ACUTE UNILATERAL VESTIBULOPATHY

Augusto Pietro Casani

Department of Medicine and Surgery, Pisa University Hospital, Italy

ABSTRACT

Acute unilateral vestibulopathy (AUV) is the recommended term (rather than the more widely used vestibular neuritis) for all pathologies involving sudden impairment of the unilateral peripheral vestibular function regardless of the exact location of the lesion. The clinical picture of AUV is characterized by acute severe rotatory vertigo, nausea, vomiting and static and dynamic postural instability. The diagnosis is based on the presence of spontaneous nystagmus (horizontal/torsional, unidirectional), gait imbalance (falling toward the side of lesion) and a positive head impulse test. Typically, no associated auditory or neurological symptoms and signs are present. AUV is thought to be caused by a viral or post-viral inflammation of the vestibular nerve (vestibular neuritis), but a vascular origin of the disease cannot be excluded, especially in the presence of several vascular risk factors. A careful bedside examination and a complete battery of instrumental test (video head impulse test, cervical and ocular VEMPs) could provide accurate information enabling to correctly diagnose AUV, both in acute and chronic stage of the disease also allowing to exclude a possible central nervous system involvement (vertebrobasilar stroke syndromes may mimic peripheral disorders). After a short course of symptomatic treatment with vestibular suppressants to alleviate the patient's neurovegetative symptoms and intense rotatory vertigo, vestibular rehabilitation is the treatment of choice although recent reports suggest that an early steroid treatment may improve long-term outcome.

Keywords: *acute vertigo, vestibular neuritis, spontaneous nystagmus, video head impulse test, vestibulopathy, stroke*

INTRODUCTION

Sudden unilateral vestibular peripheral deficit is a pathological condition often described as vestibular neuronitis, although the term itself implies a pathogenesis that has not yet been demonstrated, namely an inflammation of the vestibular nerve. It is one of the most common disorders of the peripheral vestibular system (1). Table 1 summarizes the key diagnostic criteria of this condition, that may be more correctly named acute unilateral vestibulopathy (AUV). Demonstrating the presence of these diagnostic criteria in a patient allows to make a diagnosis of AUV. However, other clinical and/or instrumental findings could provide a better description of the pathological picture, especially regarding alterations of the vertical semicircular canals and otolith organs.

HISTORICAL BACKGROUND AND DESIGNATION

The first description of a patient affected by AUV was made by Ruttin in 1909 (2) at the Meeting of the Austrian Society of Otology, where he described a patient with sudden vertigo, dynamic ataxia, and vomit. After other occasional reports, in 1952, Dix and Hallpike (3) coined the term vestibular neuronitis to distinguish this clinical picture from Menière Disease. They defined vestibular neuronitis as "some form of organic disease confined to the vestibular apparatus, localized between its peripheral receptors and the vestibular nuclei in the CNS." Bohmer (4)

Table 1. Diagnostic criteria of AUV

Acute or subacute vertigo associated with nausea or vomiting lasting more than 24 hours
Spontaneous nystagmus with peripheral features (horizontal, unidirectional, inhibited by visual fixation)
Horizontal semicircular canal deficit demonstrated by HIT and/or caloric test
Static and dynamic postural imbalance with tendency to fall towards the affected side
No associated hearing loss or unchanged hearing during the vertigo attack
No neurological deficits

adopted the term acute unilateral peripheral vestibulopathy to describe a clinical syndrome characterized by acute sudden onset and unknown origin. In international literature the term vestibular neuronitis is often used, implying in its pathogenesis the direct or indirect effects of a viral infection, analogue to facial nerve paralysis (5). The Classification Committee of the Bárány Society (CCBS), deputed to the classification of neuro-otologic syndromes, proposed to name vestibular neuronitis as acute unilateral peripheral vestibulopathy (6,7).

ETIOLOGY

AUV belongs to the large group of idiopathic disorders, though most recognized pathogenetic theories suggest that the disease originates from an inflammation of the vestibular nerve. It is likely that the disorder is caused by a reactivation of the herpes simplex type 1 virus (HSV-1), originated from the vestibular ganglion (8,9), even though recent studies reported that latent vestibular ganglion (also called Scarpa's ganglion) infections can be found in a lower portion of patients than expected (10).

Moreover, histopathological findings in AUV include a reduction in the number of fibers of vestibular neuroepithelium, superior vestibular nerve and vestibular ganglion, which is compatible with a viral infection (11,12). Analogously, Bell's paralysis was associated with HSV-1 DNA in cerebrospinal fluid (13).

Magnetic resonance imaging (MRI) findings further corroborate the hypothesis of an inflammatory pathogenesis (14). In fact, in 70% of a group of 29 patients with AUV, the administration of intravenous gadolinium enhanced the imaging of the vestibular nerve and inner ear structures (15). Interestingly, the intensity of spontaneous nystagmus in those patients correlated with the contrast media diffusion level. However, no conclusive evidence can be drawn on the viral pathogenesis of AUV, also because the most frequently involved viruses (herpes simplex virus, cytomegalovirus, Epstein-Barr virus, adenovirus, influenza) are highly prevalent in the general population and therefore a higher antibody titration against those viruses could be registered independently from AUV. Also, immunohistochemistry does not provide any definitive validation regarding the viral origin of a vestibular nerve degeneration. Moreover, it is not clear why a virus would spare some portions of the vestibular or acoustic nerve, or why many AUV patients lack features typically associated with a viraemia (especially the higher prevalence with age).

