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Positinal Testing In Acute Vestibular Syndrome: A Transversal And Longitudinal Study

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POSITIONAL TESTING IN ACUTE VESTIBULAR SYNDROME: A TRANSVERSAL AND LONGITUDINAL STUDY.

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ABSTRACT

Objective:

We sought to evaluate the clinical utility of positional testing in peripheral and central acute vestibular syndrome (pAVS, cAVS, respectively).

Methods:

Consecutive AVS patients underwent video-oculography in upright, supine and head hanging positions and video-head impulse test (VHIT), at presentation (<14 days from onset), 3-month and 1-year follow-up.

Results:

15 pAVS and 15 cAVS patients were included. Mean age (SD) was 53.3 (16.6) (11 males) in pAVS group and 56.5 (17.8) (12 males) in cAVS group (p= .04). Acutely, in supine, 14 (93%) pAVS and only 7 (47%) cAVS patients showed stronger unidirectional nystagmus when turning to the slow phase side. 1 patient in each group showed ageotropic (i.e., towards the ceiling) nystagmus. The remaining cAVS patients showed either stronger nystagmus when turning to the fast phase side, or geotropic (i.e., towards the ground) nystagmus. During follow-up, ageotropic and geotropic nystagmus were common in both groups. Cubic regression analysis showed a significant influence of the ipsilateral VHIT gain on supine nystagmus intensity and direction (R^2= .546; p<

.001). In head hanging, 5 (33%) cAVS patients showed paroxysmal nystagmus (3, downbeat; 2, upbeat) and 2 other showed augmentation of saccadic intrusions. Positional downbeat nystagmus and saccadic intrusions were still present after 1 year.

Conclusion:

The presence of acute geotropic nystagmus, stronger nystagmus when turning to the fast phase side and acute or chronic head hanging paroxysmal vertical nystagmus should raise the suspicion for central AVS. Chronic geotropic and ageotropic nystagmus following AVS might be an underrecognized manifestation of vestibular compensation.

KEYWORDS

Acute Vestibular Syndrome

Positional Nystagmus

Vestibular

Semicircular Canals

Otoliths

INTRODUCTION

The use of positional testing (including the Dix-Hallpike, Mcclure, and head hanging maneuvers) as a diagnostic tool is not indicated in the acute stage or follow-up of patients presenting with *spontaneous* vertigo and nystagmus for at least 24 hours (i.e., acute vestibular syndrome, AVS), being usually avoided, among other reasons, due to head motion intolerance.[1,2] For distinguishing between central and peripheral causes of AVS, recent algorithms have been devised, based on several distinctive ocular motor features usually assessed in the upright position.[3] Nevertheless, brainstem and cerebellar lesions may also present with *positional* (persistent and/or paroxysmal) vertigo and nystagmus, with or without associated spontaneous nystagmus in the upright position.[4,5] Indeed, both central spontaneous and positional vertigo and nystagmus may co-exist in an individual patient, albeit in variable combinations.[6] To the authors' best knowledge, the presence of central paroxysmal positional nystagmus (CPPN) has not been systematically and prospectively investigated in central AVS. Another parameter with potential diagnostic utility in AVS is positional modulation of spontaneous nystagmus. In patients with peripheral AVS (i.e., vestibular neuritis), spontaneous nystagmus is more intense when patients lie on their affected ear, a finding that has been ascribed to an ipsilesional reduction of otolith function.[7,8] Studies addressing such modulation in central AVS patients are lacking. In this exploratory work with central and peripheral AVS patients, we studied the influence of head position on spontaneous nystagmus in

both groups and investigated the incidence and characteristics of CPPN in central AVS group, both in the acute phase and during follow-up.

METHODS

Study design and setting, protocol approvals, and patient consents. This was a prospective, observational, transversal and longitudinal study that enrolled patients from January 1, 2015 to January 31, 2017. The setting of recruitment was the emergency room (ER) of Coimbra University Hospital Centre, Portugal. Study protocol was approved by our Local Ethics Hospital Committee. Written informed consents were obtained from the participants, in accordance with the Declaration of Helsinki.

Participants

We recruited 30 consecutive ER patients (mean age 54.9, SD 17.0, range 22-82 years; 22 males) with AVS, 15 with central AVS (cAVS) (mean age 53.3, SD 16.6, range 23-78 years; 11 males) and 15 with peripheral AVS (pAVS) (mean age 56.5, SD 17.8, range 22-82 years; 22 males) ($p= .04$, $p> .1$, respectively). We included patients who experienced continuous vertigo or dizziness within the preceding 14 days of ER admittance (mean duration of symptoms, 6.1, SD 4.7, range 0.12-14 days) and had predominantly horizontal spontaneous nystagmus in upright position, plus one of the

following: nausea or vomiting, head motion intolerance, or new gait or balance disturbance. We excluded patients with previous vestibular or oculomotor disorder, predominant or exclusive postural vertigo or dizziness at AVS onset, and recurrence of vertigo with migraine or hearing loss during the follow-up period of 12 months. All patients underwent detailed neurological and vestibular evaluation (J.L., A.I.M.) (including the presence of spontaneous nystagmus, horizontal head impulse test [HIT], presence of skew deviation and gaze-evoked nystagmus [GEN]), video-oculography (VOG) and video-head impulse test (VHIT) on the day of ER admittance. All patients underwent diffusion-weighted head MRI between 48 hours and 14 days after symptom onset (mean duration, 9.5, SD 3.7, range 2-14 days), except one patient in whom an acute ischemic pontine stroke was evident on the head CT scan performed on the second day after symptom onset and MRI was contraindicated due to pacemaker. Examiners were not explicitly masked to neuroimaging. cAVS diagnosis required the presence of a causative lesion on neuroimaging, while pAVS diagnosis required normal neuroimaging and lack of neurological signs at onset and during the follow-up period. Apart from the presence of nystagmus, 11 (73%) cAVS patients showed additional neurological findings (table 1). Underlying lesions in cAVS patients were unilateral and circumscribed, and included medullary (n=4), pontomedullary (n=2), pontine (n=2), midbrain (n=1) and middle cerebellar peduncle (n=1) ischemic stroke and pontomedullary (n=2), pontine (n=1), cerebellar periventricular (n=1) and middle

cerebellar peduncle (n=1) demyelination. All (n=15) pAVS patients had vestibular neuritis. Seven cAVS and 8 pAVS patients had rightward lesions (p= .71). Neurovestibular exam, VOG, and VHIT were repeated at 3-month and 12-month follow-up visits (visits 2 and 3, respectively). All patients except 3 completed the study without complications. One patient died and 2 lost follow-up, between the second and third visit.

