ACTA OTORHINOLARYNGOLOGICA ITALICA 2022;42:560-568; doi: 10.14639/0392-100X-N1975

VESTIBOLOGY

Can hyperventilation test and duration of spontaneous nystagmus help differentiate between vascular and inflammatory aetiology of acute unilateral vestibular deficit?

Possono il test di iperventilazione e la durata del nistagmo spontaneo aiutare a differenziare l'eziologia vascolare da quella infiammatoria del deficit vestibolare unilaterale acuto?

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SUMMARY

Objective. To relate clinically the duration of spontaneous nystagmus and hyperventilation-induced nystagmus (HVIN) to vascular or inflammatory aetiology of acute unilateral vestibulopathy observed in a very early stage.

Methods. This is a retrospective study on 198 patients with acute unilateral vestibulopathy.

Results. In the short-lasting nystagmus group (spontaneous nystagmus < 48 h), mean age and cardiovascular risk were significantly higher; the rates of negative HVIN and paretic HVIN were 41.7% and 58.3%, respectively. In the long-lasting nystagmus group (spontaneous nystagmus > 48 h), mean age and vascular risk were lower; HVIN was absent in 12.6% of the cases, HVIN excitatory patterns were observed in 40.3% of cases and a paretic pattern in 47.1%.

Conclusions. A vascular aetiology should be considered the most likely in patients with spontaneous nystagmus < 48 hours: all patients were > 60 years old, cardiovascular risk was higher and HVIN was always absent or paretic. In the group with nystagmus > 48 hours, similarly, data indicate a higher incidence of paretic HVIN in older patients and higher vascular risk, even if the data does not allow us to lean clearly towards one of the two aetiological hypotheses.

KEY WORDS: acute unilateral vestibulopathy, hyperventilation test, vestibular bed-side examination, vestibular neuritis, hyperventilation-induced nystagmus

RIASSUNTO

Obiettivi. *Correlare la durata del nistagmo spontaneo e i pattern del nistagmo da iperventilazione (HVIN) alla eziologia infiammatoria o vascolare della vestibulopatia acuta monolaterale (VAM), osservato in uno stadio molto precoce.*

Metodi. *Studio retrospettivo. Inclusi 198 pazienti con VAM.*

Risultati. *Nel gruppo con durata del nistagmo spontaneo < 48 ore, l'età media dei pazienti e il rischio cardiovascolare erano significativamente più alti; HVIN negativo e pattern paretico sono stati osservati nel 41,7% e 58,3% rispettivamente. Nel gruppo con nistagmo spontaneo > 48 ore l'età e il grado di rischio cardiovascolare erano più bassi; l'HVIN negativo era presente nel 12,6% dei casi, i pattern eccitatori nel 40,3% dei casi, il pattern paretico nel 47,1%.*

Conclusioni. *L'eziologia vascolare appare più probabile nel gruppo con durata del nistagmo spontaneo < 48 ore, in cui tutti i pazienti avevano più di 60 anni, il rischio cardiovascolare era più alto e l'HVIN o assente o con pattern paretico. Nel gruppo con durata del nistagmo> 48 ore i dati indicano ugualmente una maggiore incidenza del pattern paretico nei pazienti più anziani e più alto rischio cardiovascolare, ma la maggiore dispersione dei dati non fa propendere verso l'una o l'altra delle due ipotesi eziologiche.*

PAROLE CHIAVE: *vestibulopatia acuta unilaterale, test di iperventilazione, bed-side examination vestibulare, neurite vestibolare, nistagmo evocato da iperventilazione*

Received: December 20, 2021
Accepted: July 29, 2022

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How to cite this article: Califano L, Locatelli G, Melillo MG. Can hyperventilation test and duration of spontaneous nystagmus help differentiate between vascular and inflammatory aetiology of acute unilateral vestibular deficit? Acta Otorhinolaryngol Ital 2022;42:560-568. https://doi.org/10.14639/0392-100X-N1975

Introduction

Acute unilateral vestibulopathy (AUV) is one of the most frequent causes of acute vertigo, with an annual incidence between 3.5 and 15.5 cases/100,000 and a maximum between 30 and 60 years without significant gender differences [1]. In the most frequent form [2], cochlear symptoms are missing; they may however be present in the case of complete cochlear-labyrinthine infarction or specific herpetic aetiology (Ramsay-Hunt syndrome) [3].