Alternatively, AUV may be the consequence of a vascular insult, considering that the inner ear is perfused by a terminal artery and that AUV patients typically present with risk factors associated with a higher vascular risk (16,17). The area perfused by the superior vestibular artery and innervated by the superior vestibular nerve (which includes the utricle and the lateral and anterior semicircular canals) is particularly vulnerable to ischemic damage. Typically, repeated vertigo crises that last for some minutes suggest a transient vestibular ischemia, and they represent a red flag for an acute vertebro-basilar infarction (18). A prolonged ischemia involving only the superior vestibular artery may determine AUV. The hypothesis regarding the vascular origin of AUV was proposed also by Lindsay and Hemenway (19) who described some patients with a clinical picture characterized by prolonged vertigo without hearing loss or other neurological signs, which resolved in some weeks to evolve into positional vertiginous crises. The postulated pathogenesis involved, during the initial acute vertiginous episode, an occlusion of the superior vestibular artery, sparing the posterior vestibular canal and the saccule (which are perfused by the posterior vestibular artery). On the contrary, the positional vertiginous episodes that followed were to be ascribed to otoconial detachment following the ischemic episode, together with canalolithiasis in the posterior canal. However, Lindsay and Hemenway's syndrome was also associated with a virus-induced lesion of the superior vestibular nerve (20). Even with the most recent imaging techniques, it is still not possible to confirm the correct diagnosis of AUV and its vascular etiology, which therefore remain just hypothetical. Nevertheless, an ischemic mechanism should be suspected in older or at-risk patients (suffering from hypertension, obesity, diabetes, or presenting a history of cerebrovascular ischemic episodes). Other etiological postulated mechanisms include an autoimmune reaction, which should affect both labyrinths. It is still possible, however, that unilateral AUV episodes are the result of an immunological imbalance following a viral infection.

LESION LOCATION

It is not clear whether AUV symptoms are caused by a lesion of the vestibular nerve, of the intra-labyrinthic vestibular organ, or both. The latter option seems to be the most likely, as demonstrated by some magnetic resonance (MR) findings (15). Some authors argue that AUV represents the vestibular analogue of sudden hearing loss in which the damage is mostly located in the cochlea rather than in the cochlear nerve (21) and that consequently the term vestibular neuronitis is inappropriate, as AUV would be caused by a lesion of the vestibular receptors. This view is corroborated by some evidence that in AUV

the five receptors in the labyrinth may be damaged. However, it must be noted that it is not possible to distinguish a lesion to a receptor from a lesion to the nerve that originates from it.

Clinical and neurophysiological evidence report that in AUV the superior portion of the vestibular labyrinth (which includes the lateral and anterior semicircular canals, and the utricle) is generally affected. The inferior portion of the labyrinth (saccule and posterior semicircular canal) is commonly spared. Lindsay and Hemenway syndrome represent a clinical proof of this phenomenon, as BPPV of the posterior semicircular canal constitutes a common sequela of AUV. The susceptibility of the superior portion of the vestibular labyrinth to damage may be explained by the fact that the superior vestibular nerve is longer than the inferior (and therefore more susceptible to a selective inflammation) (22) or by anatomical differences in bone canals constituting the two portions of the bony labyrinth (23). However, it is also possible that both portions of the vestibular labyrinth (the superior and the inferior) are affected, or that only the inferior one is (14). Surprisingly, also single vestibular receptors could be damaged: our experience regard 51 patients suffering from AUV using vHIT, CT and both cVemps and oVemps. Most patients demonstrated a pathological high-velocity HC VOR gain (98%) and CP (91%). Some dissociated findings were found between CVT and HC vHIT (5 cases): some patients presented a normal caloric response despite a pathological HC VOR gain; conversely, no patients exhibited a pathological caloric response despite a normal HC vHIT. The second most affected receptor was the AC (83%), followed by the utricle (72%) and PC (45%), while the saccule was the least damaged (44%) (Fig. 1). Nineteen out of 59 patients exhibited involvement of all five vestibular end organs (32%). Thirteen out of 59 patients exhibited an impairment of HC, AC, and utricle (22%); among whom, one had a normal low-velocity and a pathological high-velocity HC function. The remaining patients exhibited a selective receptor injury (46%). Among these, 13 patients exhibited an impairment of the receptors innervated by both the upper and lower branch of the VN (22%), while 14 only by its superior division (24%). AUV patients with exclusive damage to the saccule and/or to the PC were not identified. These results are reported in Fig. 2. Our data suggest that most patients with AUV exhibited total end-organ damage; this finding can be related to a damage to the entire labyrinth or, more probably, to a vestibular neuritis involving both divisions of the VN. The second most frequent pattern we found was that it was more likely to be related to a superior vestibular neuritis. We did not identify cases of AUV that exhibited isolated dysfunction of the PC and/or the saccule. The remaining patients experienced selective damage to the vestibular end organs, which can be explained by a partial nerve lesion (25). Recently, it has been reported that AUV may be caused also by a mild and limited damage to the lateral semicircular canal (26). By using the head-impulse test (HIT), which verifies the function of each semicircular canal, and the vestibular evoked myogenic potentials (VEMPs), whose output reflects the activity of the otolith organs (utricle and saccule), it is now possible to classify AUV into three types: superior, total, and inferior (27).

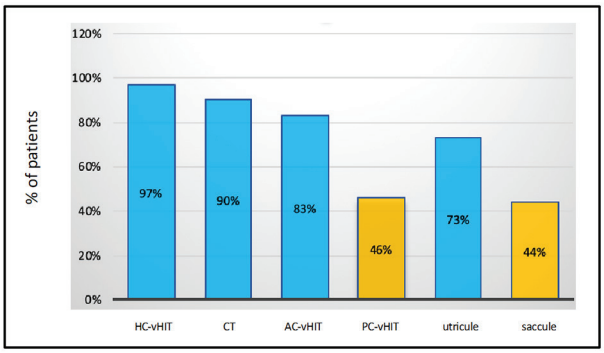

Fig. 1. Involvement of vestibular receptors in our series of patients affected with AUV. AC: anterior canal; HC, horizontal canal; CT: caloric test. In yellow are receptors innervated by the inferior vestibular nerve. In blue are the receptors innervated by the superior vestibular nerve.

