Predicting the Outcome after Acute Unilateral Vestibulopathy: Analysis of Vestibulo-ocular Reflex Gain and Catch-up Saccades

Niccolò Cerchiai, MD1, Elena Navari, MD1, Stefano Sellari-Franceschini, MD1, Chiara Re, MD1, and Augusto Pietro Casani, MD1

Abstract

Objectives. (1) To describe the relationships among the main instrumental features characterizing an acute unilateral vestibulopathy and (2) to clarify the role of the video head impulse test in predicting the development of chronic vestibular insufficiency.

Study Design. Case series with chart review.

Setting. Tertiary referral center.

Subjects and Methods. Sixty patients suffering from acute unilateral vestibulopathy were retrospectively analyzed: 30 who recovered spontaneously (group 1) and 30 who needed a vestibular rehabilitation program (group 2). The main outcome measures included Dizziness Handicap Inventory score, canal paresis, high-velocity vestibulo-ocular reflex gain, and catch-up saccade parameters. The tests were all performed between 4 and 8 weeks from the onset of symptoms.

Results. The high-velocity vestibulo-ocular reflex gain correlated with the Dizziness Handicap Inventory score (P = .004), with the amplitude of covert and overt saccades (P < .001), and with the prevalence of overt saccades (P < .001). Patients in need for vestibular rehabilitation programs had a significantly lower gain (P < .001) and a higher prevalence and amplitude of overt saccades (P = .002 and P = .008, respectively). Conversely, we found no differences in terms of response to the caloric test (P = .359).

Conclusions. Lower values of high-velocity vestibulo-oculomotor 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.

Keywords

acute unilateral vestibulopathy, vertigo, video head impulse test, caloric test, chronic vestibular insufficiency, dizziness, vestibular rehabilitation, vestibular compensation, prognosis

Received May 4, 2017; revised September 5, 2017; accepted October 12, 2017.

A acute unilateral vestibulopathy (AUV) results in asymmetry in the vestibulo-ocular and vestibulo-spinal responses, caused by damage of the peripheral vestibular structures.1 On one hand, the static signs (spontaneous nystagmus, skew deviation, postural abnormalities) mostly disappear spontaneously; on the other, many patients have difficulties recovering the dynamic functions of their vestibular reflexes due to poor compensation mechanisms.2 The literature shows that approximately 50% of patients develop either continuous or paroxysmal dizziness after AUV; this can result in chronic dizziness, disequilibrium, spatial disorientation, and limitations in daily activities.3-5 Patients who experience residual symptoms after AUV can be approached with vestibular rehabilitation (VR) programs. The use of VR has exponentially increased over the last 25 years, and it has proven its efficacy in reducing the symptoms and improving posture, gait, gaze stabilization, and quality of life.6 However, clear indications to VR still do not exist.

The relationship among clinical aspects, vestibulometric parameters, and clinical recovery after AUV has generated
great interest over the years. Authors have tried to correlate the prognosis with the results of the caloric test,7 posturography,8 vestibular evoked myogenic potentials,9 the rotating chair test,10 and the video head impulse test (vHIT).11 Despite the constant improvement of vestibulometric techniques, there is still no agreement about their utility in predicting the realization of good vestibular compensation: patients who do not complain about dizziness can have an abnormal vestibulometric pattern and vice versa. The employment of the latest release of vHIT firmware, allowing analysis of the compensatory catch-up saccades (CSs), seems to offer new interesting perspectives.12

After describing the relationships among high-velocity vestibulo-ocular reflex (VOR), characteristics of CSs, canal paresis (CP), and the Dizziness Handicap Inventory (DHI), this study clarifies the role of vHIT in predicting the long-term outcome after AUV. This could be of great interest to clinicians in identifying patients who are less likely to recover from AUV.