The superior division of the vestibular nerve is the most frequently affected [4]; the superior and inferior branches are sometimes both injured, and much more rarely only the inferior one is impaired [5]. The reactivation of a latent herpes simplex virus type 1 infection is the most probable cause, although it is not definitely proven [1]. Vascular damage to inner ear structures is also a possible cause. Because of the overlap between the distribution of the superior vestibular nerve and the anterior vestibular artery, the two aetiologies are clinically indistinguishable. The utriculus, lateral and anterior semicircular canals are usually involved in either viral superior vestibular neuritis or ischaemia of the anterior vestibular artery. A recent review by Simoes et al. identified important gaps in the literature regarding the exploration of a vascular aetiology of AUV and no studies were identified regarding the risk of future vascular events [6].

Immuno-related disorders, demyelinating lesions of the root-entry zone of the eighth cranial nerve, metastasis and thiamine deficiency are considered much rarer aetiologies of AUV.

Spontaneous unidirectional nystagmus is the main sign of AUV. It usually lasts more than 7-10 days, but its duration is sometimes limited to hours or a few days. After about one month, most patients no longer show spontaneous nystagmus, due to either peripheral recovery or central compensation, even if some clinical and instrumental signs of the deficit may persist for many years [7]. The "HINTS" protocol provides a high diagnostic sensitivity in identifying peripheral forms *vs* central forms in the acute stage of the disease [8].

Spontaneous nystagmus is "modulated" by clinical tests: head shaking test, vibratory test, hyperventilation test (HVT) and lateral decubitus. On the affected side, the head impulse test (HIT) evokes catch-up saccades [9], and the caloric test shows labyrinthine hyporeflexia/areflexia; on video-HIT (v-HIT) impaired gains of the vestibulo-ocular reflex (VOR) of lateral and superior semicircular canals are seen, and catch-up saccades are evident [10].

HVT is *"the only test that unmasks unilateral vestibular disease without testing the dynamic properties of the vestibule-ocular reflex"* [11]. Hyperventilation causes hypocapnia, intracellular alkalosis, lowering of plasmatic and liquoral Ca^{2+}, affecting the acid-base balance. These metabolic modifications have an excitatory effect on nervous tissue [12].

Table I. Hyperventilation-induced nystagmus (HVIN) patterns in acute unilateral vestibulopathy.

HVIN absent	No effect on spontaneous nystagmus
Paretic HVIN	Spontaneous nystagmus is temporarily enhanced
Excitatory HVIN	Spontaneous nystagmus is temporarily reduced or inhibited
Strongly excitatory HVIN	Spontaneous nystagmus is temporarily reversed

In spinocerebellar ataxia type 6, hyperventilation causes further functional deficit of Ca^{2+} α1A -voltage-dependent channels through variations of pH and extracellular Ca^{2+} [12]. This clinical model predicts how HVT can act on nystagmus either in the case of primitive cerebellar dysfunctions or when the normal cerebellar inhibitory action had previously partially compensated a vestibular deficit. HVT can disrupt the central compensation of a peripheral vestibular asymmetry, as seen by the appearance or accentuation of paretic nystagmus (fast phases towards the healthy side), respectively, in eighth cranial nerve schwannomas and AUV [14-17].

Several HVIN patterns have been described in AUV [15] (Tab. I): 1) HVIN absent: no effect on spontaneous nystagmus; 2) paretic pattern, which temporarily reinforces spontaneous nystagmus; 3) excitatory pattern, which temporarily inhibits spontaneous nystagmus; 4) strongly excitatory pattern, which temporarily reverses spontaneous nystagmus.

In the case of AUV, HVIN excitatory patterns can be caused by: a) increase of neuronal excitability of a partially damaged receptor which would determine transient up-regulation of the central mechanisms of compensation; b) modification of the thresholds of membrane channels; c) transient improvement of neural conduction in partially and transiently microdemyelinated areas that could have been caused by impairment of the blood-nerve barrier due to, for example, the diffusion of gadolinium in the vestibular nerve in some cases of vestibular neuritis [18].

Excitatory patterns are observed in the early stages of AUV and disappear within a few days, and then replaced by the paretic pattern when, with all probability, the blood-nerve barrier has reestablished itself. The paretic pattern decreases over time, even if it may be observed even months later, in a now-compensated clinical phase. The HVIN patterns observed in the acute phase have no predictive significance for mid- or long-term prognosis [15].