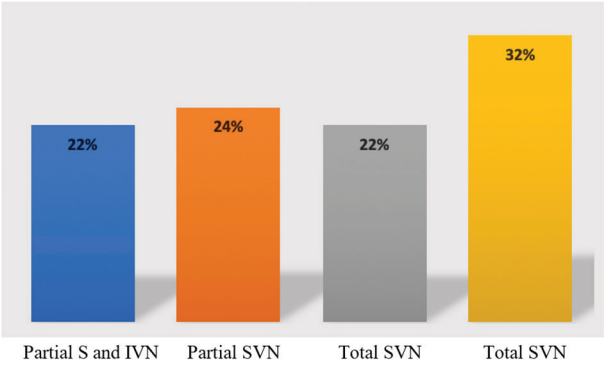

Fig. 2. Results of the instrumental assessment in patients suffering from AUV according to vestibular nerve (VN) partition. I: inferior. S: superior.

EPIDEMIOLOGY

AUV is one of the most common forms of acute vertigo (28), but the epidemiological data regarding this topic is surprisingly low. The only relevant data come from a perspective study carried out in Croatia in the years 2011–2012 from which the annual incidence of AUV was estimated to be 13 over 100 000 people, with no seasonal variations (29). AUV has an

incidence around 10 times lower than benign paroxysmal proximal vertigo (BPPV) (30) and it has been reported to be 10 times more prevalent than Menière Disease (31).

Clinical Features

Symptoms

The main symptoms of AUV are:

- prolonged rotatory vertigo (almost always lasting more than 24 hours) and possibly oscillopsia;
- postural imbalance, both static and during walking;
- nausea and/or vomiting.

Vertigo arises with varying levels of acuity, worsening in few hours. It is described as the feeling as though the surrounding environment is spinning that lasts more than a day. Patients report severe difficulties in walking and generally lie down turning their head on the healthy side, as this position reduces vertigo and nystagmus. True vertigo and vagal symptoms back off in few days, while the dynamic imbalance can persist for weeks or months. While collecting the patient's clinical history, it is important to search for those symptoms that would allow a differential diagnosis with other diseases of the labyrinth, of the brainstem, and of the cerebellum. Consequently, it is important to ask to the patient whether they have experienced previous episodes of vertigo (differential diagnosis with vestibular migraine, recurrent vertigo of the adult, transient ischemic attacks), whether they are experiencing also unilateral hearing loss and tinnitus (differential diagnosis with Menière Disease, labyrinthitis, labyrinthic infarction, anterior cerebellar artery infarction), and finally whether other symptoms are present that may hint for a central form of vertigo, such as headache, diplopia, dysphagia and dysphonia.

Signs

The cardinal signs of AUV are:

- spontaneous persistent unidirectional nystagmus beating towards the healthy side, lasting more than 24 hours;
- head impulse test positive on the horizontal plane;
- unilateral caloric paresis, or paralysis on the affected side.

Most AUV episodes could be diagnosed and subsequently treated based on the forementioned signs, together with the patient's clinical history and in the absence of signs of central vestibular involvement. Other diagnostic tests may be used in support of the diagnosis of AUV, such as vestibulo-spinal tests, head shaking test (HST), and mastoid vibratory test (MVT), or to better define which portion of the vestibular system has been affected (HIT for the vertical canals, VEMPs).

Spontaneous Nystagmus

Spontaneous nystagmus in AUV is determined by an imbalance in the bilateral vestibular equilibrium, caused by a sudden decrease in the discharge frequency of one of the two vestibular peripheral organs and nerves. The slow phase is therefore directed towards the affected side, while the fast phase towards the healthy side. The beating is not affected by head or gaze position, and it is therefore defined as unidirectional (1,5). The nystagmus is inhibited by gaze fixation. In the first days from the onset it is easily diagnosed with direct observation, while subsequently it can be seen only by using Frenzel glasses (5). Tridimensional video-oculography allows to record and analyze the features of the nystagmus, including a small vertical component that may be present due to a compound damage of the lateral and vertical semicircular canals (1). Although the intensity of spontaneous nystagmus in AUV is characterized by significant interindividual differences, it has been estimated that the mean angular speed in the acute phase is around 10°/sec, which is analogous to the speed recorded after a vestibular neurectomy (1). Spontaneous nystagmus gradually reduces, and its persistence with time depends both on the recovery ability and on the compensatory mechanisms (see "Natural History").

Head-Impulse Test (HIT)

A suspicion of AUV is confirmed by HIT, with the recording of a vestibulo-ocular reflex (VOR) deficit on horizontal plane rotation. In fact, when the patient's head is rapidly rotated towards the affected side, the eyes rotate jointly with the head, and to maintain fixation correction saccades are recorded. Consequently, correction movements are directed towards the healthy side. This is the sign that demonstrates a dynamic VOR deficit at high frequencies, which is highly specific for a unilateral peripheral vestibular damage (1,7). Since this type of deficit cannot be compensated by other sensory systems, it may persist if the peripheral vestibular activity does not recover. In AUV, HIT is extremely useful for an early differential diagnosis with cerebellar injuries, especially when the caloric stimulation test is difficult to conduct or interpret. The simultaneous presence of spontaneous nystagmus and a positive HIT is suggestive for AUV, while a normal HIT hints that a central lesion is possibly the cause of the acute clinical picture. Unfortunately, some issues must be known to the examiner to avoid diagnostic mistakes (1,32). Firstly, a certain degree of experience and training is necessary to reliably perform the HIT, as unexpe-

rienced operators tend to record a higher number of false positives. The main issue with HIT is the fact that in some patients the correction saccades occur during the head rotation, and consequently at the end of the movement the eyes have already gained fixation on the image. This phenomenon is known as covert saccades and is responsible for causing several false negatives at HIT. Therefore, in case of HIT questionable or negative results, video recording of HIT (video HIT) should be used to visualize the covert saccades. However, video HIT is difficult to apply in the acute setting and at the patient's bedside.

