Vestibular Neuritis

Diagnosis Code 386.12

Introduction:

Vestibular neuritis, inflammation of the balance nerve, is the second or third most common cause of peripheral vestibular vertigo with benign paroxysmal positioning vertigo thought to be the most common. The purpose of this article is limited to that which appears to be caused by viral injury to the vestibular nerve. Many causes of dizziness, vertigo, rocking, floating, near-black out, fainting, imbalance, foggy-headedness, or motion intolerance exist. Vertigo is a relatively common problem, which has about a 1-year prevalence estimate of 3-5%.[1,2] By comparison, coronary heart disease has an annual prevalence rate of about 4%.[3] Migrainous vertigo has a prevalence of 0.89% and benign paroxysmal positional vertigo 1.6%.[4] Meniere's disease and benign positioning vertigo which many believe may at least some of the time be secondary to vestibular neuritis are briefly mentioned in this article but are not addressed in detail. Vertigo with psychological overlay, called *phobic postural vertigo*, may be a sequela of vestibular neuritis, as well.[5] An enormous study from Taiwan used national health diagnosis code data from office visits for vertigo to study the overall prevalence of unspecified vertigo.[6] An overall prevalence rate was 3.1% or about 3.13 per 100 population. Of that number, nearly 38% had had a recurrence at least once. Of those, 48% had 2 recurrences, 14% had had 3 recurrences and 16% had had more than 3 recurrences. It is not likely that all of them had recurrent vestibular neuritis but a ready inference from this study is that if recurrent vestibular neuritis is the 2nd or 3rd most common disorder, it may well have a recurrence rate that is under-estimated by smaller studies. Differentiating vestibular neuritis from other acute brainstem disorders, vestibular migraine, and management of acute, chronic, and recurring vestibular neuritis will be addressed briefly. Vertigo, then, is a common problem and acute viral vestibular neuritis is a major part of the picture.

Acute initial vestibular neuritis is said to have an annual incidence of 3.5 per 100,000 population accounting for 7% of the patients at outpatient clinics specializing in the treatment of vertigo. The reactivation of a latent herpes simplex virus type 1 (HSV-1) infection is thought to be likely cause[7] (but this author has found that at least 10-15% of vestibular neuritis patients have negative HSV 1 and HSV 2 IgG titers). Vestibular neuritis is a diagnosis of exclusion.[8] Vestibular neuritis is also described as "acute viral vertigo", "acute vestibular neuronitis", or "chronic or recurring viral vestibular neuritis". These terms, however, are not completely synonymous. Each has its own features which do overlap and have the common thread of viral inflammation of the vestibular nerve.

Acute Viral Vertigo symptoms:

Acute vestibular neuritis is typified by either abrupt onset of vertigo or rapidly worsening vertigo over a period of minutes to hours. It is characterized initially by rotatory vertigo (a spinning sensation) with an acute period lasting up to several days. For some, the sensation is a sense of tumbling, or tilting and it matters not whether it is a sense that the person or the room is moving. The principle physical finding is spontaneous nystagmus most often with a rotational component toward the unaffected ear but this finding is not unique to acute vestibular neuritis. Accompanying symptoms include inability to walk, not because of lack of coordination but because of poor balance.[9,10] There is no associated arm or leg weakness and syncope is not a

primary feature nor is a cardiac disturbance, though panic with the disorder is not rare. There are no associated other neurologic symptoms. The specific vertigo-sense of movement pattern may appear to oscillate side to side, front to back, or to tumble in an oscillating fashion. Initially, vertigo is constant regardless of body position. Any quick movement tends to exacerbate symptoms. Within hours to days, vertigo at rest abates but any quick movement continues to provoke symptoms for days to weeks, sometimes for much longer, sometimes permanently. Acutely, lying still is the preferred position, usually in the dark, and some find a specific position that is least symptomatic. Nausea, vomiting, and retching are common and diarrhea or rectal urgency may occur. Many prefer to curl up in the bathroom or with an emesis basin. Profuse sweating is common at onset and vision may be described as "in a fog" with difficulty focusing. Observers most commonly report horizontal but rotary nystagmus to some degree is present a high percentage as a spontaneous nystagmus, present without provocation. It may become horizontal or vertical with lateral gaze. Early nystagmus may beat towards the affected ear acutely, but relatively shortly, typically before initial medical evaluation, it beats away from the effected ear, most rapidly as horizontal nystagmus with a rotational component with gaze away from the affected ear. The rotary component of the nystagmus may be subtle and is thought to occur because vestibular neuritis is thought to affect the superior more than inferior vestibular nerve.

Based on an epidemiological survey in Japan by major neuro-otology clinics (otolaryngologists) during 1988-1990 (3 years), there is no gender preference. The peak of age distribution was 40-50 years. Up to 30% of all cases had had common colds prior to the disease.[11]

Physical findings in vestibular neuritis:
Physical findings include an abnormal head-thrust test or Halmagyi head thrust, also called the *head impulse test* (HIT) or the *rapid head impulse test* (rHIT) or if video-recorded, the *video head impulse test* (vHIT).[1] In this test, the *vestibulo-ocular reflex* is tested and is abnormal. In the normal vestibulo-ocular reflex, with horizontal head rotation in one direction, vestibular input causes quite precise opposite-direction eye rotation so that the eyes appear to remain still. With the HIT in patients with acute vestibular neuritis, eye rotation fails in the direction towards the affected ear and the eyes appear to follow the head with the turn ("doll's eyes"); with a head thrust to the non-affected ear, the eyes follow more appropriately (unless both ears are involved). The HIT can be abnormal for other reasons and is not 100% sensitive but it is the physical examination test in addition to presence of nystagmus most likely to be abnormal. Nystagmus, though, often fades within days whereas the HIT remains abnormal for longer periods, sometimes permanently. A period of rapid horizontal headshake, generally for about 30 seconds, commonly induces latent horizontal nystagmus if it is not present at rest. This is so called *head shake induced nystagmus.* HIT and headshake induced nystagmus are not specific for vestibular neuritis but are commonly but not always present in vestibular neuritis.