Table 1. Additional ocular motor and neurologic findings in cAVS patients.

Patient	**Etiology**	**Associated findings**
16	Right medullary infarction	Right Horner's syndrome; Leftward hypometric saccades; Right facial palsy; Right hearing loss; Right facial and left limb sensory loss
17	Right medullary infarction	Right facial palsy; Left upper and lower limb sensory loss; Dysphagia; Dysarthria
18	Left medullary infarction	Changing direction-torsional nystagmus during vertical pursuit
19	Left medullary infarction	Left Horner's syndrome; Right upper and lower limb sensory loss; Lower limb ataxia
20	Right pontomedullary infarction	Right facial palsy; Right 6th nerve palsy; Right Horner's syndrome
21	Right pontomedullary demyelination	Right gaze palsy
22	Left pontomedullary infarction	None
23	Left pontomedullary infarction	Left hearing loss
24	Right pontine demyelination	Leftward decomposed pursuit
25	Left pontine infarction	Rightward decomposed pursuit
26	Left pontine infarction	Leftward decomposed pursuit; Right limb weakness and ataxia
27	Left midbrain infarction	Ptosis; Vertical gaze palsy; Bilateral limb ataxia; Dysarthria
28	Right cerebellar (dorsolateral 4thV) demyelination	None
29	Right cerebellar (MCP) demyelination	None
30	Left cerebellar (MCP) infarction	None

cAVS, central acute vestibular syndrome; 4thV, fourth ventricule; MCP, middle cerebellar peduncle.

Video-oculography

Eye movements were recorded using binocular video-oculography (Interacoustics VO425, Assen, Denmark; 105Hz). Initially, patients sat on a chair with the head manually restrained, facing the center of a wall-projected screen, at a viewing distance of 1.5 meters. After 5-point calibration, spontaneous nystagmus was assessed without visual fixation and while fixating a centered 0.8° target, for 30s each. Gaze evoked nystagmus was assessed while fixating an identical target, located ±30° horizontally and ±20° vertically. During pursuit, the target was moved sinusoidally 60° horizontally and 40° vertically with a starting velocity of 10°/s. During saccades, the target was randomly stepped between 5° and 30° horizontally and vertically. Post-head shaking nystagmus without visual fixation was induced by manually shaken horizontally the patient's head ~30° flexed at a rate of about 3 Hz with an amplitude of about ±15° for 15 s, observing for nystagmus during 60s. Vibration nystagmus was induced by placing a handheld Brookstone Mini Muscle Massager (100 Hz) against the right and left mastoid prominence for 30s on each side. Positional nystagmus was assessed without fixation for ~30s in the following positions: immediately after lying down from sitting with the head straight and ~30° flexed and then rotated ~90° to the sides (i.e., Mcclure maneuver), and after head-hanging from sitting, with the head straight and ~30° extended (head-hanging maneuver) followed by a similar maneuver with the head

rotated ~45° to the sides (i.e., Dix-Hallpike maneuver). Patients were asked to keep their eyes in the straight-ahead position to avoid contamination from GEN. Nystagmus in Mcclure positions was further classified as bilateral unidirectional (i.e., beating toward the same direction in both positions), bilateral ageotropic (i.e., beating toward the ceiling in both sides), bilateral geotropic (i.e., beating toward the ground in both sides), unilateral geotropic or ageotropic (i.e., nystagmus was absent in one side) or absent in both sides. Mean slow phase velocity (SPV) of horizontal nystagmus was analysed using built-in software. Vibration nystagmus data was not available in visit 1 in 8 patients (5 cAVS; 3 pAVS) and in visit 2 in 5 (3 cAVS; 2 pAVS). All video and tracing recordings (n=783) were visually inspected off-line (J.L., A.I.M.) to ensure correct eye position and nystagmus stability.

Identification of central paroxysmal positional nystagmus (CPPN)

CPPN was defined as a transient decaying vertical or horizontal nystagmus induced by positional changes which was not resolved with repeated canalith repositioning maneuvers designed for benign paroxysmal positional vertigo and was associated with a causative lesion on neuroimaging.[4]

Video-head impulse test

For quantitative analysis of the vestibulo-ocular reflex (VOR) during high acceleration head rotations, monocular video-oculography (EyeSeeCam, Munich, Germany; 250Hz) was used. In brief, patients' head was briskly moved in the maximally-excitatory direction for each horizontal semicircular canal plane (e.g., rightward rotation, for the right horizontal semicircular canal) by the examiner while fixating a visual target at 1.5-meter distance. 20 valid trials were performed for each side. VOR gain (eye velocity divided by head velocity at 60 milliseconds) was calculated with built-in software.

MRI

MRI (Magnetom Symphony 3 Tesla) protocol (MPRAGE T1 3D and 3D T1 sequence [VIBE] FS before and after gadolinium injection; DWI [b0 and b1000 images]; FLAIR and DP-T2 [3-mm-thick axial slice, 0.9-mm gap]; T2* [4-mm-thick axial slice, 1.2-mm gap]; 3D heavily T2W sequence [CISS]) was performed in 29 patients.

Statistical analysis

Normality of the data was determined using the Shapiro-Wilk test. Within each group, the mean horizontal SPV was compared between Mcclure positions: head rotated

towards the side of the slow phase of nystagmus versus head rotated towards the side of the fast phase of nystagmus. Slow phase and fast phase head rotation sides were ascribed based on the directions of the slow and fast phase of nystagmus in upright position in visit 1 and remained so for the rest of the study. Of note, SPV comparisons were only performed in assessments where nystagmus was unidirectional and present in both rotation sides. As this prerequisite was often absent in visits 2 and 3 in both groups, this was only performed for the first visit. The affected side in cAVS patients corresponded to the side of the causative lesion on neuroimaging whereas in pAVS patients corresponded to the side of the slow phase of nystagmus observed in upright position in the first visit. The Mann-Whitney test was used to compare VOR gain (VHIT) between-groups both in the affected and non-affected side in the 3 visits. The Wilcoxon-signed rank test was used to compare mean SPV between Mcclure positions. Univariate cubic regression analysis was performed to evaluate the influence of VOR gain (VHIT) on SPV and direction of nystagmus during Mcclure positions. Kappa coefficient was used to estimate the overall level of agreement for the presence of nystagmus inversion between supine and upright assessments. Correction for multiple comparisons to control for family-wise error was performed using the Bonferroni method for between-, within-groups and kappa analysis, and the corrected level of significance was set at 0.008 (0.05/6), 0.025 (0.05/2) and 0.025 (0.05/2), respectively. Statistical analysis was performed using SPSS 21 (IBM Corp., Armonk, NY).

