucocutaneous manifestations are what we see, but this is only the lip of the volcano. The neuritic manifestations are numerous and are seen by general practitioners as well as specialists, especially otolaryngologists, neurologists, dermatologists, and internists. The multiple manifestations of herpes simplex reactivation are:

Vertigo, acute hearing loss, unilateral headache, unilateral fullness of the ear, unilateral tinnitus, lump in the throat, unilateral neck or temporo-mandibular joint pain, unexplained cough, tendency to recurrent attacks.
Pathophysiology of Herpes Simplex Reactivation

Approximately 80% of humans carry the herpes simplex virus in the ganglions of cranial and spinal nerves. Our discussion will be confined to the cranial nerves and Cervical 2 and 3. Once the virus gets into the ganglion, it resides in the ganglion and waits there in a latent stage until it is reactivated and then causes a ganglionitis. The virus then migrates down the nerve to cause mucocutaneous vesicles, and up the nerve to cause a localized meningo-encephalitis at the brainstem.

When the virus leaves the neural cell membrane, it takes up a coat of neurolipoprotien around it, and it deposits that neurolipoprotein in the perineural compartment. This neurolipoprotein causes an immune mediated reaction, which causes demyelinitization 8 - 10 days after the disease process has taken place. Therefore, when you see the mucocutaneous vesicle, this is the lip of the volcano, i.e. this superficial sign indicates what is going on deeper, i.e. inside the ganglion. Depending on which nerve the virus is reactivates in, signs and symptoms develop which have been described as various disease entities, e.g. Bell’s palsy, Ménière’s disease, etc.. Herpes simplex is the big masquerader. It causes the inflammatory ganglionitis, which then causes a viral induced immunological response, not autoimmune. In addition, a metabolic response is invoked by local changes, and the virus can also cause vasospasm. Fortunately these responses can be influenced by prednisone treatment, but unfortunately we do not have an antiviral agent to destroy the virus. We can only suppress its activity by means of acyclovir given in the acute stage. However, daily doses of acyclovir for long periods (up to one year) are already recommended to suppress eruptions of genital herpes.

Dr Adour continued: The structure of cranial ganglions need to be considered also. Ganglions contain bipolar sensory cells and in the cranial nerves there is a relationship with motor and inhibitory fibres which is unique. In the cranial nerves the motor and inhibitory fibres pass through the ganglion and any disease affecting the sensory nuclei will also affect the motor and inhibitory fibres. Unlike the motor fibres in the peripheral systems (which are separated form the sensory ganglion), the motor fibres of the cranial nerves traverse the ganglion. So, any process which takes place inside the ganglion is going to affect the motor cells - they become involved as innocent bystanders. What people forget is that any sensory system has an inhibitory system, and those inhibitory fibres must traverse the ganglion. What happens if you have inhibitory systems like that which are affected? You are going to get a hyperactive state and we will discuss that with every individual cranial nerve. That becomes very important - remember the inhibitory fibres.
Background to the new concept

Today Bell’s palsy is still called ‘idiopathic facial palsy’. However, in 1919 a publication from Italy by Antoni reported that detailed clinical examination of patients with idiopathic facial palsy revealed that other nerves were often involved. Antoni named the condition “acute infectious polynéuritits cerebraîs acustico-facialis”, thus indicating an infection as the causative agent. This report from Antoni was rediscovered by Dr Adour and he then examined his Bell’s palsy patients more thoroughly. Already in 1969 Dr Adour suggested that Bell’s palsy was a polynéuritits probably caused by reactivation of the herpes simplex virus. At that stage it was theory, but in 1996 Murakami et al (Japan) found the HSV-1 genomes in the endoneural fluid from Bell’s palsy patients, who had decompression surgery performed. This was not found in patients with Ramsay Hunt syndrome (herpes zoster oticus) or in other controls.

In 1952 both Furstenberg and Lempert suggested that idiopathic endolymphatic hydrops (Ménière’s disease) had a viral etiology because the vertigo and hearing loss were often accompanied by burning sensation in the pharynx, earache, and numbness of the face. Schuknecht had already stated that the inner ear endolymphatic hydrops in Ménière’s disease could not explain the fluctuating low tone hearing loss which occurred in the early stages of the disease. In 1980 Adour and co-workers suggested that Ménière’s disease was a form of cranial polyganglionitis caused by reactivation of the herpes simplex virus. They reported on other clinical findings which are sometimes present during a Ménière attack, e.g. pain deep inside the ear (due to glossopharyngeal nerve involvement). In 1997 Arnold and Niedermeyer reported the presence of HSV IgG in the perilymph of patients with Ménière’s disease, and concluded that HSV may play an important role in the etiopathogenesis of Ménière’s disease.