Standing feet side by side, touching together with eyes-closed (the Romberg test[2]), the person usually, but not always falls toward the affected ear. Standing heel to toe, eyes closed (the tandem Romberg test) is more sensitive. This testing may be limited by accompanying nausea, often with emesis. Irrigation of the ear canals with warm and cool stimuli produces little to no response in the affected ear.[12]

[1] See http://en.wikipedia.org/wiki/Vestibulo-ocular_reflex
[2] See http://en.wikipedia.org/wiki/Romberg_test

In the author's experience, benign paroxysmal positioning vertigo (BPPV) not infrequently appears within hours to days of onset of acute symptoms in some patients. In BPPV, the Dix-Hallpike test (Nylen-Barany maneuver)[3] has classic latent onset of rotary nystagmus and this form of positioning nystagmus responds to the *canalith repositioning maneuver* (Epley maneuver).[4]

Skew deviation or abnormal eye movement may be found in up to 15% of vestibular neuritis patients.[13] Skew deviation is not generally considered a peripheral vestibular nerve lesion unless the effects on the vestibular nerve are incomplete. In skew deviation, as the eyes are tracked upwards, they deviate laterally from each other and double vision may be noted.[5]

Differentiating from other disorders:
Acute vertigo sometimes has associated symptoms. More chronic vestibular disturbance or recognizable patterns of recurring vertigo must be considered at the outset. With those ruled out, findings infrequently associated with vestibular neuritis include ear fullness or tinnitus or tightness in the neck. Panic is commonly associated with vertigo though long experience suggests that panic from vertigo is much more likely than vertigo from panic though hyperventilation can induce various vestibular symptoms. With acute viral vestibular neuritis, there should be no swallowing problems, no diminished sensation in the face, hands, or feet, no true double vision, no disconjugate eye movement, no acute visual loss, and no specific limb clumsiness. Benign paroxysmal positioning vertigo can have a sudden onset independent of vestibular neuritis but it may also be a sequela of vestibular neuritis, often starting within days. It is differentiable by the Dix-Hallpike test and its classic pattern of response. Vestibular and basilar migraine can cause acute onset vertigo, sometimes with nausea and vomiting but should not last days and typically does not have the physical abnormalities found in vestibular neuritis: the vestibular ocular reflex, headshake testing, and gaze testing should be normal or very nearly normal. Differentiating brainstem dysfunction from peripheral vestibular dysfunction is based on several assessments. Warm versus cool distinction in the hands and feet should be intact unless other neurologic conditions co-exist. Ability to touch the finger to the examiner's finger should be accurate and ability to rub one's heel up and down the shin should be normal. While acute brainstem disorders can also cause vertigo, such as vestibular pseudoneuritis due to acute pontomedullary brainstem lesions or cerebellar nodular infarctions, vestibular migraine, and other acute brainstem disorders, these should be differentiable with a high degree of accuracy. Cerebellar nodular infarctions can present with isolated vertigo as a symptom, like vestibular neuritis. Unlike acute vestibular neuritis, nodular cerebellar infarction patients typically have distinctive findings such as complete absence of nystagmus or direction changing nystagmus.[14] Most commonly, cerebellar nodular infarctions are readily called as a cerebellar disorder in terms of normal ear responses to warm and cool stimulation and quite abnormal eye movement assessment whereas vestibular neuritis patients have a high incidence of poor caloric responses on one side and quite suggestive nystagmus and head thrust test response patterns.[15] Notable, though, head thrust abnormalities are present acutely in many vestibular neuritis cases but they may resolve rapidly and may not be present later such that the prevalence rate may be below 50% in the non-acute condition. Quite uncommon in acute vestibular neuritis but common in

[3] See http://en.wikipedia.org/wiki/Dix%E2%80%93Hallpike_test
[4] See http://en.wikipedia.org/wiki/Epley_maneuver
[5] See http://en.wikipedia.org/wiki/Skew_deviation

brainstem origin vertigo, is skew deviation as explained above. Skew deviation may be absent in brainstem strokes involving the vestibular nerve root entry zone and may only be differentiable from vestibular neuritis on MRI but this subtlety is relatively rare.[16] Vertical ocular pursuit is commonly abnormal in brainstem origin vertigo. Considering vertical smooth ocular pursuit, rapid head thrust testing (see above rHIT), and presence or absence of skew deviation, acute vestibular neuritis patients should not have all three positive but up to 30% may have up to two of these assessments abnormal.[17] Vestibular neuritis patients should not also have both abnormal vertical pursuit and skew deviation. Viral inflammatory involvement of the vestibular nuclei in the brainstem may occur with viral vestibular neuritis, as well but appears not often recognized.[18] In summary, vestibular pseudoneuritis, acute pontomedullary brainstem lesions or cerebellar nodular infarctions, vestibular migraine, and an initial vestibular Ménière's disease event may superficially look like vestibular neuritis. Panic with vertigo can be a distraction but an isolated panic attack with vestibular complaint should be differentiable by finding no clinical abnormalities. A disorder called *phobic postural vertigo* may be a sequela of vestibular neuritis or may arise without apparent antecedent event but this group of patients has no test-positive vestibular system abnormalities by definition. This author, however, thinks that most have a vestibular system lesion below our ability to test and that many may also have emotional overlay.

