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Original Article

Hyperventilation-Induced Nystagmus in Acute Unilateral Vestibulopathy: A Correlation with Vestibulo-ocular Reflex Gain and Clinical Implication

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BACKGROUND: Hyperventilation-induced nystagmus test (HINT) is capable of generating a response in 77.2% of cases of acute unilateral vestibulopathy (AUVP); both nystagmus toward the affected side (excitatory pattern) and toward the healthy side (inhibitory pattern) have been described. The aim of the study is to investigate the clinical and prognostic role of the test by evaluating its correlation with vestibulo-ocular reflex (VOR) gain.

METHODS: We evaluated 33 AUVP patients by performing the HINT and video head impulse test (V-HIT) during the acute phase and then at 15 and 90 days after the onset of the symptoms. The correlation between the VOR gain of the affected side and test responses was evaluated first, phase by phase, and then considering the pattern shown during the first assessments.

RESULTS: Patients with a negative HINT had a higher mean VOR gain than patients with a positive test at both 15 and 90 days. Patients who showed an inhibitory pattern at the first assessment had a continuous improvement in V-HIT performance, while patients with an initial excitatory response had a transient decrease in gain at the subsequent evaluation ($P = .001$). No difference between these 2 groups emerged at 90 days ($P = .09$).

CONCLUSION: The finding of a negative HINT during the follow-up correlates with good V-HIT performance and could be an indicator of good recovery. The inhibitory pattern is associated with a subsequent improvement; and it would be indicative of compensation. but, despite this, the prognostic value of the test is limited.

KEYWORDS: Hyperventilation, hyperventilation induced nystagmus, nystagmus, vertigo, vestibular neuritis, vestibulo-ocular reflex

INTRODUCTION

Hyperventilation-induced nystagmus test (HINT) is a procedure that can be easily performed during a bedside evaluation of dizzy patients without causing them excessive stress.[1]

It is well reported that the metabolic changes induced by hyperventilation can elicit a nystagmus in various vestibular disorders and that HINT can be used to reveal vestibular imbalance due to its ability to bring out asymmetries both at a central and a peripheral level.[1,2,3]

A unique feature of the HINT is its capability to generate a nystagmus in the absence of any dynamic stimulation of the labyrinth and, for this reason it has good sensitivity in cases of diseases that involve the central nervous system or the vestibular nerve.[2,4,5,6]

A positive test has been reported in 91.7% of cases of acoustic neuroma, in 75% of cases of multiple sclerosis, and in 72.7% of cerebellar diseases.[5]

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Acute unilateral vestibular neuritis, also called acute unilateral vestibulopathy (AUVP), is one of the most common causes of vertigo. Despite this, to date, data about HINTS in AUVP are limited.[7]

A previous study reported that an evoked nystagmus has been observed in 77.2% of cases of acute vestibular neuritis and in 37.6% of cases of compensated vestibular neuritis.[5]

Both nystagmus directed toward the affected side (excitatory pattern) and toward the healthy side (inhibitory pattern) have been described. The excitatory response is less common; it can be observed almost exclusively during the acute phase, and it tends to be replaced by an inhibitory pattern during the follow-up.[8] The test seems to correlate with the severity of dizziness, but a clear prognostic value has not yet emerged.[9]

Aim of this study is to indicate the clinical role of HINT in AUVP, in particular the correlation between the evoked pattern and the gain of the vestibulo-ocular reflex (VOR) evaluated with the video head impulse test (V-HIT). Patients were evaluated both during the acute phase and during the follow-up in order to understand if the different patterns were related to the clinical course and prognosis.

MATERIAL AND METHODS

We evaluated 33 patients affected by vestibular neuritis (20 males, 13 females; mean age 54.06 ± 14.64) between December 2021 and December 2022. All the patients fulfilled the criteria for acute unilateral vestibulopathy according to the Barany Society: presence of spontaneous unidirectional nystagmus, history of rotatory vertigo with an acute onset lasting more than 24 hours, positive clinical head impulse test (HIT), absence of hearing loss, and contralateral normal vestibular and cochlear function.[7] In order to have a homogeneous group, we selected patients who showed signs of superior vestibular neuritis.

Contrast-enhanced MRI of the brain was always required in order to exclude a central lesion or a vestibular Schwannoma, and all patients received the same medical therapy.