The proposal for this new syndrome of PGE originated from astute clinical observations. The clinical signs were there all the time but were not detected probably due to clinicians not paying enough attention to the patient’s complaints. More detailed clinical examination of patients makes sense when they have the conditions which will be described in the rest of this article.
Clinical Manifestations of PGE

The PGE conditions ascribed to Herpes Simplex-1 are Bell’s palsy, Ménière’s disease (idiopathic endolympathic hydrops), vestibular neuritis, viral cochleitis, viral labyrinthitis, idiopathic sudden hearing loss, carotidynia, blocked ear without detectable abnormality, some cases of otalgia and pain in the throat, hypersensitive scalp, dysphonia, temporo-mandibular joint syndrome (TMJ - also called Costen syndrome), and globus syndrome. A well-known PGE condition due to the Varicella Zoster virus is Ramsay Hunt syndrome (herpes zoster acustico-facialis).

Trigeminal Nerve

Sensory branches: The pain is due to inflammation of the nerve roots. Hypesthesia or numbness is due to decreased function of the nerve endings. When inhibition is decreased a hypersensitivity to touch takes place. The term ‘photophobia’ indicates intolerance to light, and ‘phonophobia’ indicates intolerance to sound. A new term ‘somatophobia’ is proposed for intolerance to touch, and this is the symptom of hypersensitivity to touch.

Motor branches: When the masseter and pterygoid muscles are affected unilaterally, the jaw shifts to the paralyzed side and there is clicking of the jaw joint. Along with the shift there is a ‘stuffy’ or ‘blocked ear’ due to paralysis of the branches to the anterior belly of the M. tensor veli palatini, and the branches to the M. tensor tympani which moves the ear drum - this used to be called ‘Costen syndrome’. So, if a patient complains of a stuffy ear and the examination shows no abnormality or hearing loss, check the other branches of the trigeminal nerve as well as other cranial nerves for involvement.

Facial Nerve

Motor branches: The facial muscles, stapedius, buccinator, platysma, stylohyoid and digastric muscles are supplied.

Secretomotor fibres: The salivary, lacrimal and nasal glands are supplied.

Special sensory fibres provide taste to the anterior two thirds of the tongue (chorda tympani nerve).

There are no somatic sensory fibres in the facial nerve trunk. Therefore Hunt’s zone of anesthesia of the auricle, or Hitselberger’s sign of anesthesia of the posterior aspect of the external ear canal, does not exist.

In Bell’s palsy the paralysis of the muscles is due to the seventh nerve motor fibres being affected, the numbness and pain in the cheek is due to trigeminal nerve involvement, the post auricular pain is due to the 2nd Cervical nerve involvement. The taste disturbance (dysgeusia) is due to the chorda tympani cell bodies in the geniculate ganglion being involved. The hyperacusis, which is better called dysacusis or phonophobia, is not related to an absent stapedial reflex, but is a function of the cochlear division of the 8th Cranial nerve (see later).

Vestibulo-cochlear nerve (Cr. VIII)

The vestibular and cochlear fibres are well known. Every sensory system has an inhibitory system also and the pathways of the inhibitory fibres of the cochlear nerve are not certain - it is thought that they possibly pass through the olivo-cochlear bundle. Loss of inhibition will result in a complaint of loudness intolerance (phonophobia), a common complaint of patients with Ménière’s disease.

Vertigo can occur alone and is then called vestibular neuritis.

Acute hearing loss which occurs alone is called idiopathic sudden sensorineural hearing loss or viral cochleitis.

Vertigo plus hearing loss occurring once only is called labyrinthitis, and if it is episodic it is called Ménière’s disease or endolympathic hydrops. However, the virus causes the disease initially (hearing and balance affected but returning to normal after an episode), and the endolympathic hydrops (chronic stage) is an end stage of the diseased hearing and balance organs. Rather than individual diseases with individual pathophysiology, Dr Adour submitted that the above diseases are a spectrum of the same process, i.e. viral inflammation, probably caused by herpes simplex reactivation.
Glossopharyngeal Nerve

Somatic sensory branches supply the pharynx, tonsils and middle ear. When a patient complains of pain on swallowing and no abnormality can be found - check the nasopharynx for inflammation. For the complaint of ‘a lump in the throat’, check the posterior pharyngeal wall for a loss of sensation - the clue to this finding lies in the phenomenon that a patient always complains of a lump in the throat after the throat has been sprayed with surface anesthetic. Therefore, the ‘globus syndrome’ of a lump in the throat is a true neuritis and not a hysterical condition.