Secondly, HIT sensibility is not optimal in case of partial acute vestibular deficit and may produce normal results. Kim and Lee (33) reported also that patients with simultaneous central and peripheral vestibular lesions gave positive results at HIT. In such patients generally simultaneous hearing loss is diagnosed. However, HIT on the horizontal plane is a useful test in the diagnosis of AUV, and it is overall associated with a low misdiagnosis rate even at the patient's bedside. HIT results depend on the semicircular canals, which are damaged. When the superior canal is involved, HIT results abnormal both on the horizontal plane, and on the superior semicircular canal plane. In inferior AUV the only damaged canal is the posterior, while in total AUV the test will obviously result positive on all three canals (Table 2). In conclusion, the diagnostic power of a positive HIT is very high in patients with a spontaneous horizontal nystagmus, and this allows for the diagnosis of a peripheral acute vestibular damage, and it makes other diagnostic tests useless or not immediately necessary (1,32).

The video head-impulse test (vHIT) is the computerized version of the head-impulse test. It incorporates a new technology that uses a high speed, lightweight video goggle to measure (left or right) eye velocity and record "catch up" saccades (and other abnormalities) in patients with impaired VOR function. The test provides a quick and objective measure of the vestibular ocular reflex (VOR) in response to head movements in the natural range of daily motions (34). The vHIT uses infrared cameras to record and measure VOR and it provides a reliable, repeatable, documented measure of vestibular function quickly and precisely. This test is more sensitive to saccades, particularly covert saccades, than the HIT, and the VOR measurement and registration are more reliable and can be used during patient follow-up (34). Currently, the results of ocular vestibular evoked myogenic potentials (oVEMPs) and cervical vestibular evoked myogenic potentials (cVEMPs) can be combined with the characteristics of the spontaneous nystagmus and the results of vHIT and CT to obtain a picture regarding the state of the peripheral vestibular function of each sense organ as well of each branch of the VN (35) (Table 2).

Caloric Test

Table 2. Clinical and instrumental results according to the selective or total vestibular nerve involvement. ASC: anterior semicircular canal; HSC: horizontal semicircular canal; PSC: posterior semicircular canal.

	Superior VN Involvement	**Inferior VN Involvement**	**Inferior and Superior VN Involvement**
Spontaneous Ny	Horizontal (*possible upbeat component*)	Downbeat Torsional	Horizontal (*possible torsional component*)
vHIT ASC	Impaired	Normal	Impaired
vHIT HSC	Impaired	Normal	Impaired
vHIT PSC	Normal	Impaired	Impaired
Caloric Test	Impaired	Normal	Impaired
oVemps	Impaired	Normal	Impaired
cVemps	Normal	Impaired	Impaired
Ocular tilt reaction	Ipsiversive (*if present*)	Absent	Ipsiversive (*if present*)

Although the caloric test (CT) provides a non-physiological stimulation and records responses with a very high inter- and intra-individual variability, it allows to collect important information on the functional activity of the lateral semicircular canal, and it is still considered fundamental for the diagnosis of AUV. Essential finding for the AUV diagnosis is the absence of response in case of a canal paralysis, and a dampened response in case of a partial canal damage (5). A complete canal paralysis should be confirmed by CT with ice water (ice water test). In the early phases of AUV an intense spontaneous nystagmus interacts with the CT-induced nystagmus, and consequently in some cases CT interpretation may be difficult. For example, in case of a left AUV, the stimulus induced by hot water on the left side should not modify the spontaneous nystagmus towards the

right side if the deficit is total, while it should attenuate it if the loss is only partial. Moreover, by stimulating the right side, which is healthy, we should record an intensification of the spontaneous nystagmus. On the contrary, the stimulus induced by cold water on the affected side should not modify the spontaneous nystagmus, or only determine a slight increase in intensity and frequency, while introducing cold water on the healthy side we should record a directional inversion of nystagmus or its disappearance. An alternative to the classic Fitzgerald Hallpike method is represented by the simultaneous caloric test with cold water, which also brings the advantage of reducing testing time in case of distressed patients. In a patient with spontaneous nystagmus beating on the right side due to left AUV, the simultaneous caloric stimulation with cold water should induce an inversion or disappearance of the spontaneous nystagmus. The description reported above is only theoretical. In fact, sudden unilateral vestibular loss on one side often causes a temporary functional impairment also on the other side, due to an adaptive compensatory mechanism which arises to reduce vestibular tone imbalance, hence decreasing the activity of the vestibular nuclei on the healthy side. This adaptation induces a reduction of 70% in the vestibular response on the healthy side, which continues until central compensation is established. Consequently, in the first phases of AUV it is not always easy to confirm vestibular impairment by caloric testing, and it is especially difficult to establish whether the loss is due to a paresis or to a complete paralysis of the vestibular function. When in doubt regarding the result of caloric testing, it is advisable to repeat the test in a few days, when spontaneous nystagmus has decreased and the response after caloric stimulation is easier to interpret.

