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Vestibulo-ocular reflex dynamics with head-impulses discriminates spinocerebellar ataxias types 1, 2 and 3 and Friedreich ataxia

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Abstract.
OBJECTIVE: Although the diagnosis of inherited ataxias is ultimately genetic, this usually means an extensive and expensive process. This justifies the search for distinct clinical signs that may potentially help orient molecular diagnosis.
METHODS: We explored the vestibulo-ocular reflex (VOR) with the video Head Impulse Test in patients diagnosed with spinocerebellar ataxia (SCA) type 3 ($n = 15$), type 1 ($n = 4$) and type 2 ($n = 4$), Friedreich's ataxia (FA) ($n = 9$) and healthy controls ($n = 40$). We estimated the latency, regression (VORr) and instantaneous VOR gain at 40, 60 and 80 ms (VOR40, VOR60 and VOR80), and determined the latency, peak-velocity and occurrence rate of catch-up saccades triggered with head-impulses.
RESULTS: VOR latency was higher in FA ($p < 0.001$) and SCA3 ($p = 0.02$) as compared to controls, discriminating FA from other ataxic patients with an overall diagnostic accuracy of 88%. VORr, VOR40 and VOR60 were significantly lower in FA and SCA3 ($p < 0.01$). VOR80 was only significantly lower than controls in SCA3 ($p < 0.01$), discriminating these from other ataxic patients with an overall diagnostic accuracy of 78%. Covert saccades were only triggered in SCA3 but with low occurrence rate and peak velocity ($11.1 \pm 28.5\%$ and $77.50 \pm 15.30°$/s) whereas overt saccades were present in all groups. VORr gain showed a negative correlation with disease severity evaluated with SARA (Spearman $r = –0.46$, $p = 0.01$).
CONCLUSIONS: vHIT provides phenotypic information that differentiates these autosomal ataxias and can serve as a strategy to orient genetic diagnosis. A correlation between VOR and SARA raises the possibility of using VOR gain as a neurophysiologic biomarker for disease severity.

Keywords: Neuro-otology, vestibulo-ocular reflex (VOR), vestibular function tests, spinocerebellar ataxia, Friedreich ataxia

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1. Introduction

Clinically differentiating the different types of cerebellar ataxias can be difficult, as there is often an overlap in neurological signs and symptoms. Although the diagnosis of inherited ataxias is ultimately genetic, this usually means an extensive and expensive process that may postpone the beginning of treatment and of genetic counseling. This justifies the search for distinct clinical signs that may potentially help orient molecular diagnosis.

Although the vestibulo-ocular reflex (VOR) is usually considered to be normal in patients with vestibular symptoms due to central nervous system (CNS) disorders [22], several studies have described significant changes in VOR function in patients with inherited ataxias [2, 8, 35, 36] and more recently in cerebellar floccular infarction [23]. Recent evidence from patients with non-inherited cerebellar ataxia and bilateral vestibulopathy further suggests that patients with pure central and mixed central and peripheral vestibular lesions may be discriminated based on the characteristics of VOR changes [17].

The Head Impulse Test (HIT) is an active clinical test of vestibular function in which the presence of a catch-up saccade at the end of head thrusts is clinically interpreted as an indirect sign of VOR deficit [13]. The video HIT (vHIT) [2, 19, 33], also a non-invasive bedside test, further allows the quantification of the VOR and the characterization of catch-up saccades triggered by head impulses [22, 23]. While the clinical HIT only allows the identification of saccades triggered after the head impulse, the vHIT allows the identification and quantification of both the saccades generated during (covert saccades) and the generated after (overt saccades) the head impulse [33].

Here, we investigated whether VOR characteristics when explored with the vHIT are useful to differentiate the most common types of autosomal ataxias.

2. Methods

We studied 23 patients with a clinical and genetically confirmed diagnosis of spinocerebellar ataxia (SCA) type 3 ($n = 15$), type 2 ($n = 4$) and type 1 ($n = 4$), and 9 patients with early onset Friedreich's ataxia (FA). A group of 40 age- and gender-matched healthy subjects without previous history of cochlear, vestibular or visual diseases, and not taking medication that may potentially affect eye movement, were used as controls.

Disease severity was evaluated with the Scale for the Assessment and Rating of Ataxia (SARA) [26], applied independently by two neurologists. All Video Head Impulse Tests were performed by the principal investigator (LL) using the same equipment and lab facilities. All subjects provided their informed written consent to the study protocol, which was approved by the Ethics Committee.