The questions are:

1. Why does HVIN have two opposite behaviours in AUV – paretic *vs* excitatory – whereas the other tests unambiguously point out the side of the acute vestibular loss?

2. Why is the duration of spontaneous nystagmus in any individuals significantly shorter than in the majority of other cases?

The study had two main objectives. 1) to highlight if, in AUV observed between the first and the fifth day from its onset, there was a relationship between HVIN patterns, age and vascular risk, and if this relationship mattered or did not in identifying the cause – inflammatory *vs* ischaemic – of the disease; 2) to evaluate whether the duration of spontaneous nystagmus more or less than 48 hours correlated with age and degree of vascular risk and examine the behavior of HVIN in both groups.

Materials and methods

The study includes 198 patients diagnosed with AUV observed between one and three days after symptom onset, without concomitant acute cochlear suffering, from January 2016 to March 2019. During the same period, we suspected a central vestibular mimic in other 26 patients, who were not included in the study, with a similar clinical scenario of acute vertigo (spontaneous nystagmus, unsteadiness, ataxia).

All patients underwent vestibular bedside examination using infrared videonystagmoscopy. Our first observation was primarily aimed at ruling out a central disease as the possible cause of acute vertigo. In sitting position: observation of spontaneous nystagmus – gaze in primary position, to the left, to the right, upward, downward –; under closed eyelids, research for gaze lateropulsion [19]; head pitching test; head shaking test (HST); vibratory test; HVT; head impulse test; evaluation of the skew deviation. In supine position: observation of nystagmus (supine, right lateral decubitus, left lateral decubitus); simultaneous binaural caloric test using ice water, 5 ml for ear, about 5°C. At the first examination, we performed v-HIT in 67 cases, preferentially in older and higher vascular risk patients, and bithermal caloric test (30° and 44°C) in 34 patients. All patients during the successive observations underwent v-HIT. The differential diagnosis between peripheral and central diseases was based on the HINTS protocol, in addition to the simultaneous binaural ice water caloric test (SBIWCT) plus v-HIT when performed. We considered as signs of peripheral lesions: unidirectional horizontal-torsional nystagmus, catch-up saccades on head impulse test and moderate ocular hypotropia towards the side of the nystagmus slow phase direction, inhibition/reversal of the spontaneous nystagmus after SBIWCT; on v-HIT, the presence of semicircular canals impairment and catch-up saccades on the affected side. Nystagmus with fast phases towards the healthy side and vertical ocular hypotropia on the impaired side provoke the so-called "uphill nystagmus", considered a sign of peripheral deficit [20].

SBIWCT works by inhibiting both labyrinths; in the case of a peripheral lesion, it breaks down vestibular asymmetry. Thus, it suppresses or sometimes reverses spontaneous nystagmus due to its prevailing inhibitory action on the healthy labyrinth. Conversely, in central diseases, SBIWCT does not modify spontaneous nystagmus because the vestibular asymmetry remains unchanged. We previously classified HVIN patterns [15] as absent, paretic, excitatory, and strongly excitatory. For the current study, we merged excitatory and strongly excitatory patterns as expressions of the same pathophysiological mechanism. HVT was carried out for 60 seconds, and monitored through "sidestream" capnography [21] to ensure that patients performed the test correctly, estimating $PaCO_2$ values. In a previous study, we identified a $PaCO_2$ value of approximately 16 mm Hg as appropriate for acting on an impaired vestibular system [17]. It should be specified that the instrumental monitoring of HVT, which we used to more objectively report the data of our study, is not necessary for a bedside setting. The operator has only to ensure that respiratory acts are enough deep and rhythmic, with a 60-second duration. We repeated vestibular examinations daily until patients were discharged between the 3rd and 10th day; non-hospitalised patients were checked after 3, 7 and 10 days from the first observation. We scheduled a further follow-up examination at about 30 days for all patients.

In all, 175 of the 198 patients underwent brain MRI, from 3 to 30 days from the onset of disease. In no case lesions of the VIII cranial nerve of pontocerebellar angle, demyelinating lesions, or signs of recent acute vascular accidents were observed, which would have been exclusion criteria. In no case gadolinium enhancement of the VIII cranial nerve was observed.