Head Shaking Test (HST)

The HST is very useful in the diagnosis of an acute unilateral vestibular deficit. In the acute phase, the test always results in an increase of spontaneous nystagmus. In patients with AUV in whom central compensation has been established and spontaneous nystagmus has disappeared, performing HST on the horizontal plane frequently induces a horizontal nystagmus beating towards the healthy side. This phenomenon happens due to an asymmetry in the velocity storage mechanism secondary to an asymmetrical peripheral stimulation. One year after the development of AUV, subjects whose affected labyrinth has not healed will result positive to HST in 70% of cases. In patients tested in the recovery phase of AUV, it is possible that HST induces a nystagmus beating towards the affected side. This mechanism depends on vestibular adaptation, which is responsible also for the disappearance of nystagmus in the first place. In fact, if vestibular adaptation has already been established, it is possible that asymmetrical inputs induce a paradoxical asymmetry in the velocity storage mechanism producing a nystagmus beating in a direction opposite to the one expected.

Moreover, HST may be very useful to uncover a central vestibular syndrome in some patients with AUV (see paragraph on differential diagnosis).

Mastoid Vibration Test (MVT)

The mastoid vibration test is not very useful during the acute phase of AUV. On the contrary, during the compensation phase, MVT is able to induce a rotatory horizontal nystagmus beating towards the non-affected side. MVT has been proved to be more sensitive than clinical HIT (without video-oculography) in determining a residual asymmetry in vestibular function (36). One year after the development of AUV, a vibration-induced nystagmus is still detectable in 60% of the patients. A limitation of MVT regards its ability to detect lesions laterality. In fact, in 5–10% of cases the vibration-induced nystagmus has been shown to beat towards the pathological side. In conclusion, the MVT results should not be overlooked, because the test stimulates the vestibular system at different frequencies compared to other tests in addition to being easy and fast to perform.

Signs of Otolithic Dysfunction

Most studies conducted on patients with AUV focus on lateral semicircular canals activity (CT, HST, HIT). However, AUV can also be associated with symptoms and signs suggestive of a concomitant involvement of the otolith system, especially in the acute phase. In those cases, it is possible to record the so-called ocular tilt reaction (OTR) characterized by:

1. Ocular Torsion

Diagnosing an ocular torsion requires the contribution of a neuro-ophthalmologist and it is not easy to perform by an otoneurologist. Nevertheless, around 80% of patients in acute phase have shown ocular torsion, demonstrating a frequent involvement of the utricle in AUV (37). The tilt is often recorded on the affected side eye, with the eye's superior pole rotated towards the affected ear.

2. Skew Deviation (SD)

Skew deviation requires ophthalmological testing to be diagnosed (cover test), but in some patients a vertical misalignment of the eyeballs is obvious even without Frenzel goggles. This sign is much less frequent than ocular torsion, being present during the acute phase in only 15% of patients, and it is always characterized by hypotropia of the ipsilesional eye.

3. Head Tilt

Head tilt towards the affected side, which is a typical sign of otolithic distress, is quite rare (4%) and it is probably evident only in patients presenting a complete loss of sensory signaling.

The ocular tilt reaction is a sign of an abnormal otolith-ocular reflex and a large amplitude SD and OTR are more common with central lesions and its presence are quite rare in AVL. The exception may be a very complete peripheral deafferentation such as postsurgical cases and severe bacterial inner ear otitis. A recent study aimed to integrate both nystagmus direction and SD in patients with horizontal Ny. If this Ny has the fast phase away from the hypertropic eye (called UPHILL) this could be considered a peripheral marker. On the contrary if the Ny is towards the hypotropic eye (called DOWNHILL) this could be considered as a central marker (38) (Fig. 3).

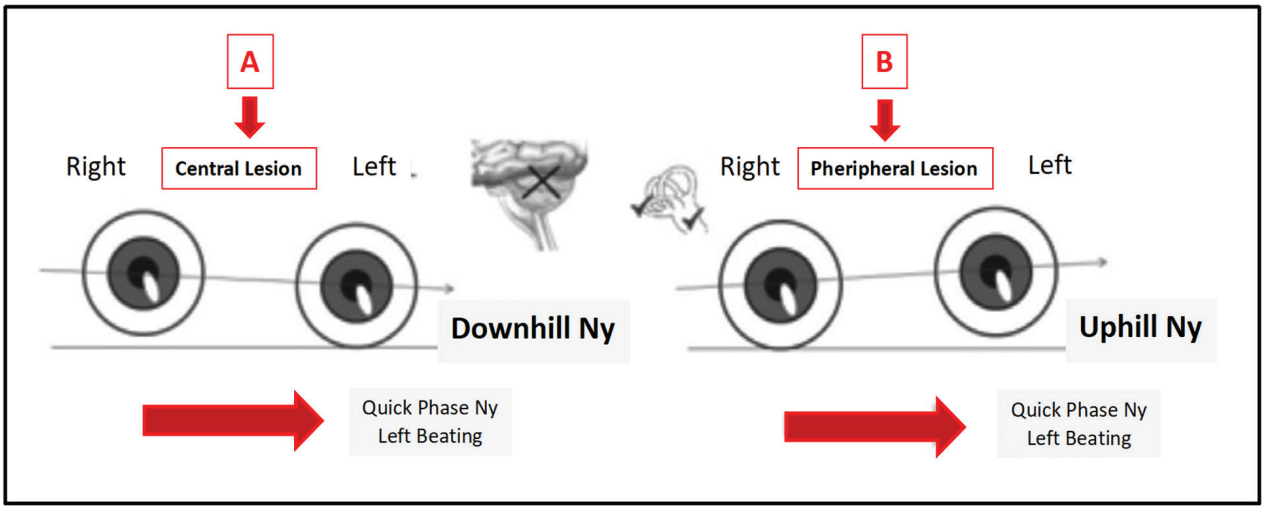

Fig. 3. The right lateral semicircular canal is damaged, and a spontaneous horizontal nystagmus arises to the left. At the same time, the right utriculus is damaged (by the same disease) and an ocular tilt reaction is present, with hypotropia of the right eye. As a result, the plane on which the nystagmus beats is inclined upward ("uphill") (B). A lesion is present after decussation of the utricular afferent fibers. Ocular tilt reaction is referred to the opposite side. The (central) resulting nystagmus is tilted "downhill" (A).