Material and Methods

We retrospectively analyzed the clinical records of patients suffering from AUV who were referred to our neurotology service from January 2015 through June 2016. Our service adheres to a precise protocol in diagnosing, treating, and following up inpatients with AUV. Specifically, we diagnose AUV as a syndrome characterized by rapid onset of severe dizziness without neurologic or audiologic symptoms, unidirectional horizontal nystagmus, unilateral vestibular areflexia/hyporeflexia on bithermal caloric test, and positive head impulse test result in the direction opposite to the fast phase of the nystagmus. All patients are treated during the acute phase with tapered doses of methylprednisolone (starting from 32 mg daily) and antiemetics; a “baseline” neurologic evaluation (including posture/gait examination, oculomotricity, caloric test, and vHIT) is performed within 72 hours from the onset, allowing the diagnosis of AUV. After hospital discharge, each patient with AUV undergoes a complete neurotologic follow-up visit, during which she or he is asked about the persistence of 3 residual symptoms (dizziness, unsteadiness, and spatial disorientation); then, the patient completes the Italian version of the DHI.13 Since this study considered the results of the follow-up visit as the real expression of the clinical recovery, only the data obtained from this latter examination were statistically analyzed.

To assess all the study objectives with sufficient statistical power, the study considered the last 30 patients who, at the time of the first follow-up visit, demonstrated good clinical vestibular compensation (absence of residual symptoms; group 1) and the last 30 patients who were in need of a VR program (persistence of residual symptoms; group 2). All the cases respected the following selection criteria: hospital admittance, clinical and instrumental signs of AUV, absence of clinical signs of central nervous system involvement, and first follow-up visit made between the fourth and eighth week of onset.

The bithermal caloric test was performed according to a modified Fitzgerald-Hallpike technique: the external auditory canal was separately irrigated with 125 mL of warm (44°C) and cold (30°C) water in a 30-second period (7 minutes lasted between tests); the responses were recorded through an infrared eye-tracking system (GN Otometrics, Taastrup, Denmark). CP was considered significant if >25%. The vHIT was performed by employing a dedicated device (ICS Impulse System; GN Otometrics): the patient was asked to stare at an Earth-fixed target (3-cm-diameter spot located 1.5 m in front); then, 20 low-amplitude (10°-20°) but high-velocity head impulses (150-200 deg/s) were randomly administered on each side for every semicircular canal. The device software automatically calculates the average high-velocity VOR gain. The software also calculates the asymmetry index (AI%) between the right and left sides according to the ICS Impulse “relative asymmetry” formula: 1 – (lower high-velocity VOR gain mean / higher high-velocity VOR gain mean) × 100. The AI% shows differences between the sides in terms of high-velocity VOR. We did not consider for this research the values obtained with vertical planes stimuli, because in our experience they are still subject to a quite high number of artifacts. The last ICS Impulse firmware version (4.0) allows tracking single CSs, automatically classified as “covert” (C-CSs) or “overt” (O-CSs), if generated during or after the head movement, respectively. For each saccade, the software provides values of latency and amplitude. The prevalence of tracked CSs (covert and overt) during the whole series of impulses is also provided. The software calculates the “PR” index, which represents the scattering pattern of the saccade latency after the stimulus: a lower PR value suggests more gathered CSs.

Informed consent was obtained from all participants, and the local ethics committee (Comitato Etico dell’Università di Pisa) approved the protocol, in accordance with the 1964 Declaration of Helsinki.

Statistical Analysis

The Kolmogorov-Smirnov test with Lilliefors’s correction and Levene’s test were used to assess normal distribution of data and homogeneity of variance, respectively. Differences between parametric and nonparametric data were assessed with the independent samples t test and the Mann-Whitney U test, respectively. Pearson’s R and Spearman’s rho were calculated to determine correlations between parametric and nonparametric variables, respectively. Significance was set at \( P < .05 \). The analyses were performed with SPSS 23 (IBM, Chicago, Illinois).

Results

All the enrolled patients suffered from an acute vestibular syndrome associated with the following clinical aspects: long-lasting vertigo without hearing loss, neurovegetative symptoms, unidirectional horizontal-torsional spontaneous nystagmus following Alexander’s law, significant CP, and unilaterally abnormal vHIT result. None of the cases showed clinical or instrumental signs suggestive of isolated inferior vestibular nerve involvement.
Patients belonging to group 1 (18 males and 12 females) and group 2 (20 males and 10 females) were not significantly different in terms of age (independent samples t test, $P = .096$; Table 1).