RESULTS

Upright Findings

On visit 1, all pAVS patients had an abnormal HIT and absence of GEN. Skew deviation was present in 2 (13%). In cAVS group, HIT was normal in 7 (48%), and GEN and skew deviation were present in 6 (40%) patients, each. Nystagmus direction during HST and mastoid vibration was concordant with that of spontaneous nystagmus in 12/12 (100%) pAVS and 8/10 (80%) cAVS patients. In 4 (27%) cAVS patients, spontaneous nystagmus was beating toward the lesion side. On the following visits, results were heterogenous in both groups. Spontaneous, HST and/or vibration-induced nystagmus inverted their direction in one or the two visits in the majority (n=25; 83%) of patients. Only in 5 (17%) patients (3 pAVS; 2 cAVS), nystagmus direction remained unchanged in all upright tests during the study period. VOR gain between pAVS and cAVS groups was significantly different only in visit 1, and only on the affected side, being lower in pAVS group (pAVS: mean 0.30 SD 0.19, range 0.00-0.63; cAVS: mean 0.66 SD 0.25, range 0.07-1.03; $p < .001$) (table 2).

Supine Horizontal Nystagmus

On visit 1, in the majority (n=12, 80%) of pAVS patients, nystagmus in Mcclure positions was bilateral unidirectional, matched the direction of spontaneous nystagmus in upright position and showed greater SPV when the head was turned to the slow phase side (i.e., the affected side) (mean SPV [SD] slow phase side, 17.6 [14.7]°/s vs. fast phase side, 10.5 [10.4]°/s, p< .001). In the remaining (n=3, 20%) patients, nystagmus was bilateral ageotropic in 1 and unilateral (i.e., present only in the slow phase side) ageotropic in 2. In sum, all pAVS patients showed ageotropic nystagmus when turned to the slow phase side. In cAVS group, results were distinct. From the 9 (60%) patients who showed bilateral unidirectional nystagmus in Mcclure positions, 5 patients showed greater SPV when the head was turned to the slow phase side, but 4 showed greater SPV when the head was turned to the fast phase side (mean SPV [SD] slow phase side, 6.3 [6.5]°/s vs. fast phase side, 4.2 [2.7] °/s, p= .407). In the remaining (n=6, 40%) patients, 2 showed bilateral geotropic, 1 showed bilateral ageotropic, 2 showed unilateral (i.e., present only in the slow phase side) ageotropic and 1 showed unilateral (i.e., present only in the fast phase side) geotropic nystagmus. Thus, 4 cAVS patients showed either geotropic (n=3) or no nystagmus (n=1) when their head was turned to the slow phase side, while the remaining showed ageotropic nystagmus on that side (table 3). On the following visits, in the majority of patients in both groups, bilateral

unidirectional forms of nystagmus were progressively replaced by either bilateral or unilateral ageotropic and geotropic forms. Of note, after 1 year, 8 out of 27 (30%) patients no longer had spontaneous nystagmus in upright position, but the majority (n=7) still demonstrated supine horizontal nystagmus (table 2 and 3).

Table 2. Clinical data in upright position.

Patient	Gender	Age	Visit 1								Visit 2						Visit 3					
			S	HST	V		VHIT		Skew	GEN	S	HST	V		VHIT		S	HST	V		VHIT	
					R	L	R	L					R	L	R	L			R	L	R	L
Peripheral AVS																						
1	f	47	→	→			0.10	1.03	-	-	←	-			0.99	0.92	-	-	→	-	0.97	0.90
2	m	31	→	→	→	→	0.42	0.79	-	-	→	→	→	-	0.80	0.99	→	→	-	→	0.88	1.04
3	m	22	→	→			0.00	0.84	-	-	→	→			0.94	1.20	-	←	-	→	0.94	1.00
4	m	79	→	→			0.36	0.96	-	-	→	-	→	→	0.49	0.78	→	- →			0.62	0.92
5	m	79	→	→	→	→	0.17	0.87	-	-	-	→	→	→	0.24	0.78	→	→	→	→	0.26	0.76
6	m	56	→	→	→	→	0.11	0.76	-	-	→	←	-	-	0.77	0.80	-	→	←	→	0.97	1.01
7	m	69	→	- →	→	→	0.63	0.93	-	+	←	- →	-	→	0.69	0.97	←	- →	→	→	0.80	0.99
8	m	50	→	→	→	→	0.06	0.74	-	-	→	- →	→	→	0.43	0.92						
9[a]	m	38	→	→	→	→	0.62	1.05	-	-	→	-	←	←	0.84	1.05	→	-	←	→	0.95	0.95
10[a]	m	82	→	→	→	→	0.29	0.88	-	+	→	→	←	→	0.82	0.98	→	→	←	←	0.86	0.83
11[a]	f	64	→	→	→	→	0.33	0.70	-	-	→	- →	→	→	0.90	0.89	→	- →	→	←	0.87	0.89
12[a]	m	60	→	→	→	→	0.25	0.76	-	-	→	→	-	→	0.70	0.98	→	→	→	→	0.65	0.72
13[a]	f	70	→	→	→	→	0.58	0.84	-	-	→	←	←	-	0.87	0.94	→	→	→	→	0.83	0.86
14[a]	m	49	→	- →	→	→	0.27	0.78	-	-	←	- →	←	←	0.60	0.92	←	←	→	-	0.81	0.72
15[a]	f	53	→	→	→	→	0.32	0.75	-	-	←	-	-	→	1.04	0.96	←	→	- →	→	0.99	0.89
Central AVS																						
16	m	55	→	→	→	→	0.80	0.82	+	+	→	←	←	←	0.62	0.63	←	←	←	←	0.80	0.82
17	m	53	→	→	→	→	0.64	0.64	-	-	←	→	-	→	0.89	0.84	←	→	→	←	0.96	0.95
18[a]	m	46	←	←			0.79	0.90	+	-	←	- →	←	←	0.89	1.03	←	←	←	←	0.94	0.97
19[a]	m	61	→	→			0.82	0.91	-	+	→	-			0.82	0.91	-	←	←	←	0.95	1.09
20	m	52	←	→	→	→	0.45	0.90	+	-	←	←	←	→	0.87	0.87	←	←	→	→	0.92	0.97
21	f	36	←	←			1.03	0.98	-	+	←	←			1.03	0.98	←	←	←	←	1.03	0.98
22[a]	f	47	→	→	→	→	0.42	0.90	-	+	→	→	→	-	0.67	1.02	→	→	→	→	0.87	0.84
23[a]	m	63	→	→			0.07	0.74	+	-	→	→	→	←	0.67	1.10	-	→	←	→	0.83	0.86
24	m	47	→	→	→	→	0.47	0.84	-	-	←	→	←	←	0.70	0.98						
25[a]	m	78	→	→	→	→	0.51	1.06	-	+	→	→	←	-	0.62	0.91						
26[a]	m	67	←	←	←	-	0.60	0.78	-	-	-	← -	-	←	0.78	0.76	-	→	←	→	0.75	0.67
27[a]	m	69	→	-			0.70	0.64	+	-	-	-			0.70	0.64	→	→	→	-	0.64	0.64
28	m	26	→	→	→	→	0.78	0.97	-	-	→	←	-	-	0.90	1.02	→	-	-	-	0.89	1.07
29	f	23	→	←	←	←	0.98	0.87	-	+	→	-	←	←	0.92	1.13	-	←	-	←	0.78	0.84
30[a]	f	77	→	→	→	→	0.92	0.85	+	-	→	→	→	→	1.06	0.99	-	→	→	→	0.88	0.90