2.1. Video Head Impulse Test (vHIT)

Horizontal head impulses were recorded with a video-oculography device [2] (EyeSeeCam, Munich, Germany), the camera mounted for left eye recording. The system was first calibrated by having the patient fixate at luminous dots projected by a head-fixed laser at predefined horizontally and vertically 8.5° angles. VOR was obtained by manually delivering at least six valid high velocity (150–300°/s) and low amplitude (10–20°) head impulses in yaw and to each side, unpredictable as regards time and direction, while patients were asked to fixate a printed dot on a white board at 140 cm distance on the midline and at eye level.

2.2. Data analysis

Data analysis was performed offline. Head impulses were detected with a velocity criterion [9]. The start of the impulse was defined at a velocity threshold of 20°/s and end of the impulse was defined when head velocity crossed zero again. VOR latency was estimated as the minimal difference between head and eye velocity from head impulse start until reaching 70°/s [1]. VOR_r gain was estimated as head velocity to eye velocity linear regression [1] and the side-to-side quotient defined as the asymmetry index between sides [25]. As there were no differences in VOR gain between sides neither in healthy subjects nor in patients ($p = 0.95$ for all comparisons; paired *T Test*), data from both sides was pooled for group analysis. To explore VOR dynamics we determined the instantaneous VOR gain estimated as the median of the eye and head velocity ratio during 35–45, 55–65, and 75–85 ms (VOR_{40}, VOR_{60} and VOR_{80}) after head impulse start.

Catch-up saccades were defined as quick eye movements (peak velocity over 30°/s above slow phase baseline velocity) triggered during (covert) or after (overt) the head impulse. Saccade start was

Table 1
Subject's characteristics

	FA ($n=9$)	SCA3 ($n=15$)	SCA 1 ($n=4$)	SCA2 ($n=4$)	Controls ($n=40$)	p
Female (%)	44.4	53.3	50.0	25.0	55.0	$\chi 2=1.52$; $p=0.82$
Age‡	36.3 ± 12.0	49.8 ± 11.9	48.5 ± 16.5	46.5 ± 14.9	41.10 ± 16.6	0.10
Disease duration‡	23.3 ± 15.7	6.8 ± 4.1	8.3 ± 4.6	15.3 ± 3.6	NA	**0.001**
SARA	22.6 ± 7.7	13.9 ± 6.1	12.1 ± 3.4	12.9 ± 6.6	NA	**0.02**

FA: Friedreich's ataxia; SCA: Spinocerebellar ataxia; SARA: Scale for the Assessment and Rating of Ataxia; NA – not applicable; ‡age and disease duration are expressed in years ± standard deviation. Bold p-values indicate $p<0.01$.

at 10°/s, latency was the difference between head impulse start and the first catch-up saccade start for each subject. Catch-up saccade occurrence rate was the percentage of head impulses with catch-up saccades.

Continuous data were analyzed using multivariate general linear model with Bonferroni adjustment to the confidence intervals and significance. Bonferroni-correction was done for *post-hoc* pairwise comparisons. Categorical data were analyzed with Pearson's Chi-Square test. Significant proportion differences between groups were evaluated with Z-test with adjusted p values (Bonferroni method) corrected for multiple comparisons. Non-parametric Spearman correlation coefficients between disease severity and VOR gain were calculated. The ability of VOR gain to discriminate between ataxic patients was further evaluated using the area under the nonparametric receiver operating characteristic curve (AUC-ROC) [28]. Sensitivity and specificity were estimated by determining the cut-off point of ROC curve in which the highest accuracy was obtained. All statistical analyses were done with SPSS® 20.0 for Mac (SPSS Inc., Illinois, USA).

3. Results

3.1. Subjects

Table 1 shows the subjects' main clinical characteristics.

Patients with SCA3 and FA had a bilateral VOR deficit while SCA2 patients showed normal VOR gain, comparable to the control group. Most SCA1 patients showed a VOR deficit, but not reaching statistical significance.

3.2. Video Head Impulse Test

Figure 1 shows illustratory vHIT for controls, SCA3 and FA patients.

3.3. VOR

Tables 2 and 3 and Fig. 2 show the main results for VOR.