Statistical analysis showed that age was negatively correlated with only high-velocity VOR ($R = –.295$, $P = .022$) and O-CS prevalence ($R = –.357$, $P = .005$).

High-velocity VOR gain was negatively correlated with CP ($\rho = –.512$, $P < .001$), O-CS prevalence ($\rho = –.661$, $P < .001$), and both C-CS and O-CS amplitude (respectively: $R = –.764$, $P < .001$; $R = –.806$, $P < .001$; Figure 1); the analysis also showed a positive correlation with O-CS latency ($\rho = .415$, $P = .001$).

The DHI score was negatively correlated with high-velocity VOR gain ($R = –.369$, $P = .004$; Figure 2) and positively correlated with age ($R = .313$, $P = .016$), O-CS prevalence ($\rho = .404$, $P = .004$), and O-CS amplitude ($R = .283$, $P = .034$), even if the correlations were quite weak. On the contrary, the DHI score was not correlated with any of the C-CS parameters. No correlation was appreciable between DHI and CP.

When the 2 groups were considered separately, there was a significant difference in terms of high-velocity VOR gain, with a significantly lower value in group 2 (0.53 ± 0.25) than group 1 (0.78 ± 0.23; independent samples t test, $P < .001$; Figure 3). The comparison of AI% showed that group 2 had greater asymmetry of high-velocity VOR between the healthy and affected sides (independent samples t test, $P < .001$). The DHI score was significantly higher in group 2 (mean scores: 7.27 ± 4.88 in group 1 and 24.83 ± 17.66 in group 2; Mann-Whitney U test, $P < .001$).

The analysis of CSs showed that the prevalence, latency, and amplitude of C-CSs were not different between the

---

**Table 1. Results of the Instrumental Assessment.**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th></th>
<th></th>
<th></th>
<th>Group 2</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>60.63</td>
<td>41.00</td>
<td>76.00</td>
<td>9.59</td>
<td>.096</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Min</strong></td>
<td>0.78</td>
<td>0.26</td>
<td>1.13</td>
<td>0.23</td>
<td>0.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Max</strong></td>
<td>19.83</td>
<td>2.00</td>
<td>64.00</td>
<td>19.88</td>
<td>45.79</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>7.27</td>
<td>0.00</td>
<td>18.00</td>
<td>4.88</td>
<td>24.83</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>7.37</td>
<td>0.00</td>
<td>38.00</td>
<td>10.93</td>
<td>13.70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Latency, ms**        | 120.64  | 72.00    | 196.00   | 36.42    | 122.00  |
| **Amplitude, deg/s**   | 116.43  | 19.00    | 271.00   | 73.23    | 157.00  |
| **PR**                 | 15.20   | 0.06     | 36.00    | 14.07    | 25.94   |
| **O-CSs, %**           | 56.57   | 0.00     | 100.00   | 38.80    | 83.27   |
| **Latency, ms**        | 245.37  | 35.00    | 528.00   | 90.67    | 222.40  |
| **Amplitude, deg/s**   | 108.67  | 31.00    | 288.00   | 60.33    | 150.87  |
| **PR**                 | 41.41   | 0.00     | 91.00    | 26.81    | 48.14   |
| **CP, %**              | 39.51   | 1.49     | 100.00   | 28.96    | 51.73   |

**Abbreviations:** AI, asymmetry index; C-CSs, covert catch-up saccades; CP, canal paresis; DHI, Dizziness Handicap Inventory; O-CSs, overt catch-up saccades; PR, scattering index for catch-up saccades; VOR, vestibulo-ocular motor reflex.

*P < .05.*
groups ($P = .326$, $P = .653$, and $P = .084$, respectively); group 1 and group 2 were not different in terms of saccades scattering as well (Mann-Whitney $U$ test: $P = .150$ and $P = .242$ for C-CSs and O-CSs, respectively). Interestingly, group 2 showed a significantly higher prevalence of O-CSs (Mann-Whitney $U$ test: $P = .002$); O-CSs also had a greater amplitude in this group (Mann-Whitney $U$ test, $P = .008$; Figure 4) but not a different latency ($P = .221$).