Pathology of acute viral vestibular neuritis:

Postmortem studies of patients with well documented vestibular neuritis show evidence of injury to the ganglion cells in the vestibular nerve just proximal to the inner ear.[19,20] Studies have also shown evidence that at least some of the time, Herpes Simplex is the putative cause.[21] Quite similar findings have been induced by herpes viral inoculation experimentally in small animals.[22] However, other literature suggests that adenovirus[23], enterovirus, Epstein Barr virus, and cytomegalovirus[24], as well as coxsackie and zoster viruses[25] can also cause vestibular neuritis. It is also clear that vestibular neuritis occurs in Ramsay Hunt syndrome implying that the Varicella Zoster virus (shingles virus) can cause vertigo.[6] "Animal studies have demonstrated that several human viruses including rubeola, herpes simplex, reovirus, mouse and guinea pig cytomegalovirus, and neurotropic strains of influenza A and mumps virus, can infect the vestibular nerve and the vestibular membranous labyrinth."[26] Controversy remains about whether the presence of virus in the vestibular nerve implies cause of symptoms. Indeed, in random cadavers, over 40% of the time, either or both HSV or VZV can be found in the vestibular ganglia.[27] Studies of postmortem human temporal bones (by R Gacek) find "vestibular nerve buds" peripheral to Scarpa's ganglion with the notion that these are regenerative neurons that have not completely reached endorgan targets.[28] Regeneration of injured nerves is known to occur peripheral to involved ganglia and that regeneration can be quite disordered as is perhaps best exemplified in Bell's palsy. I.e., some degree of permanent vestibular impairment from neural injury is not unexpected and is in fact common in vestibular neuritis. It appears to be worse the more severely affected the caloric response abnormality found[29] and the ready inference is that a lesser but persisting degree of vestibular impairment exist in those with less obvious endorgan pathology. Limits exist below which finding vestibular imbalance may exist but tests are technically in the range of normal. I.e., the absence of callable abnormality on vestibular function tests does not rule abnormality out and that is quite consistent with the temporal bone vestibular nerve pathology Gacek reports.

[6] The author's experience is that 100% of vestibular neuritis patients have positive VZV titers but the pertinence of that finding is unknown.

Recovery from acute viral vestibular neuritis:

With acute loss of peripheral vestibular nerve function, *de-afferentation,* the offending vestibular end organ is unable to send head movement information to the vestibular centers in the brain. There is evidence of a brain vestibular processing center de-activation in this disorder, a good correlation with the notion that the vestibular nerve is impaired in function.[30] Even at rest, in the absence of movement, the brain expects tonal or a degree of constant information from the vestibular endorgans. Just the absence of information creates an imbalance between the two inner ears which normally function in a push-pull fashion. I.e., in whatever plane of head rotation or linear acceleration, one side has increased neural activity and the other exhibits decreased activity. If the response of one side is impaired, the resulting imbalance creates nystagmus and disequilibrium. For most vestibular neuritis patients, severe symptoms abate within two to three days but may last less than a day or last five days or longer. If nausea and vomiting are present, hospitalization may be required for hydration but most improve sufficiently within hours after receiving nausea suppression to go home. The disorder typically affects just one eighth nerve but can rarely be bilateral.

Recovery from vestibular neuritis is spontaneous but can be helped by use of steroids. Peripheral labyrinthine function recovers to some degree in about 60% within 12 months. Adaptation is a part of recovery consisting of proprioception (muscle and joint sensors), visual substitution, and other central compensation. Physical therapy focusing on vestibular exercises can be helpful, as well.[31] Associated positional and positioning nystagmus disappeared in about 60% within 3 months. About half of the cases had long term persisting loss of ability of the affected ear to be stimulated and these patients were more likely to have prolonged symptoms.[32]

For many but not all, lingering position change or rapid movement associated disequilibrium persists for days to years. One definition of acute viral vertigo includes a single-sided loss of ability of cool or warm ear canal irrigation with water or air to cause vertigo, called a "canal paresis" or weakness. Persons with persisting or permanent canal paresis typically have prolonged or even permanent disequilibrium with rapid movement though the degree of disability is usually quite mild. Rare individuals with marked bilateral dysfunction may have more notable disability. Those with motion intolerance physiology seem to be more persistently symptomatic as well. Those with persisting dysfunction often benefit from vestibular physical therapy but a relative few cannot return to pre-illness activities which require good balance. Not rarely, benign paroxysmal positioning vertigo is a sequela, manageable with the canalith repositioning maneuver.

Recurrences of acute viral vertigo (vestibular neuritis):

Recurrences of acute viral vertigo had been thought to be uncommon, generally with an incidence rate in earlier publications of under 5% with follow up of under 10 years.[33,34] A more recent study found vestibular neuritis to have a nearly 11% recurrence risk by telephone interview and benign paroxysmal positioning vertigo, often a sequela of vestibular neuritis, had a greater than 15% recurrence risk.[35] In the same study, recurrence of vertigo symptoms of any type was at a 26% incidence suggesting that some degree of recurrent symptoms is not rare at all and that fits with our clinical experience.