Patients were subdivided into two groups: a) spontaneous nystagmus < 48 hours; b) spontaneous nystagmus > 48 hours. We chose the cut-off value of 48 hours because the duration of spontaneous nystagmus in AUV is usually longer, and it might be a good indicator of a self-limiting lesion of the vestibular system. Vascular risk was assessed using the "Global Cardiovascular Risk - Heart Project" Calculator of the Italian Istituto Superiore di Sanità [22] (Fig. 1 and Tab. II). As established in the Heart Project, patients with previous acute vascular events in their personal medical history were considered at the maximum risk (grade VI). For our study, we merged low-moderate risk (grades I, II, III) and moderate-high-very high-risk categories (grades IV, V, VI), obtaining only two classes of risk: "lowest class" and "highest class". Statistical

Table II. Personal data and risk factors considered in the Istituto Superiore di Sanità.

"Heart Project calculator"	Male/female
Age	35-69 years old
Smoking	People who smoke regularly every day, even a single cigarette, or have stopped less than 12 months ago
Systolic pressure	Expressed in mmHg
Diastolic pressure	Expressed in mmHg
Total cholesterolaemia	Expressed in mg/dl
HDL cholesterolaemia	Expressed in mg/dl
Diabetes	Diagnosis or two successive determinations of fasting blood glucose greater than or equal to 126 mg/dl
Hypertension	People who regularly take anti-hypertensive drugs

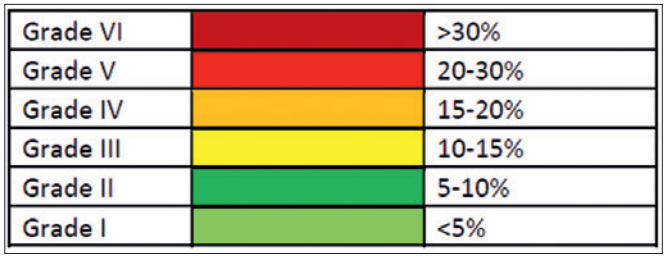

Figure 1. Grading of ten-year cardiovascular risk (modified from Progetto Cuore, ISS).

analysis was performed with Unpaired T-test, Fisher's exact test and Chi-square test, and significance level set at 0.05 with 95% confidence interval. Analyses were performed using Graph pad Quick Calcs software (multivariate analysis).

Results

There were 198 patients, 111 males and 87 females, with a mean age of 57.7 +/- 15.67 years (range 18-86 years). Twenty-four patients had spontaneous nystagmus for less than 48 hours after symptom onset (range 10-45 hours), and 174 patients for more than 48 hours. Based on the HINTS protocol, plus v-HIT and SBIWCT, we clinically excluded or considered very improbable a central mimic in all. Additionally, vestibular Menière crisis and acute migraine related vertigo were considered clinically highly unlikely.

Patients with spontaneous nystagmus duration < 48 hours had a significantly higher mean age than those with spontaneous nystagmus duration > 48 hours (76 +/- 9.43 years *vs* 56.03 +/- 12.58 years; $p < 0.0001$).

HVIN was evoked in 166/198 patients (83.8%): a paretic pattern was seen in 96 cases (48.5%) and excitatory patterns in 70 cases (35.3%), while HVIN was absent in 32 patients (16.2%).

The age difference between patients with positive HVIN and those with negative HVIN, respectively 58.1 +/- 12.82 years *vs* 65.2 +/- 12.96 years, was statistically significant ($p = 0.0042$). Furthermore, patients with paretic HVIN had a significantly higher mean age than patients with excitatory HVIN, respectively 66.01 +/- 12.35 years *vs* 47.4 +/- 11.76 years ($p < 0.0001$).

We observed the paretic pattern in 14/24 patients with spontaneous nystagmus < 48 hours (58.3%), while in the remaining 10 cases (41.7%) HVT did not modify the spontaneous nystagmus. In patients with spontaneous nystagmus > 48 hours, a paretic pattern was observed in 82/174 cases (47.1%), excitatory patterns in 70 cases (40.3%) and HVIN was absent in 22 cases (12.6%) (Tab. III). In this subgroup, the difference in the mean age between patients with paretic HVIN (63.7 +/- 10.02 years) and those with HVIN excitatory patterns (46.7 +/- 13.88 years) was also significant ($p < 0.0001$).