Vagus Nerve

Motor fibres supply the pharynx, larynx, heart, lungs, bronchi and gastrointestinal tract. Somatic sensory fibres accompany the motor fibres and a unique branch to the ear canal is called Arnold’s nerve. Inflammation of the tenth cranial nerve can lead to pain in the throat, ear and carotid artery. Carotidynia (moderate to severe pain with palpation of the carotid artery), is probably due to loss of inhibition to the nerve endings surrounding the carotid sheath. These patients often have a paresis or paralysis of the superior laryngeal nerve (the nerve most often paralysed in the body - Adour). The unilateral loss of sensation in the laryngeal inlet allows mucus and saliva to enter the larynx and a cough results because the swallowing reflex is not initiated in time - the patient complains of a cough, especially when lying on the affected side. The motor fibres of the superior laryngeal nerve stretches the vocal cord, and when affected the patient is unable to sing high notes. On examination the larynx is rotated to the affected side and the vocal cord is shorter.

A feeling of a plugged ear is due to the tensor veli palatini muscle being affected - let the patient put out the tongue and sing a high note - the palate will move asymmetrically.

Herpes particles have been found in the ganglion of the heart of patients who had sudden death syndrome, probably due to arrhythmia.

Cervical Nerves

Pain behind the ear and hypesthesia in this area is due to involvement of Cervical nerves 2 and 3. This is a common phenomenon with Bell’s (Antoni’s) palsy and can also occur with acute vestibulo-cochlear symptoms, e.g. Ménière’s disease. Somatophobia of the scalp can occur - patients complain of pain on touching the hair or skin of the scalp.

Conclusion

Dr Adour concluded: “I have presented the pathophysiology of Herpes Simplex Virus, demonstrated the signs and symptoms associated with HSV reactivation, and offered a concept of polyganglionitis which explains what heretofore was unexplained. Take this concept back to your practice and be assured it will be useful. Remember that recurrent Herpes Simplex is the most frequent cause of acute neurological disease.

And above all - THINK POLYGANGLIONITIS.

I would hope it will not be another 25 years before this concept is proven, as was the case with Herpes Simplex-1 facial palsy (Bell’s palsy)”.


Pathophysiology of Herpes Simplex Virus
Craniocerebrospinalmphaganglionitis

<table>
<thead>
<tr>
<th>Cranial Nerve</th>
<th>Decreased Function</th>
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<th>Decreased Inhibition</th>
<th>Diagnosis</th>
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<tr>
<td>II</td>
<td>Scotomata</td>
<td>OPTIC</td>
<td>Photophobia</td>
<td>Migraine Headache</td>
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<td>V [Motor Division]</td>
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<td>Contracture</td>
<td>Temporomandibular</td>
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<td>of Mastication</td>
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<td>Joint Syndrome</td>
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<td>Hypesthesia</td>
<td>Dysesthesia</td>
<td>Hyperalgesia (Pain)</td>
<td>Atypical Facial Pain</td>
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<td>Tic Douloureux</td>
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<td>VII [Motor]</td>
<td>Facial Paralysis</td>
<td>FACIAL</td>
<td>Contracture &amp; Synkinesis</td>
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<td>VII [Somatic Sensory]</td>
<td>Hypoguesia/Ageusia</td>
<td>---- &gt; Dysgeusia &lt; ----</td>
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<td>BELL'S PALSY</td>
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<td>VII [Autonomic]</td>
<td>Decreased Submandibular Salivation</td>
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<td>VIII [Cochlear]</td>
<td>Hearing Loss</td>
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<td>Phonophobia (Hypacusis)</td>
<td>Sudden Hearing Loss</td>
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<td>Tinnitus</td>
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<td>+ Vestibular Vertigo</td>
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<td>Spontaneous Nystagmus</td>
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<td>Hyperalgesia</td>
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<td>Decreased Gag Reflex</td>
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<td>Neuralgia (Sluder's Syndrome)</td>
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<td>IX [Special Sensory]</td>
<td>Hypoguesia/Ageusia</td>
<td>---- &gt; Dysgeusia &lt; ----</td>
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<td>Part of Bell's Palsy</td>
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<td>Cricothyroid, Esophageal</td>
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<td>Dysphagia</td>
<td>or Spastic Dysphonia</td>
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<td>Hyperalgesia (Pain)</td>
<td>Cricopharyngeal Spasm</td>
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<td>Hyperalgesia (Pain)</td>
<td>Choking and Coughing</td>
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<td>Spells, Carotidynia</td>
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<td>Bradycardia</td>
<td>CERVICAL 2</td>
<td>Paroxysmal Tachycardia</td>
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<td>Heart Block</td>
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<td>Hypossecretion</td>
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September 1980
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Drawing by Max Brödel shows the membranous labyrinth and its afferent nerve supply.

Note: The vestibular nerve’s two divisions are inside the internal auditory canal, which contain the two vestibular ganglia (Scarpa), in close proximity to the facial nerve (N. fac.) and the cochlear nerve (N. cochl.).

The efferent nerve supply to the cochlea (olivo-cochlear bundle) is in the vestibulocochlear anastomosis (Oort).

The three semicircular canals are the superior (sup.), posterior (post.) and horizontal (also named lateral - lat.).
In September 2001 Arbusow et al published in Audiology & Neuro-Otology: "HSV-1 not only in human vestibular ganglia but also in the vestibular labyrinth".