Overall, in our experience of evaluating thousands of dizzy patients who see us for lingering vestibular complaints, we find that a careful history done weeks to months after acute symptom

onset, much more effectively than at the time of acute stress, finds many patients who when pressed, remember a remote history of a similar vertigo episode, often with the help of a family member. In recurring vestibular neuritis, the classic vestibular neuritis symptom pattern repeats but varies a great deal in severity. The recurrences may be weeks to years apart. Eventually, many develop asymmetric hearing loss and ear specific symptoms and some develop Meniere's disease and/or benign paroxysmal positioning vertigo. BPPV (benign paroxysmal positioning vertigo) may then become a recurring residual of flare ups of recurrent vestibular neuritis (BPPV has many other etiologies). At least since 2001, the literature has been showing a link between vestibular neuritis and Meniere's disease.[36] In chronic vestibular neuritis, the onset of the above symptoms is followed commonly by fluctuating vestibular complaints on a daily or nearly daily basis. Motion intolerance is a common additional symptom and seems especially like in persons with persisting complaints out of proportion to findings on vestibular function assessment. Many notice a residual rocking-floating sensation which we presume to be due to otolithic organ involvement; otolithic organ dysfunction is a well-known consequence of vestibular neuritis.[37,38,39] While these patients commonly walk well, a common complaint is a sensation of not feeling well balanced or feeling drunk. If these patients have testably normal vestibular function, they are often called *phobic postural vertigo.* These patients often do have or develop psychological overlay.[40] Psychological intervention may be somewhat helpful,[41] but this author thinks the primary issue is vestibular disturbance and that the psychological effects are secondary. Distinguishing chronic fluctuating vestibular neuritis from fluctuating labyrinthine dysfunction is probably not possible. The cause of chronic, recurring vestibular neuritis is thought to be viral and relatively recent postmortem pathology supports that notion.[42] Another study shows that the vestibular ganglion and vestibular nerve are commonly colonized by Herpes simplex.[43]

Recurrent and chronic vestibular neuritis:

The question is *what is the appropriate management and at what dosages of medication, if any.* For management of acute viral vertigo, there is no evidence that antivirals improve outcome but there is evidence that steroids do improve outcome.[44] The vast majority of the single-event acute vestibular neuritis patients improve spontaneously with no special management other than use of vestibular suppressants and nausea suppressants early on. Most are much improved within 5 days but a few have lingering symptoms for weeks to months. Use of steroids acutely, generally within 2-3 days, is associated with more rapid improvement and a lower risk of longer term symptoms.[45] For those with lingering symptoms, vestibular physical therapy can be helpful. In general, recurrences are uncommon (see below).

For chronic and recurring vestibular neuritis and its derivative disorders, Meniere's disease and benign paroxysmal positioning vertigo (the latter has more than one etiopathogenic pathway), there is evidence that long term antivirals are effective but dosage is not specified.[46,47] The notion that *recurrent* vestibular neuritis is Herpes-Simplex-associated is growing.[48] A literature search on PubMed with "vertigo herpes" found literally dozens of references, many of which conclude that neurotropic viruses like HSV likely play a role.[49,50,51,52] Many other references argue for and against as would be expected.

Viral reactivation:

Newer studies are now elucidating a mechanism whereby re-activation of virus in cells colonized by HSV is controlled by a complex mechanism of CD8+ effector T cells with specific gamma

interferon.[53,54] Another study looked in detail at the glycoprotein antigens produced as HSV reactivates in neural tissue, antigens which are specifically recognized by CD8 T cells which influence these CD8 cells to participate in the inflammatory response to HSV reactivation.[55] Evidence suggests that low level production of a specific HSV glycoprotein prior to viral DNA synthesis is what keeps HSV specific CD8 T cells in the infected tissue and activates them to respond, preventing viral reactivation.[20,56] Stress-induced glucocorticoids appear to suppress these HSV specific CD8 T cells and may play a role in re-activation of latent HSV.[57,58] In addition, experimental suppression of HSV specific CD8 T cells induces reactivation of HSV infection.[59] It also appears that CD4 T cells are important in HSV clearance.[60] However, the local control of HSV in neural ganglia appears mostly dependent on a local population of HSV specific CD8 T cells, apparently independent of blood circulating CD8 T cells.[61] The latter implies that peripheral antibody titers are not likely to change with flare-ups, especially if not severe enough to cause major loss of neural tissue. Most interestingly, shingles, Herpes Zoster/Varicella related disease, appears to have a quite similar CD8 T cell relationship within the ganglia of affected nerves.[62] Of course, shingles is a viral neuritis resulting from reactivation of a latent Herpes family virus as is postulated to occur from Herpes Simplex for both vestibular neuritis and Bell's palsy. Our experience is that all patients who have vestibular neuritis whom we have checked have positive VZV IgG titers but not all have positive HSV IgG titers. An interesting question is whether the causative virus might sometimes or even often be VZV in at least some of the more severely affected persons. Indeed, some researchers do believe that a correlation between the influenza type B, Coxsackie B5, and VZV plays a role in vestibular neuritis.[63]

Much more is known about how the Herpes family viruses interact with the immune system and neural tissue such as the vestibular nerve and other cranial nerve ganglia that cannot be reviewed, here. Our clinical experience is that among those patients with chronic vestibular neuritis symptoms, a high percentage, as R Gacek suggests, improve and stay improved on long term antivirals.