[a]leftward lesions were transformed into rightward lesions, for sake of clarity; ← , nystagmus fast phase beating toward the right (from the patient's perspective); → , nystagmus fast phase beating toward the left (from the patient's perspective); - → , nystagmus fast phase beating toward the left subsequently inverted its direction to the right; -, absence of nystagmus; empty cells reflect lack of measurement; AVS, acute vestibular syndrome; f, female; m, male; R, right; L, left; VN, vestibular neuritis; Med, medullary; PonMed, pontomedullary; Pon, pontine; Mid, midbrain; Cer, cerebellar; I, infarction; D, demyelination; S, spontaneous nystagmus; HST, head shaking test; V, vibration; VHIT, video-head impulse test; Skew, skew deviation; GEN, gaze-evoked nystagmus; 4thV, fourth ventricule; MCP, middle cerebellar peduncle.

Table 3. Clinical data in supine position.

Patient	Visit 1			Visit 2			Visit 3		
	SP	HS	FP	SP	HS	FP	SP	HS	FP
Peripheral AVS									
1			-	-	-	-		-	
2				-		-	-		-
3						-			
4									
5				-					
6							-	-	.
7			-						
8									
9							-	-	-
10								-	
11								-	
12						-	-	-	
13				-			-		-
14									
15									
Central AVS									
16				-					
17									
18						-			
19			-		-			-	
20									
21									
22							-	-	
23								-	-
24				-					
25				-		-			
26				-	-				
27	-			-	-	-	-		
28									
29		-		-	-	-			
30			-				-		

AVS, acute vestibular syndrome; SP, slow-phase side supine; FP, fast phase side supine; HS, head straight supine; ←, nystagmus beating toward the slow phase side; →, nystagmus beating toward the fast phase side; - →, nystagmus beating toward the fast phase side subsequently inverted its direction to the slow phase side; -, absence of nystagmus; for criteria for selection of slow and fast phase side, see text for details; for each assessment, the greater the number of superimposed arrows, the higher was the slow phase velocity (SPV) value; empty cells reflect lack of measurement

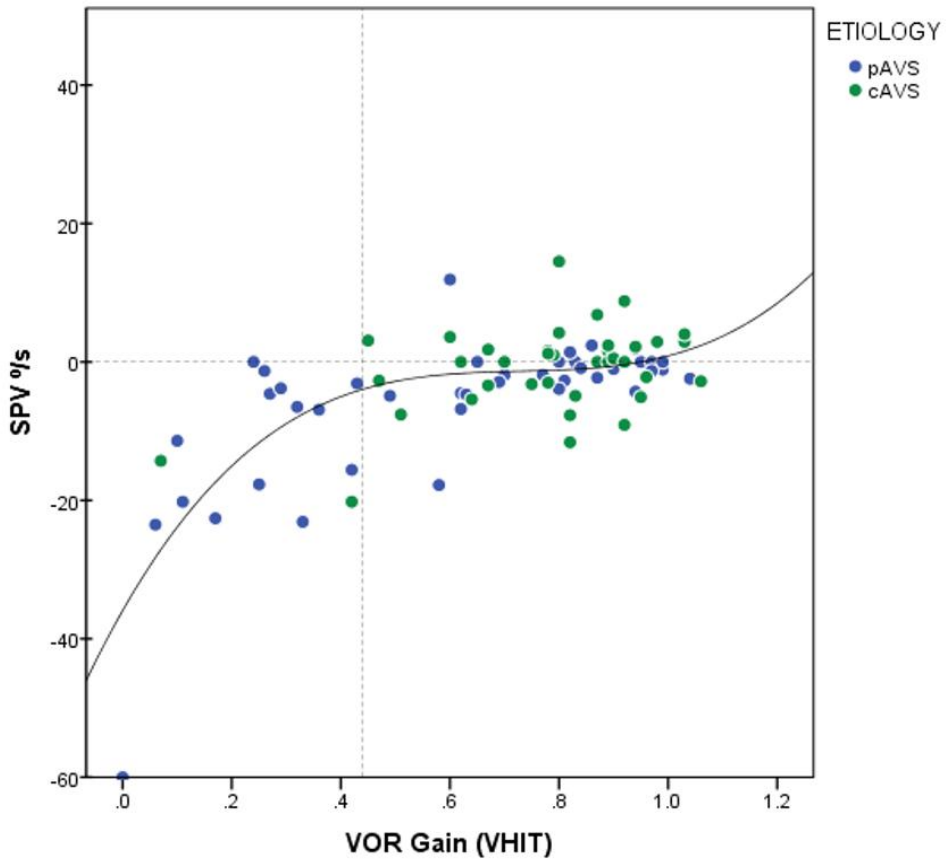
Influence of VOR gain (VHIT) on supine horizontal nystagmus