**Fig.1.** After primary infection (stomatitis herpetica) HSV-1 ascends to the geniculate ganglion (GG) via the chorda tympani**, and via the faciovestibular anastomosis to the vestibular Ganglion (VG). Viral migration to the vestibular nuclei (VNC) and the human labyrinth is possible along the vestibular nerve. aSC, hSC, pSC = Anterior, horizontal, and posterior semicircular canals; cc = commissural connections. Arbusow, Theil, Strupp, Mascolo & Brandt: Audiology & Neuro-Otology 6:259-62, 2001.

Abstract: “Reactivation of herpes simplex virus type 1 (HSV-1) in the vestibular ganglion is the suspected cause of vestibular neuritis. Recent studies reported the presence of HSV-1 DNA not only in human vestibular ganglia, but also in vestibular nuclei, a finding that indicates the possibility of viral migration to the human vestibular labyrinth. Distribution of HSV-1 DNA was determined in geniculate ganglia, Vestibular ganglia, semicircular canals, and macula organs of 21 randomly obtained human temporal bones by nested PCR (i.e. the patients died from causes not related to cranial nerve dysfunction, and other viral infections were excluded). Viral DNA was detected in 48% of the labyrinths, 62% of the Vestibular ganglia, and 57% of the geniculate ganglia. The potential significance of this finding is twofold: (1) Inflammation in vestibular neuritis could also involve the labyrinth and thereby cause acute unilateral vestibular deafferentation. (2) as benign paroxysmal positional vertigo often occurs in patients who have had vestibular neuritis, it could also be a sequel of viral labyrinthitis.”

The authors stated that this was the first demonstration of HSV-1 DNA in the human semicircular canals and otolith organs. The authors suggested that horizontal rotatory nystagmus (to the non-affected ear) seen in acute vestibular neuritis may be caused not only by viral inflammation of the superior vestibular nerve, but also a sequel of viral inflammation of the peripheral labyrinth. They also hypothesized that this inflammation of the labyrinth could cause loosening of the otocoria leading to the canalolithiasis and benign paroxysmal positional vertigo. These suggestions may lead to using a term such as vestibulo-neuro-labyrinthitis for the clinical symptom complex currently described as vestibular neuritis.

** The chorda tympani nerve is the nerve of taste for the front two thirds of the tongue.
Advances in Oto-Rhino-Laryngology
Vol. 60

Series Editor

W. Arnold Munich

Viral Neuropathies in the Temporal Bone

Richard R. Gacek Mobile, Ala
Mark R. Gacek Mobile, Ala

100 figures, and 8 tables, 2002
A number of otologic disorders have mystified clinicians over the years. These have been referred to as 'idiopathic' indicating lack of a known cause. Although animal models are useful in elucidating basic physiologic mechanisms, recurrent neuropathies (vestibular, facial) of the temporal bone (TB) are unique to humans. Therefore, human TB specimens represent the best source of information providing insight into the pathology of these neuropathic disorders.

For hundreds of years, Bell's palsy (IFP) and Ménière's disease (MD) have been regarded as idiopathic. Although displaced otoconia have been implicated in the mechanism of benign paroxysmal positional vertigo, the precise stimulus for degenerated otoconia has also been unknown (idiopathic). Only vestibular neuronitis was assumed to be an inflammatory disorder of the vestibular nerve because of its clinical association with viral-type illnesses and supported by serologic evidence of elevated viral antibodies.

The description of endolymphatic hydrops (EH) in TB from patients with the clinical symptoms of MD [1, 2] provided the impetus for a long series of investigations into the concept of obstruction in longitudinal flow of endolymph to the endolymphatic sac. The theory received support from the experimental demonstration of EH following obstruction of the endolymphatic duct in some animals (guinea pig, gerbil, rabbit) [3, 4]. However, failure to produce EH in nonhuman primates [5] and the absence of vertigo in the successful animal models of EH detracted from the EH theory of MD and accounted for the equivocal results obtained by treatments designed to reduce endolymph.

In a similar way, the previous concept of IFP held that an ischemic event leads to edema of the facial nerve and compression within the surrounding bony canal. Surgical decompression to relieve intraneural pressure did not achieve superior results compared to no treatment in a large number of consecutive patients with IFP [6]. Molecular amplification of herpes simplex virus 1 by PCR on vestibular nerves (ganglia) from patients with MD [7] and IFP [8] supports a viral role in these idiopathic disorders.

We have demonstrated in human TB specimens from patients with IFP, MD, vestibular neuronitis and benign paroxysmal positional vertigo a pattern of degenerative changes in the facial nerve (meatal ganglion) and vestibular nerve (and ganglion) which is similar to morphologic changes in herpes zoster of the trigeminal nerve. This evidence has been summarized in the series of reports contained in this volume of Advances in Otorhinolaryngology.