Subjective Visual Vertical (SVV) Test

The subjective visual vertical analysis allows to evaluate the static function of the otolith system. Over 90% of patients with AUV in the acute phase show a pathological SVV tilt towards the affected side, always in concordance with ocular tilt direction. However, it is not clear whether SVV is the sensorial consequence of ocular tilt or the perceptive correlation of a vestibular tone imbalance on the rolling plane (37).

Vestibular Evoked Myogenic Potentials (VEMPs)

The dynamic activity of the two otolith organs (utricle and saccule) can be evaluated with two types of evoked myogenic potentials, which can be elicited with stimuli administered both by air and by bone conduction. Cervical VEMPs (cVEMPs) especially test the saccule, while ocular VEMPs (oVEMPs) analyze utricular function (39), and therefore both cVEMPs and oVEMPs contribute greatly to a specific diagnosis of the damaged area. Consequently, in superior AUV, oVEMPs will be altered and cVEMPs will be spared, while in complete AUV both types of VEMPs should be pathological. The only alteration of cVEMPs is necessary for the diagnosis of inferior AUV, together with its peculiar spontaneous nystagmus and a positive Video-HIT conducted on the posterior semicircular canal plane. The incidence of VEMPs alterations in acute phase AUV is reported with a certain degree of variability. In fact, in some reports oVEMPs alterations are predominant (as expected) but in others the percentage of pathological cVEMPs is so high to suggest that the involvement of the inferior branch of the vestibular system is more frequent than what has been previously suggested (37,39-41). It is possible, at least partially, that this variability depends on the different techniques and parameters adopted.

CLINICAL EVOLUTION AND PROGNOSIS

The clinical evolution of signs and symptoms in AUV is strongly dependent upon two main elements: restitutio ad integrum (which means anatomical and functional restoration to the original condition) and vestibular compensation. The preferable evolution is represented by complete recovery of vestibular function spontaneously or thanks to therapy, analogously to what happens with Bell's paralysis or sudden hear-

ing loss. Alternatively, in case of a persistent deficit, it is likely for a mechanism of static compensation to arise, in which spontaneous nystagmus will not be detected anymore, but at least one among the dynamic tests (HST, NIT, MVT; caloric reflex testing, VEMPs) will be altered. In fact, the central vestibular system can compensate much more easily static imbalances than dynamic ones (37). In a few patients, an effective compensation does not occur, and the spontaneous nystagmus persists. In most cases, spontaneous nystagmus (as observed by Frenzel goggles) disappears in around 30 days. However, by electronystagmography (ENG) in the dark it is still possible to record spontaneous nystagmus even one year after the acute event (42). In case of incomplete, or however reversible, vestibular lesions, it may be possible to record the phenomenon of recovery nystagmus, which peculiarly beats towards the affected side. This happens when spontaneous nystagmus has already subsided, when functional recovery (partial or complete) happens in the pathological labyrinth. In fact, the restoration of an afferent input to the vestibular nuclei may determine a new imbalance, with a functional prevalence of the nuclei ipsilateral to the lesion, and therefore generating an opposite-beating nystagmus.

Otolith function is characterized by a faster normalization than semicircular canal function, probably because otolith nervous paths are damaged less severely. In fact, in a time of 6 weeks from the original damage it is unlikely to detect SD. However, ocular tilt (25%), SVV alteration (25%) or cVEMPs anomalies (15%) may persist longer (37). Recently it has been demonstrated that video HIT too may offer important pieces of information regarding AUV prognosis. Lower values of high-velocity vestibulo-oculo-motor reflex gain and a high prevalence of overt saccades are related to a worse prognosis after acute unilateral vestibulopathy. This is of great interest to clinicians in identifying which patients are less likely to recover and more likely to need a vestibular rehabilitation program (Fig. 4) (43). Furthermore, a consistent number of patients that have undergone