MAIN POINTS

- Patients with acute unilateral vestibulopathy who show an inhibitory response would be those who have already started to compensate; this is supported by their continuous improvement in video head impulse test (V-HIT) performance.
- The excitatory pattern can be attributed to the presence of active inflammation and lack of compensation.
- Patients showing an excitatory pattern will have a tendency to show a drop in vestibulo-ocular reflex (VOR) gain at the subsequent assessment.
- The information provided by hyperventilation-induced nystagmus test (HINT) may allow us to make short-term assumptions, but the pattern shown in the acute phase has no long-term prognostic value.
- The findings of a negative HINT during the follow-up of patients with a previously positive test correlate with good V-HIT performances and could be considered an indicator of good recovery.

The first assessment was performed during the acute phase, within 5 days of the onset of the symptoms (mean time = 2.75 ± 2.05 days). Subsequent assessments were performed at 15 and 90 days after the event in order to evaluate the patients during the subacute and chronic phase.

In order to evaluate patients during the acute phase, we performed the first assessment with V-HIT and HINT as soon as possible, generally at the time of first access to the clinic or, if this was not possible, in the days immediately following. To be included in the study, all patients had to show, at the time of this first assessment, acute phase symptoms such as continuous rotational vertigo, spontaneous nystagmus, and autonomic symptoms.

During each assessment patients underwent a complete vestibular evaluation including a HINT and a V-HIT.

Video head impulse test was performed using ICS impulse (GN Otometrics; Taastrup, Denmark). The test was performed by evaluating the VOR on the horizontal plane, specifically the horizontal semicircular canal.

Hyperventilation-induced nystagmus test was conducted by asking patients to take 1 deep breath per second for approximately 90 seconds; this modality has proved sufficient to lower the serum CO2 level enough to act on the vestibular system.[6] Eye movements were recorded with video by Frenzel. The tests were considered positive when a nystagmus with a slow phase velocity of at least 5°/s was evoked for at least 5 seconds.[5,6] The responses were defined as follows:

- In the presence of spontaneous nystagmus:

Excitatory: reduction or reversal of nystagmus
Inhibitory: increase in nystagmus intensity and frequency

- In the absence of spontaneous nystagmus:

Excitatory: induction of a nystagmus beating toward the affected side
Inhibitory: induction of a nystagmus beating toward the unaffected side

The correlation between the HINT response and the VOR gain of the affected side was analyzed phase by phase, and then the patients were divided into 2 groups according to the pattern shown in the first assessment.

Gain values (G) of patients showing nystagmus directed toward the affected side at the first assessment (e group) were compared with those of patients who had contralesional nystagmus (i group).

The gain trend was analyzed by calculating the differences in gain in the affected ear both between the first and second evaluations ($\Delta G1 = G2 - G1$) and between the first and third evaluations ($\Delta G2 = G3 - G1$).

The data was compared using Student's *t*-test, a value of < 0.05 was considered significative.

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. Ethical committee approval was received from Regional Ethics Committee of Umbria region (Approval number: 4056/21). Written informed consent was obtained from all patients who participated in this study.

RESULTS

During the acute phase, all patients exhibited spontaneous nystagmus with torsional and horizontal components. Hyperventilation-ind uced nystagmus was excitatory in 13 patients (39.4%) and inhibitory in 14 patients (42.4%). In 6 subjects (18.1%), no changes in the nystagmus were induced.

In all the subjects with positive HINT hyperventilation, which led to an increase or decrease in the frequency and amplitude of the slow phase of nystagmus in both horizontal and torsional components. No atypical responses were detected.

At 15 days from the event, no patient had spontaneous nystagmus. We identified 4 excitatory patterns (12.1%), 19 inhibitory patterns (57.6%), and 10 negative tests (30.3%).

At 90 days from the event, we identified 1 excitatory pattern (3%), 13 inhibitory patterns (39.4%), and 19 negative tests (57.6%).

The evoked nystagmus presented torsional and horizontal components in these cases as well.

During the acute phase, patients with negative HINT had a mean gain of 0.43, while patients with positive HINT had a value of 0.52. The mean gain was 0.54 in patients with excitatory patterns and 0.50 in those with inhibitory ones.

At the second assessment, the average gain of the patients with negative HINT was 0.76, while in patients with positive HINT it was 0.47. The mean gain was 0.39 in case of excitatory patterns and 0.48 in case of inhibitory ones.