VOR latency was longer in SCA3 and FA, as compared to controls ($p \leq 0.022$ and $p \leq 0.001$, respectively). VOR latency AUC-ROC was 0.88 (95% CI, 0.76 to 1.00) for FA. For a threshold of 13.2 ms, the sensitivity was 100.0% and the specificity 82.6%. VOR_r, VOR_{40} and VOR_{60} were lower in SCA3 and FA, as compared to controls ($p \leq 0.006$ for all comparisons) with a high proportion of FA (100%), SCA3 (80%) and SCA1 (75%) patients having an unilateral or bilateral abnormally low VOR_r (below 0.77, defined as mean VOR_r minus 2SD found in control group). VOR_{80} was only lower in SCA3, as compared to controls ($p \leq 0.004$). VOR_r gain showed a significant negative correlation with disease severity evaluated with SARA (Spearman $r=-0.46$, $p=0.01$). VOR_{80} AUC-ROC was 0.78 (95% CI, 0.61 to 0.95) for SCA3. For a threshold of 0.66, the sensitivity was 73.3% and the specificity 77.0%. VOR_{80} and (VOR_{80}–VOR_{40}) did not correlate with latency.

3.3.1. Catch-up saccades

Table 2 shows the main characteristics of catch-up saccades triggered with head impulses.

Covert saccades were only present in three SCA3 patients and with a low occurrence rate (11.1 ± 28.5%) (see Fig. 1B for an illustratory example). Overt saccades (triggered after the head impulse) were present in all groups, with an occurrence rate only significantly higher in SCA3 patients than in controls ($p<0.001$).

Overt saccades occurrence rate and peak-velocity showed a significant negative correlation with VOR_{40} (Spearman $r=-0.32$ and $r=-0.63$, respectively, $p=0.01$).

4. Discussion

The main findings of this study are: 1) Most SCA and FA patients had a VOR deficit, with the exception

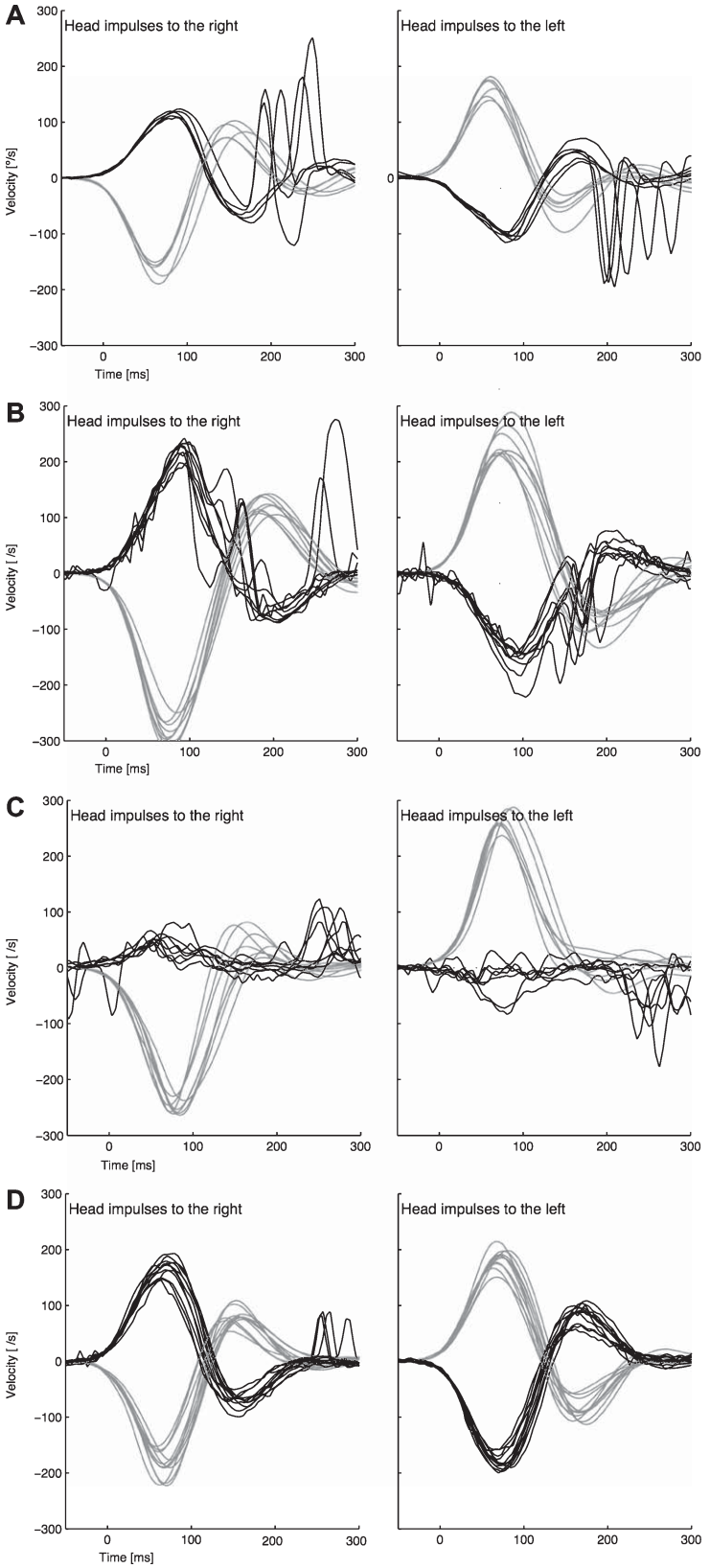
A
Head impulses to the right
Head impulses to the left
Velocity [°/s]
Time [ms]
B
Head impulses to the right
Head impulses to the left
Velocity [/s]
Time [ms]
C
Head impulses to the right
Heaad impulses to the left
Velocity [/s]
Time [ms]
D
Head impulses to the right
Head impulses to the left
Velocity [/s]
Time [ms]

