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Original Article

Is Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome (CANVAS) a Vestibular Ganglionopathy?

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OBJECTIVES: CANVAS is an acronym for cerebellar ataxia, neuropathy and vestibular areflexia syndrome. Limited autopsy data has suggested that CANVAS is caused by a focal dorsal root ganglionopathy that damages Scarpa's (vestibular) ganglion, but spares the Spiral (hearing) ganglion. If the vestibular areflexia of CANVAS is in fact due to ganglionopathy, then there should be global reduction of all vestibular responses.

MATERIALS and METHODS: With this hypothesis in mind, a retrospective review of 5 subjects who met the clinical criteria for CANVAS was performed. Recent advances in vestibular testing have made it possible to quantify responses from all 5 vestibular end organs in the inner ear. Results of the Video head impulse test (VHIT), video oculography, caloric test and vestibular evoked myogenic potential (VEMP) were examined to determine if all 5 end organs are nonfunctional in CANVAS.

RESULTS: Severe reduction of function of the six semicircular canals and ocular VEMPs were observed. Only the cervical VEMPs were present and reproducible, consistent with either partial sparing of the inferior vestibular ganglia, specific embryologic resistance of the saccule to the degeneration or a mechanism for cervical VEMPs that does not require an intact vestibular ganglion.

CONCLUSION: Our results suggest that Scarpa´s ganglia dysfunction could be the mechanism for loss of semicircular canal and utricular function in CANVAS patients, but the preservation of the cervical VEMP response is unexplained.

KEYWORDS: Cerebellar ataxia, vestibulopathy, neuronopathy, ganglionopathy, video head impulse test, VEMP

INTRODUCTION

Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS) is a recently described progressive neurodegenerative multisystemic disease whose exact prevalence remains unknown. About 2% of patients with bilateral vestibular weakness in our clinic have CANVAS, but it probably makes up just a tiny number of patients worldwide [1]. This syndrome appears mainly sporadically and occasionally affects siblings. While it has been suggested that CANVAS is a late-onset recessive disorder [2], there may be other variants with different inheritance as well [3].

The vestibular areflexia and sensory loss in CANVAS have been attributed to a sensory neuropathy that affects the dorsal root ganglia [4]. Post-mortem histopathological studies of three patients showed marked loss of Purkinje cells (predominantly in the vermis and lateral cerebellum) and of Scarpa's, trigeminal, and facial ganglion cells but not of spiral ganglion (hearing) cells [4]. The auditory nerve, vestibular end organs (cristae and maculae), and brainstem were unaffected. These findings suggest that the vestibular areflexia of CANVAS is due to neuronopathy (vestibular ganglionopathy) [4-6].

Patients with CANVAS also have a non-length-dependent, multimodality sensory deficit. Sensory potentials show a loss of upper and lower limb responses in these patients. However, motor nerve conduction is almost completely preserved [7]. This suggests that sensory deficits in CANVAS are due to dorsal root ganglionopathy rather than a "neuropathy," which would typically affect both motor and sensory function as well as be length dependent.

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A dorsal root ganglionopathy explains both vestibular areflexia and sensory loss, and might also produce sensory ataxia symptoms resembling cerebellar damage, but without any actual cerebellar lesion, due to deafferentation of the cerebellum. The CANVAS literature suggests that the "CA" portion of CANVAS requires impaired tracking of visual targets, gaze-evoked nystagmus or vertical down-beating nystagmus [8].

The video head impulse test (vHIT) has refined vestibular diagnosis of peripheral vestibular disorders. The multiaxial VHIT is a valuable tool to measure function of all semicircular six canals. The vestibular nerve is composed of a superior branch that transmits sensory information from the superior and horizontal semicircular canals as well as the utricle, and an inferior branch transmitting information from the saccule and posterior canal. In CANVAS, degeneration of the vestibular ganglion (superior and inferior portions) should cause a global canal hypofunction on vestibular testing of the semicircular canals, and there should be no responses from the otoliths as well. By combining the VHIT and vestibular-evoked myogenic potentials (VEMP) tests, it is possible to assess all five sensory end organs of the vestibular system. Accordingly, to test the hypothesis that the CANVAS is a ganglionopathy disease of vestibular system, we examined these data in five patients with CANVAS.