Univariate regression analysis showed a significant influence of VOR gain on the SPV and direction of nystagmus during Mcclure positions in a cubic fashion (R^2= .546; p< .001). Specifically, lower VHIT values on one side were associated with greater nystagmus SPV and the presence of ageotropic nystagmus when the head was turned to that side. Indeed, all patients with VOR gain values below 0.44 had positional ageotropic nystagmus on that side. As the VOR gain increased, such influence was changed and both low SPV ageotropic and geotropic nystagmus were common in pAVS and cAVS groups (figure 1).

Nystagmus inversion agreement between positions

Nystagmus often inverted its direction in supine position in relation with the original direction of spontaneous nystagmus in upright position in visit 1. This occurred in 21 (70%) (11 pAVS; 10 cAVS) patients in 1 or more visits (table 2 and 3). The percentage of agreement between supine and upright assessments for the presence of nystagmus inversion was 78.9% (kappa=0.59, p< .001) in the pAVS group and 57.1% (kappa=0.14, p= .404) in the cAVS group.

Figure 1. Univariate regression analysis between VOR gain and SPV and direction of nystagmus of ipsilateral supine position.

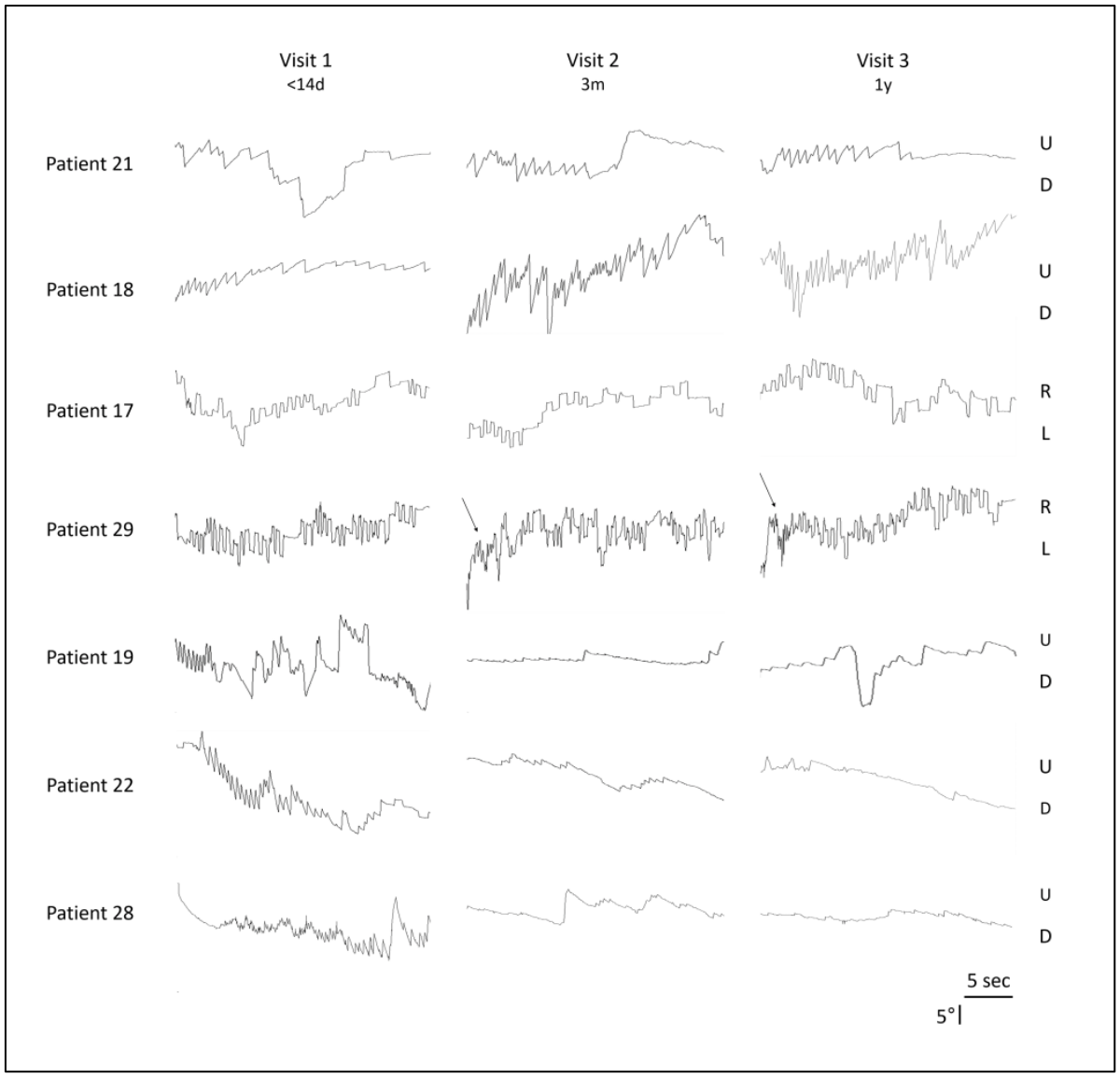


Negative SPV values correspond to ageotropic nystagmus, positive SPV values correspond to geotropic nystagmus and 0 value corresponds to absence of nystagmus. °/s, degrees per second; VHIT, video-head impulse test; pAVS and cAVS, peripheral and central acute vestibular syndrome; VOR, vestibulo-ocular reflex; SPV, slow phase velocity. Horizontal dashed line corresponds to 0°/s SPV and vertical dashed line corresponds to 0.44 VOR gain threshold. See text for details.