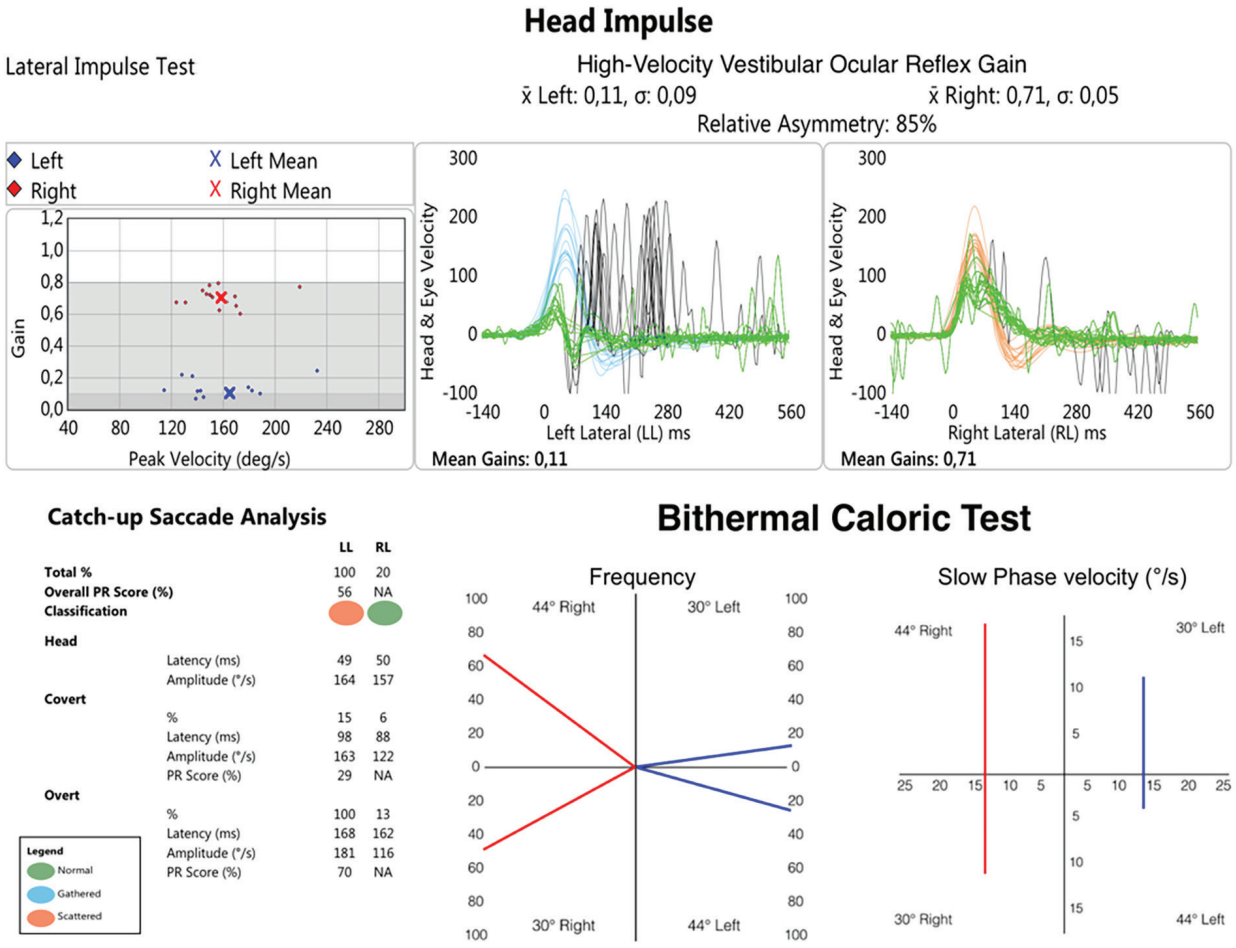

Fig. 4. A typical vestibulometric pattern in a patient with poor recovery after AUV and needing VR. Note the high number and amplitude of O-CSs and the low value of HF-VOR. On the contrary, bithermal caloric test shows a mild reduction of slow phase velocity of the caloric-induced nystagmus.

a severe and prolonged vertigo episode may develop persistent perceptive postural dizziness (PPPD) (44).

DIFFERENTIAL DIAGNOSIS

AUV can be caused by peripheral (internal ear/vestibular nerve) or central diseases (cerebellum/brainstem). Differential diagnosis with numerous peripheral vestibular diseases (peri-lymphatic fistula, Menière disease, vestibular schwannoma) should not be a problem, considering that many peripheral pathologies present also hearing issues and other peculiar features. On the contrary, benign paroxysmal positional vertigo (BPPV) affecting the lateral canal may deceive the examiner, as it sometimes presents with a pseudo-spontaneous nystagmus. Therefore, all patients with spontaneous nystagmus should undergo the Pagnini-McClure test (which is diagnostic for lateral canal BPPV). Only exception to this rule is the rare "canalith jam" in which spontaneous nystagmus does not change direction with head movements (45). Regarding the differential diagnosis of AUV with central vestibular diseases, most help is provided by the coexistence, in central pathologies, of other neurological signs and symptoms, and by the different clinical presentations at onset. For example, both multiple sclerosis and vestibular migraine rarely present with features like AUV. On the contrary, special attention must be paid to cerebellar or brainstem infarction, also because it has been demonstrated that bedside vestibular examination is more sensible to diagnose a recent ischemic event than magnetic resonance imaging (46).

Most frequent central cause for a prolonged vestibular episode is represented by cerebellar infarction of postero-inferior cerebellar artery (known as mPICA) in which the fundamental anatomical structure responsible for the onset of vertigo is the nodule, which is strictly connected to the ipsilateral vestibular nucleus, and which directly receives afferent inputs from the labyrinth. Ischemic lesions in the territory supplied by mPICA are characterized by a severe postural imbalance, cerebellar/brainstem neurological signs and spontaneous multidirectional nystagmus (gaze-evoked), which make the diagnosis relatively easy. Unfortunately, small lesions affecting the nodule may manifest in around 20% of patients, without the typical cerebellar signs, with a clinical picture identical to AUV (vestibular pseudoneuritis), which makes the differential diagnosis extremely difficult (47). Moreover, also ischemic lesions involving the antero-inferior cerebellar artery (AICA) may cause prolonged vertigo, but rarely as an isolated presentation. Except for rare reports of vestibular pseudo-neuritis, most AICA infarctions also involve unilateral hearing loss due to cochlear ischemia, and multiple brainstem signs, such as facial nerve paralysis or Horner syndrome. A peculiar finding is represented by multidirectional asymmetrical nystagmus (Brun nystagmus). The HST has proved to be a useful tool to diagnose a central cause also in those patients where other oculo-motor signs hint for a peripheral presentation. In particular, the examiner should look for the onset of a vertical nystagmus after performing the HST on the horizontal plane, or alternatively for a spontaneous nystagmus inversion (48).