At 90 days from the event, patients with negative HINT had a mean gain of 0.84, while patients with positive HINT had a mean gain of 0.58. In this phase, the mean gain was 0.59 in the case of excitatory patterns and 0.51 in the case of inhibitory ones.

No correlation between gain and HINT's response was found in the acute phase.

Student's *t*-test showed that during the subacute and chronic phases patients with negative HINT had significantly higher gain values than those with positive test. $P < 0.001$ in both cases.

Among patients with positive HINT, there were no gain differences in relation to the pattern exhibited at each single stage.

These results are shown in Table 1 and Figure 1.

Considering the initial pattern, the average gain in the e group was 0.54 during the acute phase, 0.42 at the second assessment and 0.64 at the third, (Table 2). In the i group the average gain was 0.50 in the acute phase, 0.61 in the subacute phase and 0.75 at 90 days. (Table 3)

No statistically significant differences in gain were found between these 2 groups during the acute and chronic phases ($P = .54$ and $P = .17$, respectively), while at the second assessment, the mean gain of the patients in the e group was significantly lower than that of the patients of the group i ($P = .02$).

ΔG1 was −0.12 in the e group and +0.11 in the group i. The difference is statistically significant ($P = .001$).

ΔG2 was 0.09 in the e group and 0.25 in the i group. Although the ΔG2 was greater in the i group this difference is not statistically significative ($P = .09$). The gain trend is shown in Figure 2.

DISCUSSION

Head impulse test and V-HIT are dynamic tests that indagate the vestibulo-ocular reflex. In the case of AUVP, HIT has an important role as it evokes catch-up saccades on the affected side, v-HIT is capable of objectively capturing these saccades and calculating the impairment in VOR gain.[10,11]

Unlike HIT, HINT is a test capable of revealing asymmetry in the vestibular pathway by generating a nystagmus without any dynamic stimulation of the system and without testing the dynamic properties of the VOR.[2]

Consistent with what has been reported in other works, we observed 86.7% of positive tests during the acute phase.[5] The irritative pattern was less common than the inhibitory one, and its prevalence was maximal in the acute phase. Most of the patients that had an excitatory HINT showed a reversal in the direction of the nystagmus during follow-up, so the 2 patterns may reflect consecutive phases.

No correlation between pattern and VOR gain was found considering the results for each phase separately, so we indicated how the VOR gain changed over time and whether this was related to the initial pattern.

The first main finding of our study is that patients who showed an inhibitory pattern at the first assessment had a progressive improvement in performance at the v-HIT during the follow-up ($\Delta G1 = 0.11$; $\Delta G2 = 0.25$). Otherwise, patients with an initial excitatory response showed a significant decrease in the VOR gain at the second assessment ($\Delta G1 = -0.12$, $P = .001$), and it took 90 days to see an improvement in gain in this group (Tables 2 and 3, Figure 2).

Consequently, during the subacute phase, the patients in the e group presented slightly lower gain values than those in the i group ($P = .02$).

To interpret those results, we have to consider that HINT is known to induce objective disturbance in postural control by disrupting central mechanisms of vestibular compensation.[2,3,12] Hyperventilation can reduce cerebral blood flow by 50% and cause a left shift of the hemoglobin dissociation curve with relative ischemia, which invalidates the functionality of those mechanisms.[4,13,14,] In light of this, a nystagmus beating toward the healthy side can be explained by the

Table 1. Response to the Test and Vestibulo-ocular Reflex Gain of Patients at Each Assessment