Central paroxysmal positional nystagmus (CPPN)

CPPN was present in 5 (33%) cAVS patients as downbeat (n=2) and upbeat (n=3) CPPN. CPPN was brought up only in straight head hanging and/or Hallpike positions. Upbeat CPPN was present only in the first visit whilst downbeat CPPN remained throughout the study period. Mean SPV of CPPN was 24.4 SD 14.5, range 12.90-50°/s. Two other cAVS patients showed positional ocular flutter and/or square wave oscillations, which also remained unchanged throughout the study period. CPPN was associated with medullary, pontomedullary and cerebellar periventricular lesions, while positional saccadic intrusions were associated with medullary and middle cerebellar peduncle lesions (figure 2).

Figure 2. CPPN and positional saccadic intrusions in head hanging positions



Patients 21 and 18 showed downbeat CPPN, while patients 19, 22 and 28 showed upbeat CPPN. Patients 17 and 29 showed continuous square wave jerks (saccadic intrusions with intersaccadic interval) which were not present in upright position. In patient 29, in visits 2 and 3, a 2-second positional ocular flutter (i.e., saccadic intrusion without intersaccadic interval) was initially present (arrows). All tracings shown were recorded during straight head hanging position, except for patients 19 (right Hallpike) and 22 (left Hallpike). In patients 21, 18, 19, 22 and 28, eye movements up (U) are represented by an upward deflection of the tracing, whereas down (D) are represented by a downward deflection. In patients 17 and 29, eye movements to the right (R) are represented by an upward deflection of the tracing, whereas to the left (L) are represented by a downward deflection. CPPN, central paroxysmal positional nystagmus

DISCUSSION

Our prospective study systematically addressed for the first time the clinical utility of positional testing in pAVS and cAVS, both in the acute stage and during follow-up. Our main findings are as follows. During the acute stage, only in cAVS patients, horizontal nystagmus in supine position inverted its direction when turning the head to the side of the slow phase or its intensity increased when turning the head to the side of the fast phase. In pAVS patients, neither of these signs was present in the acute stage. About half of cAVS patients showed CPPN or continuous saccadic intrusions on positional testing. During follow-up, supine unidirectional nystagmus was progressively replaced by ageotropic and geotropic nystagmus in both groups. Downbeat CPPN and positional saccadic intrusions remained throughout the study while upbeat CPPN was only observed in the acute stage.

In acute pAVS patients, spontaneous nystagmus beated away from the affected side in upright position, a finding which in vestibular neuritis, is believed to reflect a vestibular tone imbalance caused by an ipsilateral reduction of semicircular canal function.[9] Importantly, the intensity (i.e., SPV) of spontaneous nystagmus consistently increased when they laid on their affected ear and decreased (or even became absent) when they laid on their non-affected ear, indicating a modulation of the vestibular imbalance by gravity. Such phenomenon has been ascribed to the co-existent ipsilesional reduction of the otolith function in vestibular neuritis,

which is believed to indirectly and/or directly modulate positional nystagmus intensity.[7,8] Specifically, in a normal individual, otoliths among other functions, predominantly respond to ipsilateral head roll and seem to reduce/suppress vestibular imbalance between semicircular canal signals, if present. Thus, if otolith function is reduced in one side, it will no longer suppress a co-existent semicircular canal-related vestibular imbalance when the head is rolled toward that side.[7,8] On the contrary, turning the head to the non-affected side will activate a normal functioning otolith organ which will dampen or supress the above-mentioned asymmetry. An alternative, non-mutually exclusive explanation for modulation of spontaneous nystagmus by gravity is based on the increasingly amount of evidence emphasizing the direct role that otoliths seem to play in the generation/modulation of horizontal nystagmus.[10] Namely, if there is a sensory conflict between the internal representation of gravitational direction by the central nervous system (estimated by different body sensors, including the semicircular canals, otoliths, visual system, etc) and the gravitational direction estimated exclusively by the otolith organs, this by itself might lead to nystagmus or modulate pre-existent nystagmus.[11] Thus, in patients with vestibular neuritis, a reduction of the otolith input when lying on their affected ear may increase the difference between the internal representation of the gravity vector and the gravity vector estimated by the otolith organs, which can lead to an increase of the SPV, as seen in our patients.[8] Over time, nystagmus when lying to the non-affected ear inverted its direction (i.e, become ageotropic) in a substantial proportion of pAVS patients, while remaining ageotropic when

lying to the affected ear (i.e., bilateral ageotropic nystagmus). Less often, nystagmus inverted its direction when lying to the affected ear (i.e, become geotropic), while remaining geotropic when lying to the non-affected ear (i.e., bilateral geotropic nystagmus). The underlying mechanisms for these longitudinal changes are not known[12]. We offer a theoretical model to account for these changes, both in the acute stage and follow-up of AVS patients (figure 3). Concerning pAVS patients, we believe that the emergence of the above-mentioned direction-changing positional nystagmus (i.e., bilateral ageotropic and bilateral geotropic) reflects the ongoing vestibular compensation occurring in both vestibular nuclei after acute peripheral unilateral vestibular deafferentation[13]. In a normal individual with the head straight in supine position, each vestibular nucleus receives equal input from the ipsilateral peripheral afferent neurons and thus the average resting discharge is approximately equal in both nuclei. If the head is turned to one side, vestibular neurons on that side will increase their firing, whilst vestibular neurons in the opposite side will simultaneously decrease their firing (figure 3).[13] In the acute stage of vestibular neuritis however, resting discharge drastically drops in the ipsilesional nucleus while increasing simultaneously in the contralesional nucleus.[13]. Thus, turning the head to the affected side will increase the firing demand on an already hypoactive nucleus, thus accentuating the vestibular imbalance and increasing ageotropic nystagmus intensity. Turning the head to the non-affected side will decrease the firing demand on the affected nucleus and will have an opposite effect on nystagmus intensity (Figure 3, A). Over time, cells in the ipsilesional nucleus commence firing again, while cells in the contralesional

nucleus, at least at early stages of compensation, decrease their firing, until a "rebalance" of activity between the two vestibular nuclei is achieved[13]. Regaining of activity in the ipsilesional nucleus may be promoted by axonal sprouting, denervation sensitivity, down-regulation of gamma-aminobutyric acid (GABA) receptors, progressive reduction in commissural inhibition and/or reweighting of the cervicospinal efferent inputs, while lessening of activity in the contralesional nucleus may be a reflection of descending cerebellar floccular inhibition to "shut down" vestibular nucleus activity[13–15]. At this phase, as a result of the decrease in neuronal activity in the non-affected vestibular nucleus, turning the head to the non-affected side will "unmask" the contralesional hypoactivity while "masking" the ipsilesional hypoactivity, by increasing the firing demand on the contralesional nucleus while simultaneously decreasing such demand on the ipsilesional nucleus, respectively. This will transiently invert the vestibular imbalance and promote the inversion of nystagmus (i.e., becoming ageotropic) when lying towards the non-affected side (Figure 3, B-C). If neuronal activity in the ipsilesional nucleus is ultimately restored up to a normal level while remaining below normal levels in the contralesional nucleus, nystagmus quick phase direction may actually beat towards the lesion both when lying with the affected ear down an up (Figure 3, D). In pAVS patients showing bilateral geotropic nystagmus, we further speculate that a hyperactive neuronal response of both vestibular nuclei might have developed. Specifically, if during vestibular compensation, the resting activity of the ipsilesional nucleus is restored up to a level that exceeds its normal prelesional discharge