The caloric test did not show a significantly different response (in terms of CP) between the groups (Mann-Whitney $U$ test, $P = .359$).

All the results are shown in detail in Table 1. Figure 5 shows a sample of raw data collected from a typical patient belonging to group 2.

**Discussion**

Although many factors can affect the outcome after AUV, the definition of an instrumental profile indicating a poor prognosis is of great interest to clinicians who have to manage patients with invalidating residual symptoms. Older experiences demonstrated the importance of this topic by identifying, in a pathologic high-velocity VOR function at follow-up, the best clinical parameter in predicting a bad outcome after AUV. The introduction of the vHIT has improved the sensitivity of the technique and overcome the limits of the manually performed head impulse test in VOR gain and CSs analysis; furthermore, the vHIT proved to be of interest to clinicians in defining instrumental hallmarks of important vestibular disorders.

However, the literature shows contrasting results about the relationship between vHIT findings and other parameters, such as age, CP, and symptom scales. Few studies have evaluated normative values of high-velocity VOR and CSs according to age. A study by Yang et al showed no significant differences in either VOR gain or incidence of CSs (ranging from 14% to 27%) among healthy subjects of a different age, while Matino-Soler et al found a higher prevalence of CSs in subjects >71 years old (66.6%) with respect to those <70 years (16.7%). A recent study by Anson et al found that aging increases CS amplitude on vHIT in 243 healthy subjects. If we consider C-CSs alone, our study is consistent with what is found on physiological conditions (ie, age does not cause any modification on C-CSs). Conversely, in our series, increasing age causes a mild decrease of high-velocity VOR gain and a higher prevalence of O-CSs (without any reflection on latency and amplitude); this also seems to reflect in progressively higher values on DHI. Further studies on physiological and pathologic conditions will clarify these contrasting results; however, our experience suggests that normal aging processes should be considered when elderly patients with AUV are evaluated with the vHIT.

The appearance of CSs after sudden and passive head impulses toward the affected side was described as a clinical
localizing sign of AUV. \textsuperscript{22} Patients with and without AUV were reported to show decreasing gain and a higher occurrence of CSs (with also greater CS velocities) in response to increasing head acceleration. \textsuperscript{17,19} In our study, the same operator (N.C.) performed the vHIT with a similar peak velocity (150-200 deg/s). Analyzing the relationship between VOR gain and CSs, we found that lower values of VOR gain are associated with a higher prevalence of O-CSs; a decrease of VOR gain also causes a small decrease of O-CS latency and a significant increase of O-CS amplitude. This is consistent with the literature, which reports greater CS amplitude in response to a larger retinal slip. \textsuperscript{23,24} Conversely, the presence of C-CSs seems to be independent from the VOR gain. A recent study confirms this latter aspect: when vestibular compensation is promoted, O-CSs progressively decrease in number and velocity and become gathered C-CSs, despite VOR gain remaining unchanged. \textsuperscript{25}

Both the vHIT and the caloric test measure the unilateral VOR but at high (5- to 7-Hz stimulus) and low (0.003-Hz stimulus) temporal frequencies, respectively. Our analysis showed a negative correlation between VOR gain and CP: although most AUVs should cause low- and high-velocity VOR hypofunction, the literature shows different results. On one hand, CP and VOR gain appear correlated.\textsuperscript{26,27} On the other, vestibular compensation seems frequency dependent (with high-velocity VOR gain recovering slower than CP).\textsuperscript{28,29}

Our choice to employ the DHI score as main symptom scale during the follow-up is supported by a recent systematic review: the authors provided a literature synthesis of the most commonly used outcome measures based on patients’ reported outcomes, finding that DHI is a good and validated instrument that is applicable for older adults.\textsuperscript{30} The analysis of correlations shows that the DHI score increases (meaning a progressively higher level of disability) in accordance with the following conditions: increase of O-CS latency and a significant increase of O-CS amplitude. This is consistent with the literature, which reports greater CS amplitude in response to a larger retinal slip.\textsuperscript{23,24} Conversely, neither a higher rate of CP nor a higher prevalence of C-CSs is relevant in worsening the symptoms.