Table 2
vHIT findings

	FA ($n=9$)	SCA 3 ($n=15$)	SCA 1 ($n=4$)	SCA 2 ($n=4$)	Control ($n=40$)	P value‡‡
VOR latency (ms)	23.7 ± 15.7	7.8 ± 15.0	3.6 ± 3.1	−1.4 ± 2.3	−2.3 ± 2.1	**<0.001**
VOR_r	0.42 ± 0.17	0.50 ± 0.30	0.77 ± 0.05	1.00 ± 0.06	0.94 ± 0.08	**<0.001**
Abnormal‡(%)	100	87	75	0	0	**$\chi 2 = 61.0$; $p < 0.001$**
VOR asymmetry	3.00 ± 2.60	4.73 ± 3.63	3.75 ± 2.87	3.50 ± 1.92	3.13 ± 2.00	0.701
VOR gain dynamics						
VOR_{40}	0.39 ± 0.13	0.43 ± 0.32	0.75 ± 0.12	0.95 ± 0.13	0.87 ± 0.09	**<0.001**
VOR_{60}	0.42 ± 0.19	0.41 ± 0.34	0.83 ± 0.25	0.95 ± 0.12	0.88 ± 0.09	**<0.001**
VOR_{80}	0.62 ± 0.28	0.46 ± 0.35	1.02 ± 0.31	0.99 ± 0.04	0.89 ± 0.14	**<0.001**
Covert saccades						
subjects with (%)	0	20	0	0	0	**$\chi 2 = 14.4$; $p = 0.006$**
occurrence rate (%)	0	11.1 ± 28.5	0	0	0	**0.02**
latency (ms)	NA	113.2 ± 15.1	NA	NA	NA	NA
peak velocity (°/s)	NA	77.50 ± 15.30	NA	NA	NA	NA
Overt saccades						
subjects with (%)	88.9	86.7	75.0	100	50.0	**$\chi 2 = 11.8$; $p = 0.02$**
occurrence rate (%)	46.1 ± 42.9	56.5 ± 36.5	19.8 ± 26.1	23.3 ± 15.4	14.4 ± 20.1	0.001
latency (ms)	223.5 ± 37.5	194.0 ± 38.5	190.0 ± 33.5	211.9 ± 22.7	174.8 ± 52.4	0.18
peak velocity (°/s)	226.4 ± 52.5	150.7 ± 72.9	101.5 ± 48.98	68.9 ± 22.9	82.5 ± 43.4	**<0.001**

Results for VOR gain and saccade occurrence rate, latency and peak velocity are expressed as mean ± standard deviation. FA: Friedreich's ataxia; SCA: Spinocerebellar ataxia; NA – not applicable. ‡Abnormal VOR gain defined as VOR_r gain below the mean minus 2SD of control values (0.78). ‡‡Pearson's Chi-Square test and independent samples Kruskal-Wallis test results for categorical and continuous data, respectively. Bold p-values indicate $p < 0.01$.