Antivirals in Vestibular Neuritis:

For chronic Herpes family viral infection, the most commonly used anti-virals are acyclovir and valacyclovir. The half-life of acyclovir, which valacyclovir becomes after absorption, is under 3 hours. Absorption of orally administered acyclovir is seldom above 20-25% and of valacyclovir under 50-60%. A typical intravenous dose would be 5 mg/kg or for an 80 kg man, about 400 mg at least 3-5 times per day but up to 10 mg/kg is reported at times to be given (see minimal inhibitory concentration information below). Thus, keeping sufficient medication on board would be affected by absorption percentage, clearance fairly rapid rates, and the minimal inhibitory concentration for the specific virus. At 50% absorption, 1 gram of valacyclovir TID would provide approximately 500 mg absorbed per dose administered or about 5.5 mg/kg for an 80 kg man.

Acyclovir inhibits viral DNA and protein synthesis by phosphorylation of viral thymidine kinase which is critical to viral reproduction. Phosphorylation results in irreversible inactivation of viral DNA polymerase but sensitivity to acyclovir varies among Herpes Simplex (HSV) polymerases.[64] Thus, the range of effective dosage varies not just between HSV and Varicella Zoster, but among HSVs. It does appear that infected cells do concentrate acyclovir triphosphate. Resistance to acyclovir, when it arises, appears most often to be related to loss of thymidine

kinase activity which is especially troublesome in immune compromised persons. The range of *in vitro* minimum inhibitory concentration is 0.02-0.9 mcg/ml for HSV-1, 0.3-2.2 mcg/ml for HSV-2, and 0.8-4 mcg/ml for VZV. For EBV, it is 1.6 mcg/ml but for CMV it is 2-57 mcg.ml.

While acyclovir distributes widely in tissues, it concentrates most in kidneys, liver, and intestines. CSF concentrations are about half of plasma and we would expect inner ear perilymph to be about equal to CSF as perilymph production comes from an inner ear glomerulus analogous to the choroid plexus.[65] Excretion is by urine with up to 90% of the drug being eliminated unaltered.

Route of absorption of which drug matters. Oral administration for acyclovir has a bioavailability of just 10-20% as it is not well absorbed in the bowel. Maximal concentration at 200 mg of orally administered acyclovir is 0.83 mcg/ml in plasma; 1.21 mcg/ml for 400 mg oral acyclovir; 1.61 mcg/ml for 800 mg. While this dosage range seems adequate for HSV-1 with high sensitivity to the drug, it may not be sufficient for HSV-2 or VZV, especially not in spinal fluid spaces if concentration is half of serum concentration. IV administration of 5 mg/kg of acyclovir results in a level of 9.8 mcg/ml at a dosage frequency of q 8h. That would be sufficient for VZV. At 10 mg/kg, q 8h, the Cmax is 22.9 mcg/ml (CMV may require much higher concentrations than this in tissue rather than in serum). The mean half-life of acyclovir in adults and children is similar, about 2.6 hrs.[66] At higher doses for longer time periods, some risk of crystalluria exists[67] but troublesome renal calculi were not found in a Pubmed search.

"Area under the curve" (time above MIC) pharmacodynamics of acyclovir are higher with valacyclovir than acyclovir (better absorption) comparing valacyclovir 500 mg BID to acyclovir 400 mg TID. Data from pregnant women receiving acyclovir vs. valacyclovir showed MICs about 3-5 times higher for valacyclovir 500 mg BID than acyclovir 400 mg TID (3.03 +/- 1.0 mcg/ml vs. 0.94 +/-0.7 mcg/ml). As well, "area under the curve" averaged nearly 18 hr. for valacyclovir vs. less than 8 hr. for acyclovir, with "area under the curve" meaning duration serum drug levels higher than the minimum inhibitory concentration.[68]

Our clinical experience mirrors that of R Gacek and is that a high percentage of patients with chronic or recurring vestibular neuritis induce remission of symptoms on high dose valacyclovir; that fewer do so on long term acyclovir and as dose drops below 500 mg valacyclovir po TID, the recrudescence rate goes up. In our experience, about 30% of patients relapse within several months after stopping antiviral therapy. It is clear as well that some patients never attain suitable relief of symptoms, that many but not all of them have some degree of permanent documented vestibular impairment, and that psychological factors and motion intolerance are common in this group of patients.

In summary, a growing body of evidence suggests that acute viral vertigo syndrome is viral, that the most likely viruses to do this are herpes family viruses, and that recurrent and chronic vestibular neuritis may benefit from use of antivirals. There is at least class IV evidence that anti-herpes medication is of value in managing chronic and recurring viral vertigo disorders, quite separate from single-event acute viral vertigo which typically resolves with supportive care, sometimes more rapidly with short term steroids. It is for these reasons that we have been using antivirals for chronic or frequently recurring vestibular neuritis since 2001 with strong clinical reason to believe that for many but not all patients, this is highly effective.