Patient	Acute Phase (< 5days)		Subacute Phase (15 days)		Chronic Phase (90 days)	
	Pattern	Gain	Pattern	Gain	Pattern	Gain
1	inhib	0.29	neg	0.69	neg	0.96
2	exc	0.48	inhib	0.35	neg	0.94
3	exc	0.46	inhib	0.26	neg	0.81
4	exc	0.7	neg	0.6	neg	0.67
5	neg	0.36	neg	0.48	neg	0.5
6	exc	0.29	inhib	0.21	inhib	0.33
7	inhib	0.22	inhib	0.36	inhib	0.5
8	inhib	0.46	inhib	0.29	inhib	0.47
9	exc	0.5	exc	0.5	inhib	0.4
10	neg	0.35	neg	0.93	neg	0.97
11	exc	0.43	inhib	0.21	inhib	0.7
12	inhib	0.63	inhib	0.65	exc	0.51
13	inhib	0.25	inhib	0.36	neg	0.42
14	inhib	0.63	neg	1	neg	1.01
15	exc	0.53	exc	0.4	inhib	0.38
16	neg	0.53	neg	0.91	neg	1.02
17	inhib	0.71	inhib	0.46	inhib	0.69
18	exc	0.69	exc	0.49	neg	0.7
19	exc	0.71	inhib	0.5	inhib	0.46
20	inhib	0.67	neg	0.72	neg	0.85
21	inhib	0.38	inhib	0.41	inhib	0.65
22	exc	0.67	neg	0.88	neg	0.92
23	inhib	0.46	neg	0.69	neg	0.82
24	inhib	0.61	inhib	0.71	inhib	0.73
25	inhib	0.61	inhib	0.73	neg	1.04
26	inhib	0.41	neg	0.65	neg	0.97
27	neg	0.25	inhib	0.75	neg	0.9
28	inhib	0.7	inhib	0.82	neg	0.92
29	exc	0.7	inhib	0.53	neg	0.5
30	exc	0.36	inhib	0.41	inhib	0.73
31	neg	0.45	inhib	0.48	inhib	0.87
32	exc	0.5	exc	0.18	inhib	0.76
33	neg	0.61	inhib	0.71	neg	0.99

exc, excitatory pattern, inhib = inhibitory pattern, neg, negative test.

loss of central compensation with a consequent restoration of the original asymmetry.

Concerning nystagmus beating toward the affected side the most accepted hypothesis is that the test is able to transiently increase the axonal conduction of the damaged nerve.

Hyperventilation is reported to enhance peripheral nerve conduction in healthy subjects, as the decrease in serum CO2 levels leads to an alkalosis with a consequent reduction in the concentration of extracellular Ca^{2+} and increased excitability.[13,15,16,17] In AUVP, a myelin lesion would make the inflamed nerve more sensitive to these changes, inducing a greater increase in its conduction, which leads to a prevalence of the affected side and an excitatory type of nystagmus.[4,18] A similar mechanism has been reported in cases of acoustic neuroma and multiple sclerosis.[6,19,20]

Our data supports this interpretation: the performance improvement both at 15 and 90 days in the patients of i group indicates that the subjects that show inhibitory patterns are the ones who have started to compensate and have already entered the recovery phase. The excitatory pattern would instead be the expression of a lack of compensation and/or active inflammation. We can speculate that, in the subjects of the e group, the transient decrease in gain at the second assessment could be explained by a progression of the damage before they start to compensate.

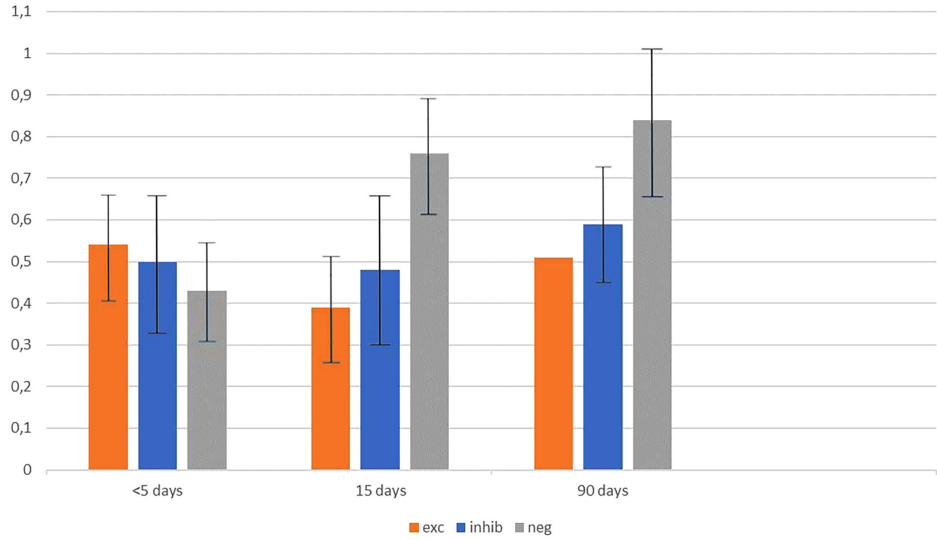

Figure 1. Mean vestibulo-ocular reflex gain values divided according to the pattern shown at each assessment. The error bar shows the variance of each single mean. exc, excitatory pattern; inhib, inhibitory pattern; neg, negative test.