The comparison of 2 completely different groups in terms of outcome allowed us to make important considerations about the utility of the vHIT in estimating the clinical recovery after AUV; however, our results are in contrast with 2 important previous experiences. Palla et al analyzed high-velocity VOR with the employment of the magnetic
search coil, without identifying any correlation between gain and dizziness. Patel et al reported the same result using the vHIT in a series of 20 patients seen from 3 to 36 months from the onset.

However, the following few aspects make our study slightly different. Our decision to analyze only the data deriving from the follow-up visit is supported by a study affirming that a spontaneous improvement of high-velocity VOR gain can take place within the first 4 weeks. For that reason, considering the parameters belonging to the very acute phase (“baseline” evaluation) would have made our results less reliable: a highly compromised VOR at the “baseline” (thus suggesting a poor prognosis) can be perfectly normal after 4 weeks. Second, the narrower range of time after AUV onset (4-8 weeks) during which we examined the patients made the results more comparable. Last, our sample is larger.

Our results indicate that a deficient high-velocity VOR gain is most likely to determine a worse prognosis (this is also reflected in higher DHI scores). Conversely, the degree of CP after 4 weeks from the onset is irrelevant for the clinical recovery, according with previous studies. The presence of O-CSs (generally also with greater amplitude) negatively affects the outcome as well, being associated with higher DHI scores and mostly characterizing patients belonging to group 2. Our results about CSs are in accordance with a study by Batuecas-Caletrio and colleagues: the time between head movement and CSs was related to the degree of vestibular disability and handicap; the random appearance of CSs after the head impulse test was associated with an increased level of disability, in contrast to CSs that occur in an organized fashion, which were associated with a lower level of disability and subjective balance.

This study has some limitations, represented first by its retrospective design. However, the literature does not provide clear parameters indicating the need for VR: a prospective design would have needed precise cutoff parameters to be applied in defining patients with poor outcomes. Second, we did not take into account some clinical and instrumental aspects, such as duration and geotropism of spontaneous nystagmus, vibration-induced nystagmus, presence or absence of vestibular evoked myogenic potentials, and posturographic assessment; all these data were not available for all the cases. For the analysis, we did not consider the data derived from the vHIT on vertical canals: although some experiences report interesting data, we maintain that they are still subjects to some artifacts. Last, a patient’s selection through the Hospital Anxiety and Depression Scale would have excluded major psychiatric comorbidities; however, we did not find significant differences in the emotional scale of the DHI among groups. Despite the aforementioned limitations, our findings underline the importance of high-velocity VOR and CS assessment through the vHIT among patients with AUV, delineating important instrumental characteristics for those who are less likely to recover.

Conclusions
Patients with lower VOR gain and a high prevalence of O-CSs (also greater in amplitude on the vHIT) after 4 weeks from the onset of AUV are more likely to develop chronic dizziness, unsteadiness, and spatial disorientation; CP and C-CS alterations do not affect the clinical outcome. This could be of great interest to clinicians in identifying patients who are more likely to need a VR program.

Acknowledgments
Thanks to Dr Nicola Vernassa for his technical support.

Author Contributions
Nicolò Cerchiai, conception and design of the study, evaluation of patients, statistical analysis, drafting the article, critical revision, and final approval of the manuscript; Elena Navari, Contribution to the study design, evaluation of patients, critical revision, and final approval of the manuscript; Stefano Sellari-Franceschini, Contribution to the study design, critical revision, and final approval of the manuscript; Chiara Re, Contribution to the study design, critical revision, and final approval of the manuscript; Augusto Pietro Casani. Conception and design of the study, evaluation of patients, critical revision, and final approval of the manuscript.

Disclosures
Competing interests: None.

Sponsorships: None.

Funding source: Mario Marianelli Foundation (via Verdi 22, 56029 Santa Croce sull’Arno, Pisa, Italy) contributed to the research and educational grants for Niccolò Cerchiai and Elena Navari.

References