Comparing the two subgroups, the differences between the presence/absence of HVIN and presence of the paretic pattern *vs* excitatory patterns were both significant (respectively: $p < 0.001$; $p < 0.0001$); the absence of HVIN and the paretic pattern were more frequent in the group with spontaneous nystagmus < 48 hours. In the subgroup with spontaneous nystagmus < 48 hours, 21/24 patients (87.5%) were older than 65 years, which is the conventional age to distinguish between "young" and "elderly" patients (range 60-89 years), whereas in the subgroup with spontaneous nystagmus > 48 hours only 56/174 patients (32.2%) were over 65 years (range 19-78 years), with a significant difference ($p < 0.0001$). In the subgroup with nystagmus > 48 hours, excitatory patterns showed a higher incidence in the "lowest risk class" – 60/135 cases (44.4%) – *vs* 10/39 cases (25.6%) in the "highest risk class". The paretic pattern was found in 54/135 individuals (40%) in the "lowest risk class" and 25/39 cases (64.1%) in the "highest risk class". Paretic/absent HVIN

Table III. Distribution of HVIN patterns in relation to cardiovascular risk and duration of spontaneous nystagmus.

		HVIN PATTERN		
Spontaneous nystagmus	Risk	Paretic	Excitatory/strongly excitatory	HVIN absent
> 48 hours (174 cases)		82 (47.1%)	70 (40.3%)	22 (12.6%)
	Grades I-III Class (135 cases)	54 (40%)	60 (44.4%)	21(15.6%)
	Grades IV-VI Class (39 cases)	25 (64.1%)	10 (25.6%)	4 (10.3%)
< 48 hours (24 cases)		14 (58.3%)	0	10 (41.7%)
	Grades I-III Class (1 case)	1 (100%)	0	0
	Grades IV-VI Class (23 cases)	13 (56.5%)	0	10 (43.5%)

Table. IV. Synopsis of clinical data at the first observation.

	Nystagmus > 48 h	Nystagmus < 48 h
HSIN towards the healthy side	172/174 (98.9%)	21/24 (87.5%)
VIN towards the healthy side	174/174	24/24
HVIN	152/174 (87.4%)	14/24 (58.3%)
Caloric hypo/areflexia on the affected side	24/24	10/10
HIT: Saccades on the affected side	167/174 (96%)	22/24 (91.7%)
V-HIT: Overt-saccades on the affected side	47/47	20/20

Note: HSIN: Head-Shaking Induced Nystagmus; VIN: Vibration-induced Nystagmus; HVIN: Hyperventilation-induced nystagmus; HIT: Head Impulse Test: V-HIT: Video Head Impulse Test.

patterns were more frequent in the "highest risk class" (29/39 cases: 74.4%), and excitatory patterns in the "lowest risk class" (60/135 cases: 44.4%) ($p < 0.001$). In the "lowest risk class", the difference between the incidences of paretic/absent HVIN *vs* excitatory patterns was not significant ($p = 0.088$), whereas in the "highest risk class", paretic/absent HVIN was significantly more frequent than excitatory patterns ($p < 0.001$).

In the subgroup with spontaneous nystagmus < 48 hours, all patients except one were in the "highest risk class" and, as already said, we observed only either absent HVIN (43.5%) or paretic HVIN (56.5%) (Tab. III).

Clinical data at the first observation are reported in Table IV.

Two illustrative cases

1. Male, 64 years old. Acute vertigo for one day. Cardiovascular risk: Heart Project class IV. 3rd grade unidirectional right beating spontaneous nystagmus; paretic HVIN; v-HIT: a) head impulse test (HIMP). Left lateral canal VOR gain: 0.41; left anterior canal VOR gain: 0.16; b) Suppression HIMP (SHIMP). Left lateral canal VOR gain: 0.28; anticompensatory saccades: present but reduced on the left side. At two days from onset: spontaneous nystagmus no longer present; right beating vibration induced nystagmus; v-HIT: a) HIMP. Left lateral canal VOR gain: 0.85; left anterior canal VOR gain: 0.69; b) SHIMP. Left lateral canal VOR gain: 0.8; anticompensatory saccades: still reduced but more efficient (Fig. 2);
2. Female, 32 years old. Acute vertigo for two days. Cardiovascular risk: Heart Project class I. 3rd grade unidirectional left beating spontaneous nystagmus; strongly excitatory HVIN; v-HIT: a) HIMP. Right lateral canal VOR gain: 0.15; right anterior canal VOR gain: 0.24; b) SHIMP. Right lateral canal VOR gain: 0.08; anticompensatory saccades: absent on the right side. Ten days after onset: 2nd grade unidirectional left beating spontaneous nystagmus; excitatory HVIN; v-HIT: a) HIMP. Right lateral canal VOR gain: 0.23; right anterior canal VOR gain: 0.24; b) SHIMP: right lateral canal VOR gain: 0.23; anticompensatory saccades: still absent on the right side (Fig. 3).