Harold F. Schuknecht, MD, predicted a viral cause for MD in his discussion of delayed EH, a form of MD. 'Assuming that viral labyrinthitis can occur in infants as a subclinical disease that results in delayed endolymphatic hydrops, we may have an explanation for the cause of Ménière's disease. Viewed in this context the disease entity known as delayed endolymphatic hydrops becomes the missing link in understanding the pathogenesis of Ménière's disease' [9]. We dedicate this series of studies to the memory of H.F. Schuknecht whose life-long professional passion was the TB.

Armed with this concept of pathogenesis for the recurrent vestibulopathies, the variable features and unpredictable nature of the 'three faces' of vestibular ganglionitis can be understood. An antiviral approach is warranted but will require substantive changes in present-day antiviral pharmaceuticals.

R.R. Gacek
M.R. Gacek
Classification of Recurrent (Viral) Vestibulopathies  
(Gacek & Gacek 2002)

The syndromes of Vestibular neuronitis, Benign Positional Vertigo (BPV), and Menière’s disease are clinical expressions of vestibular ganglionitis probably caused by the alpha Herpes virinae family. Several factors may determine the “face” presented in individual patients. These are 1) the amount of virus present (viral load), 2) the virus type and strain, 3) the location and number of affected vestibular ganglion cells, and 4) host resistance. It is possible that other forms of recurrent vertigo are expressions of vestibular ganglionitis.

Gacek & Gacek: Anterograde virus strain (hearing preserved)

Superior vestibular ganglionitis (vestibular neuritis, vestibular Menière disease)  
Inferior vestibular ganglionitis (BPV = benign positional vertigo)  
Superior and inferior vestibular ganglionitis (vestibular neuritis and BPV)

Fig. 12. Schematic of anterograde virus flow after reactivation in the VG. This direction of virus flow avoids hearing loss but may account for passage of virus to second-order neurons in the vestibular nuclei. U = Utricle; S = saccule; RW = round window.
**Gacek & Gacek: Retrograde virus strain** (hearing affected)

*Superior vestibular ganglionitis (Menière disease, neurolabyrinthitis)*

*Subtype, utricular ganglionitis (Tumarkin’s otolithic crisis)*

*Superior and inferior vestibular ganglionitis (Menière disease and BPV)*

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*Fig. 6.* Schematic retrograde virus flow from the VG. Release of toxic viral products into the perilymphatic space causes fibrosis in the vestibule (stippled area) and toxicity to anical spiral ganlion cells. U = Utricle; S = saccule; RW = round window.
Demyelination of vestibular nerve axons in unilateral Ménière’s disease

Robert F. Spencer, PhD
Aristides Sismanis, MD, FACS
Jefferson K. Kilpatrick, MD
Wayne T. Shaia, MD

Abstract
We conducted a study to determine whether vestibular nerves in patients with unilateral Ménière’s disease whose symptoms are refractory to medical management exhibit neuropathologic changes. We also endeavored to determine whether retrocochlear abnormalities are primary or secondary factors in the disease process. To these ends, we obtained vestibular nerve segments from five patients during retrosigmoid (posterior fossa) neurectomy, immediately fixed them, and processed them for light and electron microscopy. We found that all five segments exhibited moderate to severe demyelination with axonal sparing. Moreover, we noted that reactive astrocytes produced an extensive proliferation of fibrous processes and that the microglia assumed a phagocytic role. We conclude that the possible etiologies of demyelination include viral and/or immune-mediated factors similar to those seen in other demyelinating diseases, such as multiple sclerosis and Guillain-Barré syndrome. Our findings suggest that some forms of Ménière’s disease that are refractory to traditional medical management might be the result of retrocochlear pathology that affects the aural portion of the vestibular nerve.

Introduction
Ménière’s disease is a debilitating inner ear disorder that is characterized by episodic vertigo, fluctuating progressivie sensorineural hearing loss (SNHL), tinnitus, and aural fullness.1 Both cochlear and vestibular forms of the disease have been recognized.2 Possible etiologies include viral, allergic, genetic, vascular, and nutritional factors; altered glycoprotein metabolism; excessive endo-lymph production; immune-mediated factors; and combinations of any of the above.3 Many patients with Ménière’s disease are responsive to traditional medical management with a diuretic, a low-salt diet, and/or a vestibular suppressant. Patients who do not respond to these therapies can be treated with alternate medications, including an oral steroid, a transystanpic steroid or gentamicin, or systemic methotrexate.4 Surgery is reserved for patients who still do not respond; surgical procedures include endolymphatic sac decompression, vestibular neurectomy, or labyrinthectomy. The choice of procedure depends largely on the status of the patient’s hearing.