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[1] Neuhauser HK. Epidemiology of vertigo. Curr Opin Neurol. 2007 Feb;20(1):40-6.
[2] Lai YT, Wang TC, Chuang LJ, Chen MH, Wang PC Epidemiology of Vertigo: A National Survey, Otolaryngol Head Neck Surg, July 2011 145: 110-116. Mar 1 [Epub ahead of print]
[3] http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5606a2.htm
[4] Neuhauser HK. Epidemiology of vertigo. Curr Opin Neurol. 2007 Feb;20(1):40-6.
[5] Brandt T, Strupp M, Novozhilov S, Krafczyk S, Artificial neural network posturography detects the transition of vestibular neuritis to phobic postural vertigo, J Neurol. 2011 Jun 8.
[6] Lai YT, Wang TC, Chuang LJ, Chen MH, Wang PC Epidemiology of Vertigo: A National Survey, Otolaryngol Head Neck Surg, July 2011 145: 110-116. Mar 1 [Epub ahead of print]
[7] Strupp M, Brandt T, Vestibular neuritis, Semin Neurol. 2009 Nov;29(5):509-19.
[8] Strupp M, Brandt T, Vestibular neuritis, Semin Neurol. 2009 Nov;29(5):509-19.
[9] Brandt T. Vertigo: its multisensory syndromes. 2nd ed. London: Springer, 1999.
[10] Strupp M, Zingler VC, Arbusow V, Niklas D, Maag KP, Dieterich M, Bense S, Theil D, Jahn K, Brandt T, Methylprednisolone, valacyclovir, or the combination for vestibular neuritis, N Engl J Med. 2004 Jul 22;351(4):354-61.
[11] Sekitani T, Imate Y, Noguchi T, Inokuma T, Vestibular neuronitis: epidemiological survey by questionnaire in Japan, Acta Otolaryngol Suppl. 1993;503:9-12.
[12] Sekitani T, Imate Y, Noguchi T, Inokuma T, Vestibular neuronitis: epidemiological survey by questionnaire in Japan, Acta Otolaryngol Suppl. 1993;503:9-12.
[13] Kim HA, Hong JH, Lee H, Yi HA, Lee SR, Lee SY, Jang BC, Ahn BH, Baloh RW, Otolith dysfunction in vestibular neuritis: recovery pattern and a predictor of symptom recovery, Neurology. 2008 Feb 5;70(6):449-53.
[14] Masson C, Sterkers O, Chaigne P, Colombani JM, Masson M, [Isolated vertigo disclosing infarction in the area of the posterior and inferior cerebellar arteries]. Ann Otolaryngol Chir Cervicofac. 1992;109(2):80-6. [Article in French]
[15] Moon IS, Kim JS, Choi KD, Kim MJ, Oh SY, Lee H, Lee HS, Park SH, Isolated nodular infarction, Stroke. 2009 Feb;40(2):487-91.
[16] Cnyrim CD, Newman-Toker D, Karch C, Brandt T, Strupp M, Bedside differentiation of vestibular neuritis from central "vestibular pseudoneuritis", J Neurol Neurosurg Psychiatry. 2008 Apr;79(4):458-60.
[17] Chen L, Lee W, Chambers BR, Dewey HM, Diagnostic accuracy of acute vestibular syndrome at the bedside in a stroke unit, J Neurol. 2011 May;258(5):855-61.
[18] Arbusow V, Strupp M, Wasicky R, Horn AK, Schulz P, Brandt T, Detection of herpes simplex virus type 1 in human vestibular nuclei, Neurology. 2000 Sep 26;55(6):880-2.
[19] Baloh RW, Ishyama A, Wackym PA, Honrubia V, Vestibular neuritis: clinical-pathologic correlation, Otolaryngol Head Neck Surg. 1996 Apr;114(4):586-92.
[20] Gacek RR, Gacek MR, The three faces of vestibular ganglionitis, Ann Otol Rhinol Laryngol. 2002 Feb;111(2):103-14.
[21] Arbusow V, Derfuss T, et.al., Latency of herpes simplex virus type-1 in human geniculate and vestibular ganglia is associated with infiltration of CD8+ T cells, J Med Virol. 2010 Nov;82(11):1917-20.
[22] Esaki S, Goshima F, et.al, Auditory and vestibular defects induced by experimental labyrinthitis following herpes simplex virus in mice, Acta Otolaryngol. 2011 Jul;131(7):684-91. Epub 2011 Apr 28.