Discussion

AUV is characterised by the sudden onset of vertigo with neurovegetative symptoms. Spontaneous nystagmus is the expression of the acute imbalance between the two vestibular hemi-systems. A viral aetiology is considered the most plausible cause; at the same time, a vascular cause is possible due to the characteristics of labyrinthine terminal blood flow. In the case of damage to one of the two factors, the overlap between the distribution of the superior branch of the vestibular nerve and the flow of the anterior vestibular artery provokes the same symptoms and signs and does

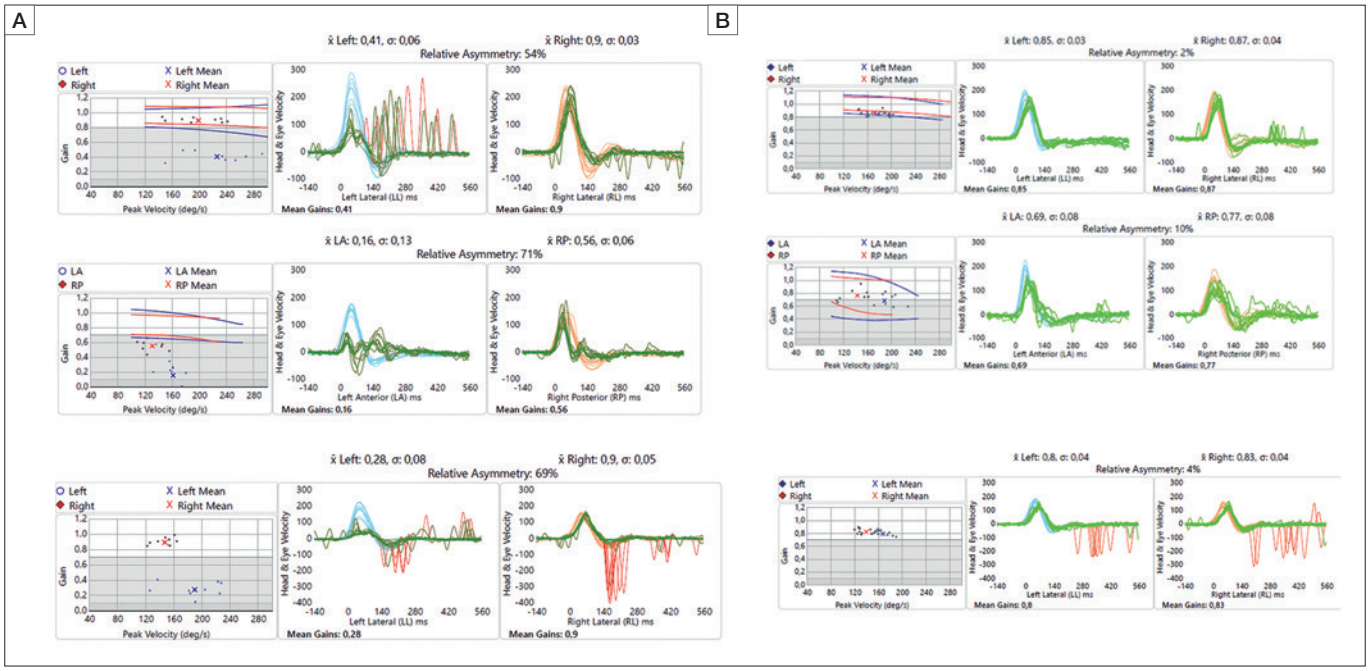

Figure 2. V-HIT: a short-lasting spontaneous nystagmus case. **Panel A**: HIMP and SHIMP at the onset of the disease; **Panel B**: HIMP and SHIMP 3 days after the onset of the disease.