It is worth noting that there were no significant differences between the 2 groups during the chronic phase in terms of mean gain and ΔG.

This can be explained by the fact that, after an initial period, all patients began to compensate, so the differences that emerged during the first few days tend to decrease over time.

Moreover, we must consider that, as the patients progress in the recovery, many other factors, such as age, comorbidities, and lifestyle, can influence compensation more than the initial state.

Based on this result, we can affirm that HINT can provide some information regarding the presence of central compensation, on the basis of which it is possible to make short-term assumptions, but it has no strong prognostic value in the long term. This is consistent with what has been reported by other authors.[9,21]

The second main finding that emerges from our study is that patients who presented a negative test during the follow-up had higher gain values than those who presented a persistently positive test ($P < .001$); regardless of the response pattern. In particular, it is worth pointing out that the mean value of gain in patients with negative tests at the last evaluation was 0.84. This value is similar to that of

Table 2. Vestibulo-ocular Reflex Gain of the Affected Side in Patients of the e Group

e Group				
Gain			**ΔG**	
G1	G2	G3	ΔG1 = G2 – G1	ΔG2 = G3 – G1
0.48	0.35	0.94	–0.13	0.46
0.46	0.26	0.81	–0.2	0.35
0.7	0.6	0.67	–0.1	–0.03
0.29	0.21	0.33	–0.08	0.04
0.5	0.5	0.4	0	–0.1
0.43	0.21	0.7	–0.22	0.27
0.53	0.4	0.38	–0.13	–0.15
0.69	0.49	0.7	–0.21	0.01
0.71	0.5	0.46	–0.2	–0.25
0.67	0.88	0.92	0.21	0.25
0.7	0.53	0.5	–0.17	–0.32
0.36	0.41	0.73	0.05	0.37
0.5	0.18	0.76	–0.32	0.26

ΔG1, difference between G1 and G2; ΔG2, difference between G3 and G1; e group, group of patients with an excitatory pattern at the first evaluation; G1, gain within 5 days from the event; G2, gain at 15 days from the event; G3, gain at 90 days from the event.

Table 3. Vestibulo-ocular Reflex Gain of the Affected Side in Patients of the i Group

i Group				
Gain			**ΔG**	
G1	G2	G3	ΔG1 = G2 – G1	ΔG2 = G3 – G1
0.29	0.69	0.96	0.4	0.67
0.22	0.36	0.5	0.14	0.28
0.46	0.29	0.47	-0.17	0.01
0.63	0.65	0.51	0.02	-0.12
0.25	0.36	0.42	0.11	0.17
0.63	1	1.01	0.37	0.38
0.71	0.46	0.69	-0.25	-0.02
0.67	0.72	0.85	0.05	0.18
0.38	0.41	0.65	0.03	0.27
0.46	0.69	0.82	0.23	0.36
0.61	0.71	0.73	0.1	0.12
0.61	0.73	1.04	0.12	0.43
0.41	0.65	0.97	0.24	0.56
0.7	0.82	0.92	0.12	0.22

ΔG1, difference between G1 and G2; ΔG2, difference between G3 and G1; G1, gain within 5 days from the event (acute phase); G2, gain at 15 days from the event (subacute phase); G3, gain at 90 days from the event (chronic phase); i group, group of patients with an inhibitory pattern at the first evaluation.