Table 3
vHIT summary of findings

	FA	SCA3	SCA1	SCA2
VOR latency	increased	increased	normal	normal
VOR gain	low	low	low/normal	normal
VOR dynamics	increase	no increase	increase	–
Covert saccades	absent	present	absent	absent
Overt saccades	present	present	present	present

of SCA2 patients; 2) VOR latency was longer in FA and SCA3; 3) VOR_r, VOR_{40} and VOR_{60} were both abnormally low in FA and SCA3, but only SCA3 had VOR_{80} significantly lower than controls; 3) Covert saccades were triggered only in SCA3 4) overt saccades were triggered in all groups, but occurrence rate and peak-velocity are negatively correlated with VOR_{40}. 5) VOR_r gain showed a significant negative correlation with disease severity evaluated with SARA.

4.1. VOR findings

VOR latency was significantly longer in SCA3 and FA [8] than controls. Both controls and SCA-1 showed negative average values, this probably resulting from slippage and camera mechanical inertia [31], but these technical issues were common to all groups. This suggests that vHIT allows estimation of VOR latency, namely for group comparison, but may not be used to determine absolute latency and initiation of the VOR. These results are in general agreement with the results obtained in other studies using the search coil technique in both FA [8] and SCA3 [10].

In previous reports for low-frequency VOR testing (caloric test or rotatory chair), SCA3 showed bilateral abnormal [11, 35], SCA1 normal [6] or abnormal [5, 16] and SCA2 normal VOR results [6, 5], all of these fairly matching our high-frequency vHIT findings. In contrast, caloric test and rotatory chair have mostly failed to identify the VOR deficit in FA hereby demonstrated [7, 12]. In controls, VOR instantaneous gain was not different at 40, 60 and 80 ms (Table 2 and Fig. 2), as a result of the characteristic linear trajectory of VOR instantaneous gain known from search coil recordings [9]. It is interesting that VOR_{40} and VOR_{60} were both abnormally low in FA and SCA3, but only SCA3

Fig. 1. Video head-impulse test (vHIT) illustratory examples. A: vHIT of a patient diagnosed with Friedreich's ataxia; with head impulses towards either side the eyes (black) do not compensate for the head (gray, each trace corresponds to one head impulse) and catch-up saccades are triggered after the head impulse (overt saccades). B: vHIT of a patient diagnosed with SCA3; with head impulses towards either side the eyes do not compensate for the head and catch-up saccades are triggered both during (covert saccades) and after the head impulse (overt saccades). C: vHIT of a patient diagnosed with SCA3: note the significant defective VOR slow phase during impulses to both sides and catch-up saccades triggered after the head impulse. D: vHIT of a control subject: Note the compensatory VOR slow phase during impulses to both sides; low occurrence rate and low peak velocity catch-up saccades are triggered after right head impulses.

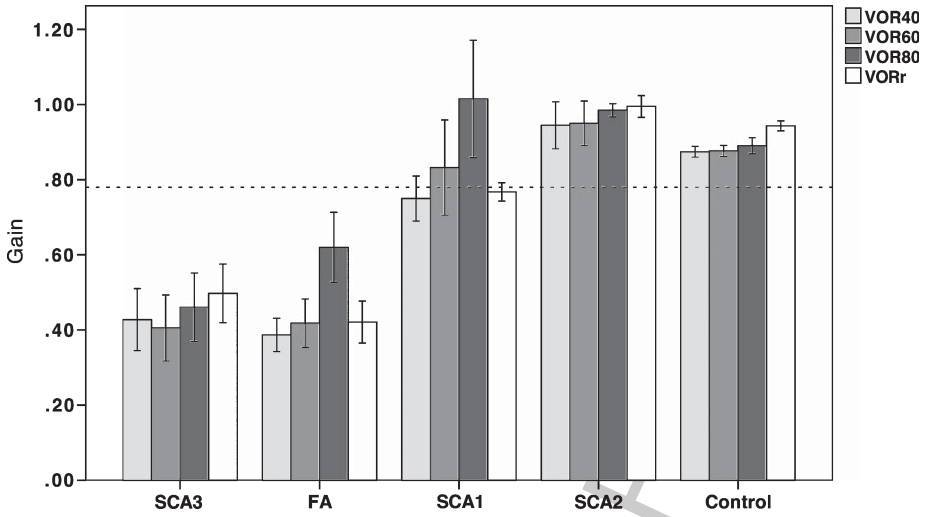

Fig. 2. VOR gain dynamics. Bar graph showing VOR_r, VOR_{40}, VOR_{60} and VOR_{80} average results for SCA3, FA, SCA1, SCA2 and controls. VOR_r, VOR_{40} and VOR_{60} were significantly lower in FA and SCA3 in comparison to SCA2 and controls ($p \leq 0.006$ for all comparisons) but regarding VOR_{80} only SCA3 was different from SCA2 and controls ($p \leq 0.004$ for all comparisons). The instantaneous gain difference from 40 to 80 ms was higher in FA in comparison to controls ($p = 0.01$). The dotted line represents VORr normal lower limit (0.77) as calculated by (average-2SD) for controls. Error bars represent standard error of mean.