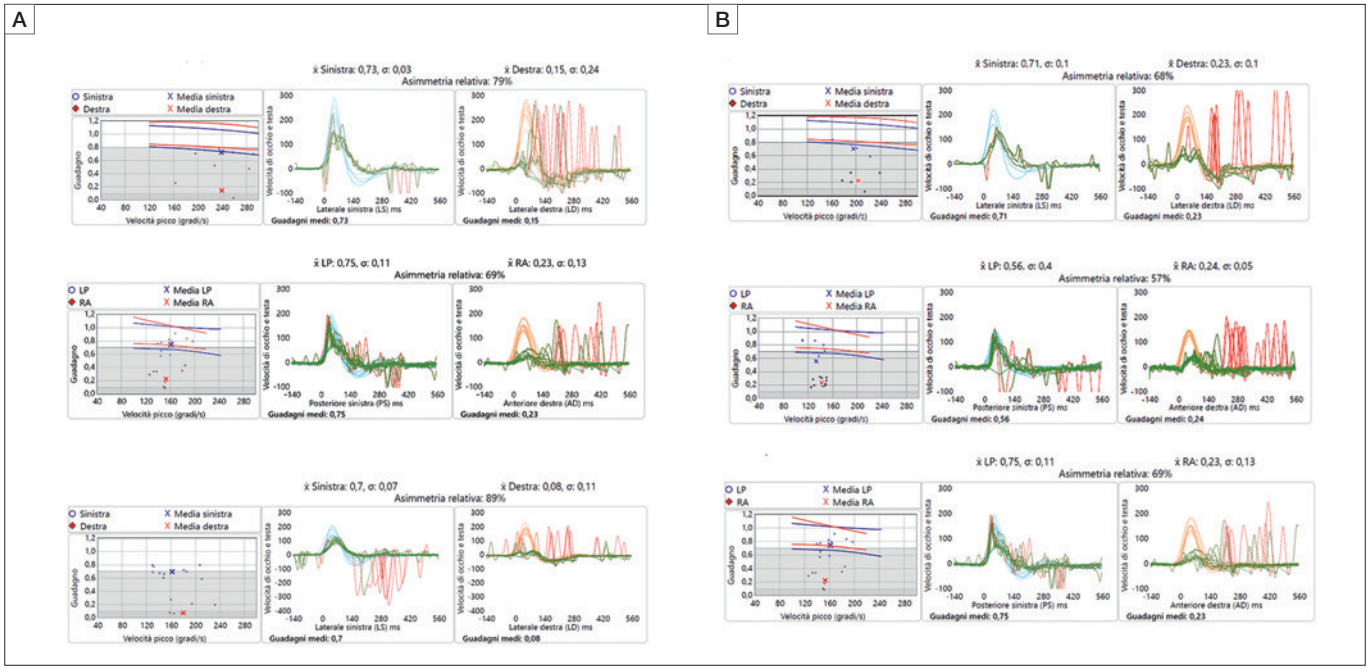

Figure 3. V-HIT: a long-lasting spontaneous nystagmus case. **Panel A**: HIMP and SHIMP at the onset of the disease; **Panel B**: HIMP and SHIMP 10 days after the onset of the disease.

not allow definition of the aetiology. To date, no test can discriminate between the two hypotheses. Aetiology is presumed on an epidemiological basis: a viral hypothesis is considered the most probable in the younger population, and a vascular hypothesis is the most probable in older patients or, independently of age, in individuals with sig-

nificant vascular risk factors. The attribution to one of the two possible aetiologies could be pivotal in follow-up. The risk of acute stroke is higher in vertiginous patients within the first month from the discharge, even if few patients (0.93%) experience a major stroke during 6-month follow-up [23]. Patients with vertigo had a 3.01 fold greater risk for stroke; patients with ≥ 3 cardiovascular risk factors had a risk of stroke that is increased by 5.51-fold [24]. ER patients discharged with a diagnosis of vertigo or dizziness had a 2-fold higher risk of developing subsequent vascular events than those without dizziness/vertigo [25]. Consequently, identifying or suspecting a vascular aetiology of acute vertigo is a decisive task, although a recent meta-analysis seems to rule out the correlation between acute vertigo and subsequent vascular accidents [6].

The direction of the slow phases of the spontaneous nystagmus, usually enhanced by HST and vibratory test, denotes the affected side. The head impulse test identifies corrective saccades in the movements towards the affected side. On the impaired side, the eye is usually hypotropic and the caloric test shows canal paresis. HIMP denotes VOR gain deficit of both lateral and anterior canals and, in the very early stage, the presence of overt catch-up saccades; SHIMP shows VOR gain deficit of the lateral canal and absence/reduction of the anti-compensatory saccades [*].