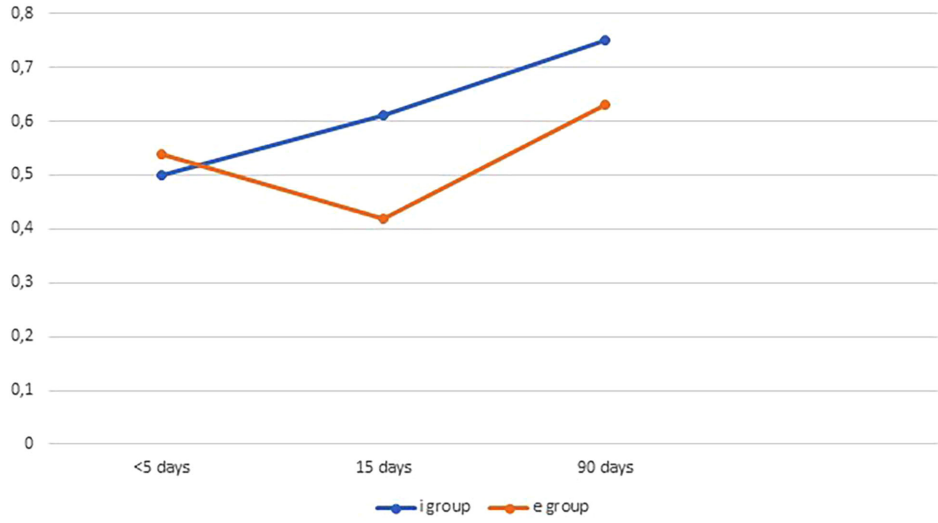

Figure 2. Gain trend in the 2 groups of patients taken in consideration. i group: patients showing an inhibitory pattern at the first evaluation, e group: patients showing an excitatory pattern at the first evaluation.

healthy patients, as many studies advocate a value above 0.8 as normal VOR.[7,22,23]

A positive HINT during the follow-up would therefore indicate a residual imbalance in the dynamic test while the negativization of a patient's test indicates an almost complete recovery and stable compensation.

This is consistent with a previous study that reported a similar correlation between test positivity and subjective symptomatology, pointing out that vestibular neuritis patients who had persistent dizziness during a follow-up were more likely to have persistent HIN than those who recovered.[9]

Regarding the patients that had a negative test at the first evaluation, it is most likely that, in those cases, hyperventilation was not able to obtain a stimulation of the system as no gain differences emerged.

Our results and conclusions work well with the hypothesis according to which the AUVP would have been caused by the reactivation of the herpes virus with consequent inflammation of the vestibular nerve.[7,24] This is considered to be the most probable etiology, but since an occlusion of the anterior vestibular artery leads to the same symptoms, the vascular etiology should be considered in a certain percentage of cases.[25,26] A recent study has highlighted that the finding of an Inhibitory/negative HINT, together with other findings, should lead to the suspicion of vascular etiology.[21] We have not investigated this aspect in our study; therefore, it is possible that we have included some patients with AUVP of vascular origin in our series. The presence of different pathogenic mechanisms as well as multiple and different compensation mechanisms both at a peripheral and central level could explain how some patients showed different results from those expected (e.g., patients 8 and 17).

Another concern is that, according to our interpretation, all patients should have shown an excitatory nystagmus at the first visit. The presence of an inhibitory HIN during the acute phase could be explained by individual differences in the speed of compensation. It should also be considered that some patients were not immediately sent for evaluation or were not able to carry out the test immediately; therefore, they could have been evaluated at different stages even though they were all within the acute phase.

Since most of the compensatory mechanisms occur in the first hours, we can hypothesize that a future study that is able to evaluate patients, starting a few hours after the onset of symptoms and involving daily reassessments could allow us to observe the transition from excitatory to inhibitory pattern in many more subjects and would allow more accurate conclusions regarding the prognostic significance of the test.

The fact that HINT can interact at both the peripheral and central levels makes it still difficult to interpret the meaning of the individual response without a complete evaluation of patients. This limits the role of HINT in AUVP, so we do not recommend using it alone to make clinical decisions, but we believe that further investigation will strengthen the role of this test.
Hyperventilation induced nystagmus test can be used during the bedside evaluation of AUVP patients. It can provide some additional information about the status of compensation, although it has limited long-term prognostic value. Our study strengthens the hypothesis that the inhibitory pattern is indicative of the presence of compensation and that the finding of a negative HINT during the follow-up of patients with a previously positive test could be considered an indicator of good recovery, but since there are still some unclear points, we always recommend interpreting HINT in the light of a comprehensive clinical and vestibular assessment.

Ethics Committee Approval: This study was approved by the Regional Ethics Committee of Umbria (Approval No: 4056/21).

Informed Consent: Informed consent was obtained from all patients who participated in this study.

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or Processing – G.G., A.D.G., G.L.; Analysis and/or Interpretation – G.C., M.F., M.G.; Literature Search – G.C., M.F.; Writing – G.C.; Critical Review – G.C., M.F., A.D.G., G.L., G.R., M.G.

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