[23] Zannolli R, Zazzi M, Muraca MC, Macucci F, Buoni S, Nuti D, A child with vestibular neuritis. is adenovirus implicated?, Brain Dev. 2006 Jul;28(6):410-2. Epub 2006 Feb 28.
[24] Ergul Y, Ekici B, Tastan Y, Sezer T, Uysal S. Vestibular neuritis caused by enteroviral infection, Pediatr Neurol. 2006 Jan;34(1):45-6.
[25] Pyykko I, Zou J, Do viruses cause inner ear disturbances?, ORL J Otorhinolaryngol Relat Spec. 2008;70(1):32-40; discussion 40-1.
[26] Davis LE, Viruses and vestibular neuritis: review of human and animal studies, Acta Otolaryngol Suppl. 1993;503:70-3.
[27] Vrabec JT, Payne DA, Prevalence of herpesviruses in cranial nerve ganglia, Acta Otolaryngol. 2001 Oct;121(7):831-5.
[28] Gacek RR, Efferent system degeneration in the human temporal bone, Ann Otol Rhinol Laryngol. 2003 Nov;112(11):947-54.
[29] Sekitani T, Imate Y, Noguchi T, Inokuma T, Vestibular neuronitis: epidemiological survey by questionnaire in Japan, Acta Otolaryngol Suppl. 1993;503:9-12.
[30] Bense S, Bartenstein P, et.al., Metabolic changes in vestibular and visual cortices in acute vestibular neuritis, Ann Neurol. 2004 Nov;56(5):624-30.
[31] Strupp M, Brandt T, Vestibular neuritis, Semin Neurol. 2009 Nov;29(5):509-19.
[32] Sekitani T, Imate Y, Noguchi T, Inokuma T, Vestibular neuronitis: epidemiological survey by questionnaire in Japan, Acta Otolaryngol Suppl. 1993;503:9-12.
[33] Huppert D, Strupp M, Theil D, Glaser M, Brandt T. Low recurrence rate of vestibular neuritis: a long-term follow-up. Neurology. 2006 Nov 28;67(10):1870-1.
[34] Mandalà M, Santoro GP, Awrey J, Nuti D. Vestibular neuritis: recurrence and incidence of secondary benign paroxysmal positional vertigo. Acta Otolaryngol. 2010 May;130(5):565-7
[35] Kim YH, Kim KS, Kim KJ, Choi H, Choi JS, Hwang IK, Recurrence of vertigo in patients with vestibular neuritis, Acta Otolaryngol. 2011 Jul 5.
[36] Gacek RR, Gacek MR, Menière's disease as a manifestation of vestibular ganglionitis, Am J Otolaryngol. 2001 Jul-Aug;22(4):241-50.
[37] Manzari L, Burgess AM, Curthoys IS, Effect of bone-conducted vibration of the midline forehead (Fz) in unilateral vestibular loss (uVL). Evidence for a new indicator of unilateral otolithic function, Acta Otorhinolaryngol Ital. 2010 Aug;30(4):175.
[38] Walther LE, Hörmann K, Pfaar O, [Recording cervical and ocular vestibular evoked myogenic potentials. Part 2: influencing factors, evaluation of findings and clinical significance, Article in German], HNO. 2010 Nov;58(11):1129-42; quiz 1143.
[39] Byun JY, Hong SM, Yeo SG, Kim SH, Kim SW, Park MS, Role of subjective visual vertical test during eccentric rotation in the recovery phase of vestibular neuritis, Auris Nasus Larynx. 2010 Oct;37(5):565-9.
[40] Ferreira LS, Pereira CB, Rossini S, Kanashiro AM, Adda CC, Scaff M, Psychological assessment in patients with phobic postural vertigo, Arq Neuropsiquiatr. 2010 Apr;68(2):224-7.
[41] Holmberg J, Karlberg M, Harlacher U, Magnusson M, One-year follow-up of cognitive behavioral therapy for phobic postural vertigo, J Neurol. 2007 Sep;254(9):1189-92.
[42] Ishiyama A, Ishiyama GP, Lopez I, Eversole LR, Honrubia V, Baloh RW. Histopathology of idiopathic chronic recurrent vertigo, Laryngoscope. 1996 Nov;106(11):1340-6.
[43] Arbusow V, Theil D, Strupp M, et.al., HSV-1 not only in human vestibular ganglia but also in the vestibular labyrinth, Audiol Neurootol. 2001 Sep-Oct;6(5):259-62.
[44] Strupp M, Zingler VC, Arbusow V, Niklas D, Maag KP, Dieterich M, Bense S, Theil D, Jahn K, Brandt T, Methylprednisolone, valacyclovir, or the combination for vestibular neuritis, N Engl J Med. 2004 Jul 22;351(4):354-61.