Researchers have examined the excised portions of vestibular nerves obtained from patients with a variety of cochleovestibular disorders, including Ménière’s disease, in several previous studies. Some of these authors have proposed that demyelination and axonal changes are underlying factors in the etiology of Ménière’s disease.5-10 However, others have regarded microscopic changes in the vestibular nerve as nonspecific, inconsistent, or insufficient to account for the reduced vestibular function, and, therefore, they consider these changes to be unrelated to symptoms and the disease process.10,14

In this article, we describe a study that we undertook to assess the type and extent of pathologic changes that occur in the vestibular nerve in patients with unilateral Ménière’s disease whose symptoms are refractory to medical management. We also endeavored to determine whether these abnormalities are primary or secondary factors in the disease process.

Materials and methods
Our study group was made up of five patients—three women and two men, aged 39 to 76 years, all white—who underwent retrosigmoid vestibular neurectomy for the treatment of intractable Ménière’s disease at the Medical College of Virginia Hospitals at Virginia Commonwealth University. The diagnosis of Ménière’s disease had been...
2003:

“Pathology of Benign Paroxysmal Positional Vertigo Revisited”

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Annals of Otology, Rhinology & Laryngology, Volume 112, (7): 574-582,

Abstract:
The pathophysiology of benign paroxysmal positional vertigo (BPPV) is not completely understood. Although the concept of degenerated otoconia transforming the posterior canal (PC) crista into a gravity-sensitive sense organ has gained popular support, several temporal bone (TB) series have revealed similar deposits in normal TBs, suggesting they are a normal change in the aging labyrinth. Furthermore, some TBs from patients with BPPV do not contain particles in the posterior canal. Five TBs from patients with BPPV were studied quantitatively and alitatively. A small cupular deposit was found in 1 TB, while none was seen in the other 4 TBs. The major pathological changes were

1) a 50% loss of ganglion cells in the superior vestibular division of all 5 TBs, and

2) a 50% loss of neurons in the inferior division of 3 TBs, and a 30% loss in 2 TBs that contained abnormal saccular ganglion cells.

These observations support a concept in the pathophysiology of BPPV that includes loss of inhibitory effect of otolith organs on canal sense organs.

Conclusion:
Observations in 5 temporal bones from patients with posterior canal BPPV suggest that the pathophysiological mechanism responsible for a position-induced vestibular-ocular response in this disorder is neural, rather than mechanical stimulation of the sense organ. Loss of the inhibitory action of otolith organs on canal activation caused by degeneration of otolith neurons (saccular, utricular) is a possible explanation of the brief canal response induced by the positional stimulus.
Menière’s Disease is a Viral Neuropathy
Richard Gacek: ORL 71:78-86 2009

Morphological and clinical evidence supports a viral neuropathy in Menière disease. Quantitative examination of 11 sectioned temporal bones from 8 patients with a history of Men. Disease revealed a significant loss of vestibular ganglion cells in both the endolymph hydropic and non-endolymph hydropic ears. Transmission electron microscopy of vestibular ganglion cells excised from a patient with Menière disease revealed viral particles enclosed in transport vesicles.

Antiviral treatment controlled vertigo in 73 of 86 patients with vestibular neuronitis (85%) and 32 of 35 patients with Menière disease (91%).

The high (90%) rate of vertigo control with orally administered antivirals provide clinical experience
A place principle for vertigo

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Received 16 March 2007; accepted 13 April 2007
Available online 24 October 2007

Abstract

Objective: To provide a road map of the vestibular labyrinth and its innervation leading to a place principle for different forms of vertigo. Method: The literature describing the anatomy and physiology of the vestibular system was reviewed. Results: Different forms of vertigo may be determined by the type of sense organ, type of ganglion cell and location in the vestibular nerve. Conclusion: Partial lesions (viral) of the vestibular ganglion are manifested as various forms of vertigo.

1. Introduction

Sensory systems must be highly organized to function effectively. The special senses are especially well developed. This organization exists at the periphery and is duplicated with ascent of the system centrally. The auditory system provides an excellent example of a place principle for hearing. The reception of frequencies in orderly fashion from low at the apex of the cochlea to high at the base is determined by the physical characteristics of the cochlear partition. Components in the cochlear duct (basilar
membrane, spiral ligament, support cells in the organ of Corti) determine the place for maximal displacement of this partition by a given traveling wave induced by an auditory stimulus. This orderly transmission of frequencies is preserved over the primary auditory neuron, and multiple central neurons to the cortex for proper integration of auditory messages. Vision and olfaction have a similar precise organization to their neural systems.