maintained a VOR_{80} that was significantly lower than controls. The instantaneous gain in FA did not result from the VOR latency increase, since it paradoxically showed a significant negative correlation with VOR_{80} and VOR_{80}–VOR_{40} (Pearson $r = -0.87$ and $r = -0.70$, $p = 0.02$ and $p = 0.04$, respectively). Furthermore, VOR_{80} discriminated SCA3 from other ataxic patients with an overall diagnostic accuracy of 78%.

4.1.1. Catch-up saccades

To the best of our knowledge, catch-up saccades triggered with head impulses have never been explored in SCA, nor in FA patients, other than the clinical identification of overt saccades during bedside exploration [11]. Overt saccade's occurrence rate and peak-velocity correlated with VOR_{40}. Still, overt saccades were present in all studied groups, though with significantly lower occurrence rate and peak-velocity in SCA2 and controls than in FA and SCA3 (Table 2). Nevertheless this suggests that overt saccades can be false-positive for establishing a diagnosis of a bilateral peripheral vestibular deficit in inherited ataxic patients, as it has been shown for non-hereditary ataxias [17].

A central origin for covert saccades, as a VOR substitution strategy, is supported by its short latency and bilateral presence in bilateral peripheral lesions [32], though this has not been confirmed. In this study, they were only present in three SCA3 patients, although with a lower occurrence rate and peak-velocity than documented in peripheral patients [3].

4.2. The site(s) of lesion

Although described as a sign of peripheral vestibular loss, a defective HIT has been described in various cerebellar disorders. Gordon et al. (2003) [11] described for the first time bilateral vestibular areflexia detected by the HIT, confirmed by absent responses to ice water ear irrigation, in a group of seven SCA3 patients. Further studies recording eye movements using magnetic search coils during HIT have revealed that SCA3 have low VOR gain [10, 32]. As these patients had no symptoms or signs of auditory or other ocular-motor cranial nerves impairment, all eye movement and VOR abnormalities in SCA3 patients could be attributed to central nervous system dysfunction [11].

Non-Hereditary cerebellar ataxia patients that, as SCA3, show a caloric VOR deficit [17], and have similar oculomotor findings as Cerebellar Ataxia Neuropathy Vestibular Areflexia Syndrome (CANVAS) patients [20, 30], also maintain or decrease VOR gain during the impulse and trigger covert saccades [17, 30]. The histopathology study of one CANVAS patient [29] has shown normal vestibular end-organs but bilateral atrophy of the vestibular

nerve, as well as cerebellum involvement, both also known to be affected in SCA3 [24].

On the other hand, non-hereditary cerebellar ataxia patients [17] that, as FA, may show normal caloric results [7] also maintain or increase VOR gain during the impulse and trigger no covert saccades. While we could not find histopathology studies in these patients, the isolated high-frequency deficit most likely results from a central cerebellar flocculus dysfunction [17]. Accordingly FA patients' temporal bones have shown relatively spared end organs and vestibular nerves [15, 27]. The different involvement of both peripheral and central vestibular system structures may therefore justify this low and high frequency VOR dissociation, VOR gain dynamics and covert saccade triggering strategy as well as the dependency of these results on disease progression [21].

4.3. Clinical correlation

A negative correlation between VOR_r gain and SARA score raises the possibility of using VOR gain as a neurophysiologic biomarker for disease severity as it has recently been suggested for SCA3 [12]. FA reached the highest scores in SARA evaluation, with most of ataxic patients presenting symptoms of severe unbalance and gait difficulties. Symptom of bilateral VOR loss such as oscillopsia [4] were mostly absent in FA and SCA3 matching previous reports [8, 11]. Since covert saccades were in most cases not triggered by SCA3 or FA patients, saccadic suppression is not responsible for the absence of oscillopsia in these groups, as has previously been suggested for peripheral vestibular patients [18] and an alteration in perception is a more likely explanation [14].

5. Conclusion

In summary, our findings demonstrate that vHIT supplies phenotypic hallmarks that discriminate these autosomal ataxias and may serve as a strategy to orient genetic diagnosis.

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Competing interests

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