In order to reduce the chance of diagnostic mistakes, some acronyms have been proposed as models to avoid mistakes (32,49).

- HINTS: Head-Impulse negative, gaze-evoked Nystagmus; test for Skew deviation positive;
- HINTS plus: HINT + sudden hearing loss;
- INFARCT: Impulse Negative, rapid Fase of nystagmus Alternating (gaze-evoked), Re-fixation with Cover Test (skew);
- STANDING: SponTAneous and positional nystagmus; Nystagmus Direction; head Impulse test; position and Gait.

In Table 3 are reported criteria that may hint for a possible central involvement and strongly advise to perform a high-resolution MRI.

Table 3. Bedside diagnosis of central lesion in patients with AUV

Gaze-evoked nystagmus (or other oculo-motor central signs)
Spontaneous peripheral-like nystagmus with negative HIT (or symmetrical caloric reflex test)
Skew deviation (which does not resolve within 48 hours)
Failure to maintain the upright position (severe ataxia of trunk and limbs)
Severe occipital headache with recent onset
Unilateral hearing loss with recent onset
Vertical nystagmus after HST on the horizontal plane

TREATMENT

The doubts regarding the AUV causative process do not allow us to define a universally accepted pharmacological treatment. On the contrary, physical rehabilitation therapy has been shown to provide evident and demonstrated functional results in controlled studies. The recovery from AUV depends on the restoration of vestibular function (which can ultimately be partial, complete, or null) and on the central compensation for vestibular asymmetry. Even patients who have not restored vestibular activity on

the affected side can return to lead normal lives. The earlier physical vestibular rehabilitation is started, the faster central compensation will be established, even though there are no definitive data whether an early physical treatment will produce a better final recovery. On the other hand, central compensation is definitively inhibited by sedative drugs.

Symptomatic medical treatment is still advisable in the acute early stage of AUV, when vagal symptoms and vertigo are extremely debilitating. The main classes of drugs used to treat acute vertigo include antihistamines, anticholinergics, antidopaminergics, and GABAergics. These mostly act on neurotransmitters involved in the signaling from primary vestibular neurons to secondary ones, on vestibular nuclear tone maintenance, and on vomit control. Patients' conditions often require parenteral administration of drugs, whose efficacy is dose-dependent. Few studies have been published on the efficacy of vestibular sedatives. Two randomized trials have reported that dimenhydrinate is more effective than lorazepam and equally effective as droperidol (50,51).

Static signs of AUV, such as spontaneous nystagmus, disappear when vestibular activity is spontaneously recovered or when central compensation is established, hence with a central vestibular nuclei remodulation of neurological activity. The latter happens thanks to the reactivation of extra-labyrinthic afferent signaling, mainly proprioceptive in origin. Therefore, it is of fundamental importance to mobilize early AUV patients and to suspend sedative pharmacotherapy as early as possible.

On the contrary, the recovery from dynamic signs of AUV happens mostly due to adaptive or substitutive mechanisms that are established especially on visuo-vestibular interactions. For example, sliding of an image on the retina during head movements constitute an error signal that helps vestibular adaptation to be established.

Consequently, physical rehabilitation for AUV should be started in the first 48 hours from symptom onset. In the early phases is necessary to use vestibular sedatives, but it is important to provide good environmental lighting to favor visual cues. As early as possible it is advisable to suspend the pharmacological therapy and to start to mobilize the patient to provide the central vestibular system with proprioceptive cues, which are essential to promote central compensation. Generally, patients accept the suspension of pharmacological therapy, if they have been adequately motivated on the goals of physical rehabilitation. It is important also to tell them that physical exercises can sometimes induce an early worsening of vestibular symptoms. In 5–6 weeks, it is generally possible to obtain a good functional recovery and to go back to leading all normal activities. However, it is sometimes possible that symptoms become chronic, and that equilibrium becomes permanently impaired. The final degree of vestibular recovery may in fact be delayed or limited by simultaneous CNS alterations (especially cerebellar ones), by visual or proprioceptive defects (for example in diabetic patients), by an exaggerated patient mobilization or use of sedative drugs. Video HIT (52) and/or fHIT (53) are instrumental exams that can monitor the efficacy of vestibular rehabilitation.

Regarding causal treatment, assuming that AUV is caused by a viral infection and inflammation, it appears reasonable to propose a therapy aimed at reducing inflammation, analogously to what is used to treat both sudden hearing loss and especially Bell's paralysis. From a randomized double-blind study involving a considerable number of patients, it appeared that methylprednisolone was effective in treating AUV. In fact, one year after symptom onset, in patients who had received corticosteroids, vestibular function was significantly better than in patients who had received a placebo. From the same study it was evident also that antiviral drugs are useless in treating AUV (54).

Reviewing the various studies conducted on the efficacy of corticosteroids in AUV, it is evident that protocols used vary considerably. In fact, the type of corticosteroid used, the chosen dose, the route of administration (per os, IM, IV), the length of treatment are extremely different, and consequently meta-analyses do not allow to draw definitive conclusions regarding the most efficient therapy to use. However, it is highly probable that an early corticosteroid administration at sufficiently high doses in patients with no contraindications increases the chances of recovery (55).

Address for correspondence:
Augusto Pietro Casani
Department of Medicine and Surgery
Ear Nose & Throat Section
Pisa University Hospital
Pisa Italy
e-mail: augusto.casani@unipi.it

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