[45] Strupp M, Zingler VC, Arbusow V, Niklas D, Maag KP, Dieterich M, Bense S, Theil D, Jahn K, Brandt T, Methylprednisolone, valacyclovir, or the combination for vestibular neuritis, N Engl J Med. 2004 Jul 22;351(4):354-61.
[46] Gacek RR. Ménière's disease is a viral neuropathy. ORL J Otorhinolaryngol Relat Spec. 2009;71(2):78-86. Epub 2009 Jan 10. PMID: 19142031 "Antiviral treatment controlled vertigo in 73 of 86 patients with vestibular neuronitis (85%) and 32 of 35 patients with MD (91%).
[47] Gacek RR. Evidence for a viral neuropathy in recurrent vertigo. ORL J Otorhinolaryngol Relat Spec. 2008;70(1):6-14; discussion 14-5. Epub 2008 Feb 1. PMID: 18235200 "The clinical response (relief of vertigo) to the administration of antiviral medication in these syndromes provides practical evidence of a viral neuropathy in patients with recurrent vertigo. Relief of vertigo after this treatment was 90% in VN, Ménière's disease and VN. The relief of positional vertigo (benign paroxysmal positional vertigo) was 66%."
[48] Gacek RR, Gacek MR. The three faces of vestibular ganglionitis. Ann Otol Rhinol Laryngol. 2002 Feb;111(2):103-14. PMID: 11860061 "In the present series, histopathologic and radiologic changes in the vestibular ganglion and meatal ganglion were consistent with a viral inflammation of ganglion cells in cases of Meniere's disease, benign paroxysmal positional vertigo, and vestibular neuronitis. Clinical observations of multiple neuropathies involving cranial nerves V, VII, and VIII on the same side in patients with recurrent vertigo are best explained by a cranial polyganglionitis caused by a neurotrophic virus, which is reactivated by a stressful event later in life. The reactivation of the latent virus may manifest as one of the above vertigo syndromes, depending on the part of the vestibular ganglion that is inflamed, the type and strain of the virus, and host resistance.
[49] Strupp M, Brandt T. Vestibular neuritis. Semin Neurol. 2009 Nov;29(5):509-19. Epub 2009 Oct 15. PMID: 19834862 "The reactivation of a latent herpes simplex virus type 1 (HSV-1) infection is the most likely cause, as HSV-1 DNA and RNA have been detected in human vestibular ganglia."
[50] Hansen S, Cayé-Thomasen P, Boesen J, Thomsen JC. Ugeskr Laeger. [Vestibular neuritis]. 2008 May 19;170(21):1809-15. Review. Danish. PMID: 18492446 Vestibular neuritis is the second most common cause of peripheral vestibular vertigo. Its assumed cause is a reactivation of herpes simplex virus type 1 infection.
[51] Bartual-Pastor J. Vestibular neuritis: etiopathogenesis. Rev Laryngol Otol Rhinol (Bord). 2005;126(4):279-81. Review. PMID: 16496559 "An animal model of vestibular neuritis using retroauricular inoculation of herpes simplex virus in mice, histologic findings in the temporal bone of individuals who had vestibular neuritis, and influenza A virus infection in cultured Schwann's cells suggest viral infection as the main aetiologic cause."
[52] Vrabec JT. Herpes simplex virus and Meniere's disease. Laryngoscope. 2003 Sep;113(9):1431-8. PMID: 12972911 "HSV is more commonly isolated from vestibular ganglia of patients with Meniere's disease than the general population."
[53] Divito S, Cherpes TL, Hendricks RL, A triple entente: virus, neurons, and CD8+ T cells maintain HSV-1 latency, Immunol Res. 2006;36(1-3):119-26.
[54] Sheridan BS, Cherpes TL, Urban J, Kalinski P, Hendricks RL, Reevaluating the CD8 T-cell response to herpes simplex virus type 1: involvement of CD8 T cells reactive to subdominant epitopes, J Virol. 2009 Mar;83(5):2237-45. Epub 2008 Dec 10.
[55] St Leger AJ, Peters B, Sidney J, Sette A, Hendricks RL, Defining the herpes simplex virus-specific CD8+ T cell repertoire in C57BL/6 mice, J Immunol. 2011 Apr 1;186(7):3927-33. Epub 2011 Feb 25.

[56] Ramachandran S, Davoli KA, Yee MB, Hendricks RL, Kinchington PR, Delaying the expression of herpes simplex virus type 1 glycoprotein B (gB) to a true late gene alters neurovirulence and inhibits the gB-CD8+ T-cell response in the trigeminal ganglion, J Virol. 2010 Sep;84(17):8811-20.
[57] Elftman MD, Hunzeker JT, Mellinger JC, Bonneau RH, Norbury CC, Truckenmiller ME, J Immunol. Stress-induced glucocorticoids at the earliest stages of herpes simplex virus-1 infection suppress subsequent antiviral immunity, implicating impaired dendritic cell function, 2010 Feb 15;184(4):1867-75.
[58] Hunzeker JT, Elftman MD, Mellinger JC, Princiotta MF, Bonneau RH, Truckenmiller ME, Norbury CC, A marked reduction in priming of cytotoxic CD8+ T cells mediated by stress-induced glucocorticoids involves multiple deficiencies in cross-presentation by dendritic cells, J Immunol. 2011 Jan 1;186(1):183-94. Epub 2010 Nov 22.
[59] Liu T, Khanna KM, Chen X, Fink DJ, Hendricks RL, CD8(+) T cells can block herpes simplex virus type 1 (HSV-1) reactivation from latency in sensory neurons, J Exp Med. 2000 May 1;191(9):1459-66.
[60] Johnson AJ, Chu CF, Milligan GN, Effector CD4+ T-cell involvement in clearance of infectious herpes simplex virus type 1 from sensory ganglia and spinal cords, J Virol. 2008 Oct;82(19):9678-88.
[61] Himmelein S, St Leger AJ, Knickelbein JE, Rowe A, Freeman ML, Hendricks RL, Circulating herpes simplex type 1 (HSV-1)-specific CD8+ T cells do not access HSV-1 latently infected trigeminal ganglia, Herpesviridae. 2011 Mar 15;2(1):5.
[62] Gowrishankar K, Steain M, Cunningham AL, Rodriguez M, Blumbergs P, Slobedman B, Abendroth A, Characterization of the host immune response in human Ganglia after herpes zoster, J Virol. 2010 Sep;84(17):8861-70.
[63] Pyykko I, Zou J, Do viruses cause inner ear disturbances?, ORL J Otorhinolaryngol Relat Spec. 2008;70(1):32-40; discussion 40-1.
[64] http://americareoncall.com/yahoo_site_admin/assets/docs/ZOVIRAX.107122238.pdf
[65] Zou J, Pyykkö I, Counter SA, Klason T, Bretlau P, Bjelke B, In vivo observation of dynamic perilymph formation using 4.7 T MRI with gadolinium as a tracer, Acta Otolaryngol. 2003 Oct;123(8):910-5.
[66] http://www.ncbi.nlm.nih.gov/pubmed/9790357
[67] Fogazzi GB, Crystalluria: a neglected aspect of urinary sediment analysis, Nephrol Dial Transplant. 1996 Feb;11(2):379-87.
[68] Kimberlin DF, Weller S, Whitley RJ, Andrews WW, Hauth JC, Lakeman F, Miller G. Pharmacokinetics of oral valacyclovir and acyclovir in late pregnancy. Am J Obstet Gynecol. 1998 Oct;179(4):846-51.