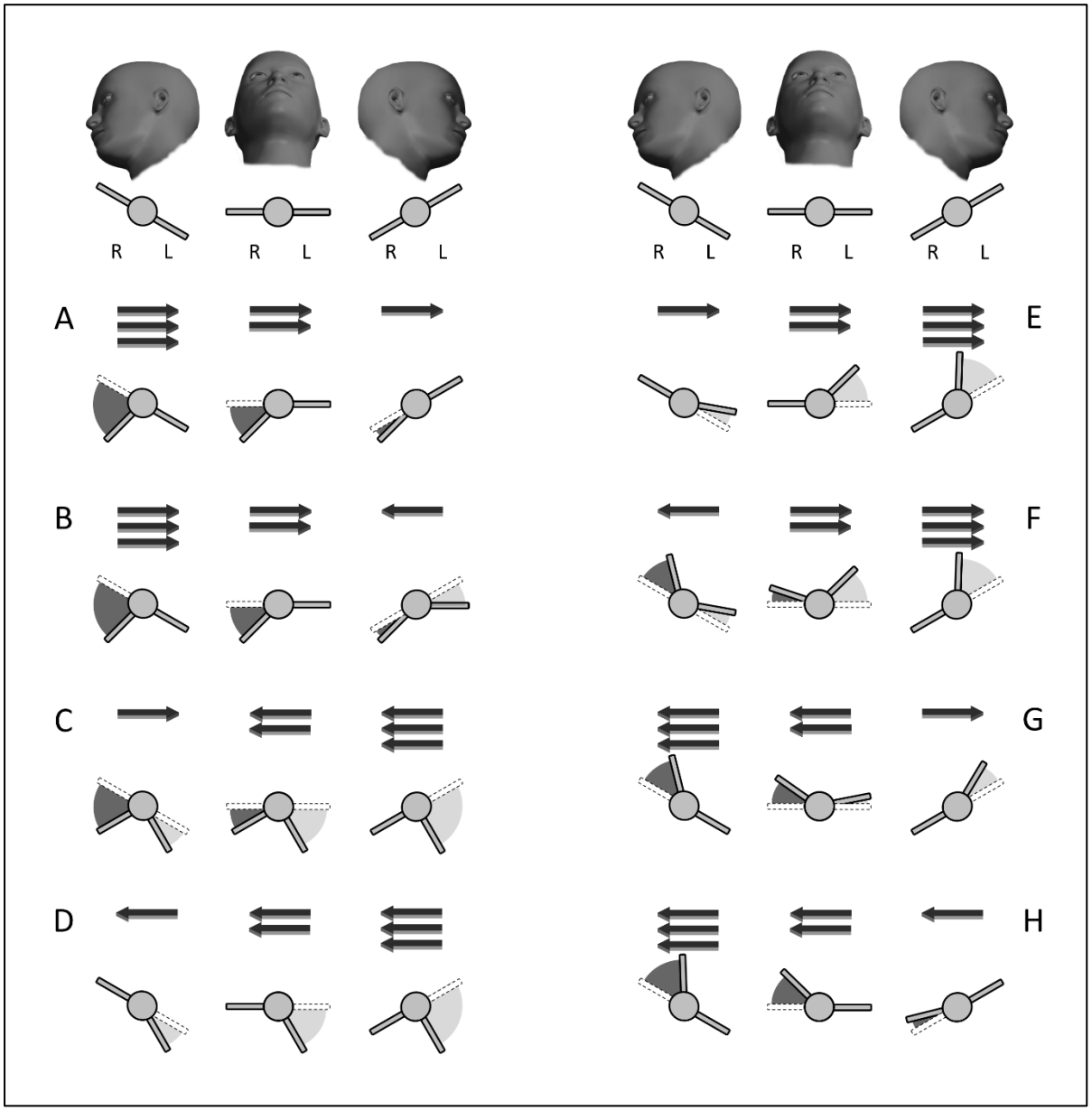
level (i.e., an hypercompensatory state), lying to the affected side will enhance such hyperactivity and will induce geotropic nystagmus, by mimicking a contralateral vestibular hypofunction. Lying to the non-affected side will produce an identical type of nystagmus (i.e., geotropic), since contralesional vestibular hyperactivity is the expected response to counteract the development of ipsilesional hyperactivity, in order to regain vestibular balance (Figure 3, F-G). Indeed, hyperactive caloric responses have been documented in vestibular neuritis, albeit only in the contralesional side[16]. Still, comparison between supine head rolling and caloric responses must be made with caution, since each response reflects the stimulation of the vestibular system at a different frequency, and vestibular disease may only affect a selected frequency range, producing disparate results between tests.[17,18]