Differently, HVIN patterns do not necessarily correlate with the side of the lesion: hyperventilation test can either enhance the spontaneous nystagmus (paretic pattern) or inhibit/reverse it (excitatory patterns). In other words, HVIN direction is not related to the side of the lesion but to the metabolic mechanisms of action of hyperventilation test on nystagmus: worsening of central compensation mechanisms, transient improvement of nerve conduction along partially demyelinated pathways, hypersensitivity of a partially damaged peripheral receptor due to hyperventilation-induced changes in calcium and acid-base balance.

Our study tried to study data on the two most frequent aetiologies of AUV: duration of spontaneous nystagmus and HVIN patterns. Both HVIN patterns and the length of spontaneous nystagmus correlated with patients' age and degree of vascular risk in a significant way. We observed higher mean age, higher vascular risk and paretic/absent HVIN more frequently in the short-lasting nystagmus group; on the contrary, lower age, lower vascular risk and excitatory patterns were prevalent in the long-lasting nystagmus group. A vascular hypothesis should be considered the most plausible in the group with nystagmus < 48 hours: all patients were over 60 years old, had higher vascular risk, and HVIN was always absent or paretic. In the group with nystagmus lasting > 48 hours, there was a higher prevalence of paretic/absent HVIN in older patients and higher vascular risk, but their greater dispersion did not allow us to lean univocally towards one of the two aetiological hypotheses: the incidences of paretic/absent HVIN and excitatory patterns were significantly different in the "highest risk group" (39 patients), not in the most numerous "lowest risk group" (135 patients).

Aetiology is more attributable to: a) younger and low-risk patients, presenting HVIN excitatory patterns and nystagmus > 48 hours. In these cases, the disease is more likely caused by an inflammatory neural process (viral neuritis) involving the superior branch of the vestibular nerve. Excitatory patterns could be explainable through a transient improvement of conduction along nerve fibers (possibly microdemyelinated areas); b) oldest and high-risk patients with nystagmus < 48 hours who never showed excitatory HVIN patterns. In these cases, the most likely aetiology is a transient vascular deficit in the district of the superior vestibular artery. In all the other intermediate situations, the aetiology remains based on an epidemiological and presumptive basis, even if in these cases HVIN patterns and duration of spontaneous nystagmus can guide the diagnosis. Our results may be useful in therapeutic choices: steroids may be the first-line therapy in younger patients, with low vascular risk and HVIN excitatory patterns, whereas older patients, with high vascular risk and absent or paretic HVIN, might be preferentially treated using vascular drugs, such as heparinoids or antiaggregants. It should be specified that this proposal is purely hypothetical, and lack defined guidelines. Additionally, if one considers such acute distress as a labyrinthine vascular accident, it is worthy of further specific diagnostic investigations in other districts, like the heart and brain. For these patients, we recommend careful follow-up.

Finally, in the same cohort we obtained similar results even when the cut-off time was set at 72 hours. In a more general way, this indicates that in AUV the short duration of spontaneous nystagmus (< 48-72 hours) is a red flag for a possible vascular aetiology.

Conclusions

The differential diagnosis between inflammatory and vascular aetiologies of AUV remains controversial. In both cases, the shared suffering of the lateral canal, anterior canal and utriculus does not allow specific discriminatory

[*] We would also prefer "Centriphugal saccades" in SHIMP because, in our opinion, a physiological mechanism cannot be "anti-compensatory".

tests. In this perspective, HVT is the only test that can be of use, even if only partially. Its pathophysiological mechanisms interfere with the responses of the vestibular system, above all nystagmus, through metabolic pathways, and not by acting directly on receptor dynamics, as, for example, the caloric test does. Both the diagnosis of vascular rather an inflammatory aetiology and proposals for different treatment remain purely hypothetical, and centred exclusively on clinical criteria. The duration of the spontaneous nystagmus and its modulation by HVT can be of help in this task, always keeping in mind assessment of individual cardiovascular risk.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

All authors contributed equally to the design and development of the study.

Ethical consideration

As a retrospective observational study, it did not require approval of Ethics Committee. This was done internally as part of our routine evaluation, so as to improve our quality of care.

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

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