Sufficient morphologic, physiologic and clinical evidence has accumulated in the past few decades to indicate an organization in the vestibular system that may account for different forms of vertigo depending on the location of pathology in the vestibular nerve. The evidence supporting such a “place principle for vertigo” will be reviewed in this report. Such a principle might aid our clinical approach to the evaluation and treatment of vertigo in patients, with recurrent vertigo. The recurrent vestibulopathies are now known to be caused by discrete vestibular ganglion cell lesions, likely viral induced. A significant body of histopathologic evidence has demonstrated that viral lesions are limited to discrete clusters of degenerating neurons in the vestibular ganglion in vestibular neuronitis, Meniere’s disease and benign paroxysmal positional vertigo (Fig. 1) [1–3]. This pattern of ganglion cell loss is typical of a viral neuropathy (4) caused by re-activation of a latent neurotropic virus (e.g. Zoster) [4]. Because the description of dizziness by patients may vary (i.e. vertigo, unsteadiness, positional vertigo), attempts have been made to classify vestibular disorders according to the nature of the imbalance symptom. An example of such a knowledge based system is that of Mira et al. [5]. This system used vertigo and dizziness to divide a long list of clinical pathologies encountered by the otologist or neurologist.

The organization of the peripheral vestibular system is determined largely by two anatomical features. These are: (1) type of sense organ. (2) Type of ganglion cell.
6. Efferent vestibular system

The final form of vestibular injury which may present as dysequilibrium relates to the efferent vestibular pathway. The vestibular efferent pathway originates bilaterally in the MVN just lateral to the abducens nucleus [29]. Axons of these neurons [30] merge with and travel with the efferent cochlear pathway (olivo-cochlear pathway) in the vestibular nerve as it exits the brainstem (Fig. 14) [31]. This common efferent bundle is clearly demonstrated by the high acetylcholinesterase activity which suggests acetylcholine as its neurotransmitter agent (Fig. 15) [32]. This efferent bundle passes through the saccular portion of the vestibular ganglion and, therefore, may be affected (loss of function) by inflammatory lesions in this area (Fig. 16). Individual efferent axons ramify as they travel in a dispersed arrangement to the sense organs (Fig. 17). This branching pattern permits a rich efferent termination on HC in the sense organ neuroepithelium.

Although an inhibitory effect is associated with stimulation of the vestibular efferent pathway [33–35], the function of this neural system in balance has not been demonstrated. However, certain established facts on efferent systems permit speculation on the role that the efferent system may play in balance.
The role of the efferent cochlear pathway has been shown to be one of modifying the physical characteristics of the sense organ to enhance sensitivity for stimulation of the primary auditory unit. By activating the contractile potential of the OHC to lengthen or shorten thus adjusting the reticular lamina and the tectorial membrane to sharpen the tuning curves for the primary auditory units (IHC and type I spiral ganglion cells) [21]. Otoacoustic emissions (OAE) generated by this “cochlear amplifier” [36] have been shown to be inhibited by the activity of the crossed (efferent) olivocochlear pathway.

Efferent vestibular activity in lower forms (fish) has been shown to be increased before vigorous movement (swimming) which would over stimulate the organ of balance (lateral line) [37–39]. Presumably this efferent activation is intended to reduce (prevent) self-stimulation by the animals activity.

This a role is compatible with the numerous demonstrations of inhibition of afferent neural transmission following stimulation of the vestibular efferent system [33,34]. Such a system may play a role in preventing auto stimulation of vestibular sense organs during physical activity.

A suggested corollary in the vestibular system would be for the efferent pathway to prevent auto-stimulation of sense organs by mechanically changing the sensitivity of the sense organs by altering the covering membrane (cupula, otoconial blanket) during vigorous physical activity. The clinical syndrome that could result from dysfunction of the efferent vestibular system might be motion sickness. A particularly efficient efferent system would be a requirement for a gymnast or figure skater.
7. A place principle for vertigo

This anatomical organization (supported by physiological correlates) provides a basis for attributing various forms of vertigo to pathology in discrete part of the vestibular ganglion. There is increasing pathologic evidence that the recurrent vestibulopathies (ventricular neuronitis, Meniere’s disease, benign paroxysmal positional vertigo) are caused by discrete ganglion injury (degeneration) from reactivation of neurotropic viruses (herpes virinae family) [1–3]. The severity and form of dysequilibrium described by such patients will depend on the location and number of vestibular ganglion cells injured by virus [40]. The location of sites in the vestibular ganglion responsible for different forms of vertigo are represented by the numbers 1–5 in Fig. 5.
1. Lesions in the most rostral part of the vestibular ganglion (type I GC) are responsible for episodes of rotatory vertigo. A strong VOR disturbance (nystagmus) signals this form of vertigo.

2. If the ganglion cell lesion is located immediately caudal to this rostral pole of the superior division type II GC are affected. Unsteadiness, especially on head movement, will be experienced because these type II GC project to commissural pathways.

3. Degeneration of ganglion cells in ventral parts of both the superior (utricle) and inferior (saccule) divisions of the vestibular ganglion, causes loss of function in the vestibulospinal tract to neck, trunk and limb muscles. Frequently these are described by patients as “drop” attacks. Ataxia may be a lingering form of this form of dysequilibrium.