In cAVS patients, bilateral geotropic nystagmus was already observed in the acute stage, albeit only when VOR gain (VHIT) was above 0.44. Indeed, below this level, positional nystagmus was always ageotropic, regardless of group, side or visit number. As VHIT consists high-frequency vestibular responses, it seems then that moderate to severe reduction of high-frequency responses is accompanied by a similar trend in low-frequency responses (i.e., vestibular nucleus hypoactivity is manifested both during high and low acceleration responses, producing low gain VHIT and ageotropic nystagmus on ipsilateral supine head rolling, respectively). In contrast, mild reduction of high-frequency responses may be associated with either ageotropic or geotropic nystagmus on that side. Here, vestibular neurons may respond differently to high- and low-frequency head movements, demonstrating

simultaneously hyperactivity during low-frequency responses (i.e., geotropic nystagmus, according to our model) and hypoactivity during high-frequency responses (i.e., VOR gain on VHIT below 1). For explaining the presence of bilateral geotropic nystagmus in the acute stage in cAVS patients, one could argue that early hypercompensatory responses might appear in cAVS patients due to the presence of relatively higher VHIT gains when compared to pAVS patients in the acute phase. However, a more plausible explanation resides in the fact that some of these patients probably show hyperactive vestibular responses *a priori* as a result of a deficient cerebellar floccular inhibitory input over the vestibular nuclei due to disruption of the fiber tracts connecting these structures[18]. Indeed, high VOR responses during low frequency stimulation have been reported in floccular lesions[18]. Also, in the acute stage, the finding of greater SPV when turning the head towards the quick phase side in these patients points to an initial unilateral desinihibition/hyperactivity of one vestibular nucleus, not yet compensated by a similar response in the contralateral nucleus (Figure 3, E, H). Interestingly, in the acute stages of Meniére´s disease, in which transient hyperactivity of one labyrinth ("irritative" phase) has been hypothesized, greater SPV when turning the head towards the quick phase side has been documented[19]. The emergence of chronic direction-changing positional nystagmus in cAVS patients probably shares the same underlying mechanisms as for pAVS patients. Positional geotropic and ageotropic nystagmus over time as a manifestation of vestibular compensation seems to be further corroborated by the significant agreement found between direction-changing positional nystagmus and inversion

of spontaneous nystagmus, HST, and/or during vibration testing in upright position, at least in the pAVS group. Nystagmus inversion in the latter assessments in upright position has been considered a classic sign of vestibular compensation[17,20].

Figure 3 title: Hypothetical mechanism for positional modulation of spontaneous nystagmus in acute vestibular syndrome.



In the upper segments, head rotation to the right, head straight, and head rotation to the left in supine position have their correspondent pattern of vestibular nuclei activation depicted below (i.e., right [R] line up and left [L] line down indicate right vestibular nucleus activation/increased level of neuronal discharge and left vestibular nucleus inhibition/decreased level of neuronal discharge, respectively, during head rotation to the right; right and left line at the same level, indicate the same level of neuronal activity in both nuclei, during head straight; right line down and left line up indicate right vestibular nucleus inhibition/decreased level of neuronal discharge and left vestibular nucleus activation/increased level of neuronal discharge, respectively, during head rotation to the right). From A to H, several patterns of positional nystagmus are shown (arrows point towards the quick phase of nystagmus; the greater the intensity [i.e., slow phase velocity] of nystagmus, the greater the number of superimposed arrows), reflecting presumable hypoactivity (A-D) and hyperactivity (E-H) of one or the two vestibular nuclei. In each segment (A-H), when the intended/estimated level of neuronal discharge in the vestibular nucleus is not matched by the real level of neuronal discharge, a dashed white line represents the former and a solid grey line represents the later. An intended/estimated level of neuronal discharge above the real level indicates hypoactivity while the opposite situation indicates hyperactivity. Dark and light grey sectors bridging the two lines represent the difference between the estimated and real neuronal level of discharge in right and left vestibular nucleus, respectively. See text for details.

Vertical CPPN was seen in one third of the cAVS patients. Importantly, none of these patients reported increased vertigo when lying down, in the acute stage. Thus, in the absence of predominant positional vertigo, CPPN may go unnoticed in AVS patients, if positional testing is not undertaken. The pathophysiology of downbeat CPPN has been recently investigated[4]. Lesions usually affecting the cerebellar nodulus and uvula presumably cause a mismatch between the gravitational orientation estimated by the vertical semicircular canals and the otoliths along with a deficient feedback loop which normally provides a correction for such error in a real-time fashion[4]. Upbeat CPPN probably shares a similar mechanism, although the distortion of the semicircular canal-related signals might be qualitatively different in nature[21]. Why upbeat CPPN disappeared and downbeat CPPN remained in our patients over time is an intriguing question which we were not able to answer and deserves further research. Interestingly, a similar progression in time is found between *spontaneous* forms of upbeat and downbeat nystagmus[22]. Up to now, ocular flutter and square wave oscillations augmented by positional maneuvers had been described in patients with degenerative ataxia, in whom a causative focal strategic lesion had not been found, apart from generalized cerebellar disease[23]. Two of our patients showed positional augmentation of saccadic intrusions in association with middle cerebellar peduncle and medullary lesions. Although the mechanism is unclear, damage of pathways and/or structures (e.g., prepositus hypoglossi nucleus) mediating normal saccadic-vestibular interaction might transiently

impair the brainstem horizontal saccade network, pecifically when the head assumes a new position in space and selected vestibular tracts are activated[24].

Our results are limited because of the reduced number of patients. Additionally, comparison of nystagmus intensity between different head positions was performed in dark using quantitative analysis. Caution is necessary when extrapolating these results to the bedside assessment, as minor differences between sides or brief nystagmus inversion in one side may go unnoticed. Also, the time points chosen for this study (i.e., <1/2, 3 and 12 months) most probably did not capture the dynamics of the vestibular compensation process in its entirety, since hypothetically one patient may have alternated between geotropic and ageotropic nystagmus several times during the study period. The use of additional vestibular testing using low-frequency stimulation (i.e., caloric responses and rotatory chair) could have shown better agreement and stronger correlation with positional testing data.

CONCLUSION

We have shown that performing positional testing routinely in patients with acute vestibular syndrome offers several advantages. In the acute phase, the presence of (i) supine geotropic nystagmus on the slow phase side, (ii) augmentation of nystagmus when lying on the fast phase side, (iii) transient decaying intense vertical nystagmus in head hanging positions which does not resolve with repositioning maneuvers and/or (iv) an increased rate of saccadic intrusions during head hanging positions should raise the suspicion for central AVS. In the

chronic phase, the maintenance of the latter 2 signs, should also point towards the same diagnosis. Additionally, just as inversion of spontaneous nystagmus direction in upright position, after head shaking and during vibration testing has been regarded as a classic sign of vestibular compensation in AVS, the emergence of positional geotropic and ageotropic nystagmus over time should be regarded the same way. The latter possibly reflect hyperactivity and hypoactivity of the vestibular nuclei, respectively.

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