4. The most common form of vertigo encountered in practice is position induced. Short duration episodes of a rotatory vertigo which is fatiguable have been described since Barany [41]. Both Barany [41] and Citron and Hallpike [42] felt this was an otolith disorder but the nystagmus response observed in this syndrome prevented acceptance of an otolith cause. Hallpike’s description of utricular degeneration [42] in the TB of BPPV was not enough to neutralize the predominant support of a canal etiology. Although the clinical response is a rotatory form of vertigo, the uninhibited response is caused by loss of the inhibitory role of the otolith organs.

5. Lesions in the saccular portion of the vestibular ganglion (inferior vestibular) may secondarily interrupt the efferent pathways to the cochlear and vestibular sense
organs. Clinically, the loss of this control may be perceived as tinnitus and motion sickness.

8. Conclusion

This review is an attempt to provide a guide to pathologies involving portions of the peripheral vestibular pathway. It is unusual that only a specific location of pathology will be present in a given patient. More often, a mixture of locations will be present. However, the goal here is to establish a map or framework to guide the evaluation and management of patients with recurrent vestibulopathy.
Proposal for a New Classification of Episodic Vertigo based on Symptoms

Dr Adour and Dr Hamersma propose the following new classification for episodic attacks of vertigo which constitute the differential diagnosis of the Syndrome of Menière:

**EPISODIC VERTIGO**

**Episodic Vestibulopathy:**

Recurrent attacks of rotational dizziness (vertigo) without any auditory symptoms, not caused by positional factors, which usually last from 5 minutes to 48 hours (also called vestibular Menière) and occasionally for many days (also called vestibular neuronitis) –

1. Caused by replication of the HSV-1 virus, i.e. Polyganglionitis Episodica;
2. Vertige de l’enfance, and
3. Vestibular epilepsy

**Episodic Cochleo-Vestibulopathy:**

Recurrent attacks of vertigo plus auditory symptoms, which usually last from 5 minutes to 48 hours (also called classic Menière disease), occasionally for many days (protracted attack), including the very severe form also called viral labyrinthitis, and those which develop in previously traumatised and deafened ears (also called secondary endolymphatic hydrops) -

1. Caused by replication of the HSV-1 virus, i.e. Polyganglionitis Episodica;
2. Autoimmune inner ear disease, and
3. Cogan’s disease.
Menière’s Disease is a Viral Neuropathy

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Presented at the Bárány Society Meeting in Kyoto, Japan on March 31, 2008.

Objective:
To present evidence which supports a viral vestibular neuropathy as the cause of Menière’s Disease (MD)

Methods:
Evidence from three sources was reviewed.

1. Quantitative and qualitative examination of eleven (11) sectioned temporal bones (TB) from eight patients with a history of MD.
2. Transmission electron microscopic (TEM) examination of the Vestibular ganglion excised from a patient with MD.
3. Clinical results of antiviral therapy in 121 patients with recurrent vertigo. Eighty-six patients with vestibular neuronitis (VN) and thirty-five with MD were treated with oral acyclovir over a 34 month period.

Results:

1. TB series:
Endolymphatic hydrops (EB) was present in 9 out of 11 TB. Vestibular cistern fibrosis was observed in 6 out of the 11 TB. Focal axonal degeneration in the vestibular nerve and degenerated meatal ganglion cells was present in all TB.

One TB contained epithelial cells with a large intranuclear inclusion body in the vestibular cistern. These epithelial cells were mixed with microcystic structures characteristic for cytomegalovirus (CMV) labyrinthitis.

All eleven vestibular ganglion cell counts revealed a significant loss compared to normal values.

2. The vestibular ganglion:
The vestibular ganglion excised to control vertigo in a 45 year old female with MD was examined by TEM. Viral capsids enclosed in transport vesicles were observed in the cytoplasm of ganglion cells (Fig. 1). Margination of nuclear chromatin was consistent with viral reactivation.
3. **Antiviral therapy:**
One hundred forty-seven (147) consecutive patients with MD and VN were treated with oral acyclovir from April 2004 to February 2007. There were 94 females and 53 males. Ages ranged from 23 to 87 years (avg. 53 years). Twenty-six patients were lost to follow-up. Vertigo was controlled in 73 of 86 patients with VN (85%), vertigo control was achieved in 32 of 35 patients with MD (91%).

**Conclusion:**

Morphological changes in the vestibular nerve and results following antiviral therapy supports the concept of a viral vestibular neuropathy in MD.

Fig. 1: Transmission electron microscopy of vestibular ganglion cell in MD. There are several viral capsids enclosed in transport vesicles from the Golgi network. (arrows).

Discussion following presentation:

The author answered a question on antiviral therapy and stated that oral acyclovir 800 mg t.i.d. for 3 weeks was given, then 800 mg b.i.d. for 4 weeks, and then 800 mg daily...