MATERIALS AND METHODS

In a retrospective chart review, over 4570 patients met the inclusion criteria for clinically definite CANVAS as proposed by Szmulewicz and colleagues [9]. Our patients had (a) impaired horizontal visually enhanced vestibulo–ocular reflexes-VVOR; (b) radiologic evidence of cerebellar atrophy; (c) abnormal nerve conduction testing showing a predominant sensory impairment (sensory potential (SNAP) documented) and sensory symptoms; d) genetic tests for SCA 3 (spinocerebellar ataxia type 3) and Friedreich's ataxia. Tests for Vitamin E, B1, and B12 deficit, paraneoplastic or medical conditions that induce a neuropathy (diabetes, alcoholic, and autoimmune disease) were all negative.

All subjects also had impairment, of late onset (>60 years) of stance and gait, progressive over many years. All patients had pathologic dynamic visual acuity test or bedside head impulse test documenting dynamic failure of bilateral vestibulo–ocular reflex (VOR). Supporting the diagnosis of CANVAS was the finding of a normal brain MRI other than cerebellar atrophy. An experimented neuroradiologist evaluated the patient MRIs. Any ostensible reduction of the volume of the cerebellar vermis discordant with the cerebellar hemispheres was considered as a relative vermis atrophy. All the subjects had gaze-evoked and/or downbeat nystagmus with naked eye. Three of the cases endorsed a sensory loss on facial areas (trigeminal nerve) to thermal and vibration stimuli, which provided evidence of other cranial nerve involvement.

The patients had both video-oculography with bithermal caloric assessment (VOG425-Interacoustics, Middlefart, Denmark) and vHIT (Eye See Cam®-Interacoustics, MIddlefart, Denmark). In addition, VEMP were measured from the cervical muscles (cVEMP, cervical VEMP) and extraocular muscles (oVEMP, ocular VEMP) using 500-Hz air-conducted tone bursts at 100 dB (Epx Eclipse®- Interacoustics, Middlefart, Denmark). The multiaxial VHIT was reviewed with specific attention to the VOR gain of all six canals and corrective catch-up saccades. The VOR gains during the vHIT were automatically measured using software in two forms, VOR60: the instantaneous velocity gain (eye velocity/ head velocity) at a 60 ms window and the regression slope (VORrs) between head and eye velocity. The normal value for VHIT VORrs gain in our laboratory is 1 (SD: 0.2) and has been reported elsewhere [10]. Normal values of VEMPS were based on data from 17 control subjects (mean age 69 years; age range, 60-80 years) who had no vertigo or nystagmus and had normal neurological examination. The VEMP amplitudes were determined as n1-p1 peak-to-peak amplitude for the oVEMPS and p1-n1 for cVEMP. Although both the absolute latency of p1/n1 latency differences is measured, it is the amplitude measure that has become most useful to detect abnormality in clinical populations. The VEMP responses were considered abnormal when they were absent (no definable and replicable VEMP response) or had amplitudes less than the fifth percentile according to the non-parametric data from the control group. The same operator performed all vestibular tests.

The VOR suppression (VORSup) was assessed by oscillating the patient in block horizontally (2 Hz) in a rotating chair while he attempted to fix on an object rotating with patient. Absence of corrective saccades during rotation indicated normal suppression VOR. VVOR was tested by passively oscillating (0.5-2 Hz) horizontally the patient head while he/she attempted to fix on stationary object (2 inches side red square, on the white wall) at 1 m in front of them. Systematic corrective saccades during rotation indicated impaired visual enhanced of VOR. Both the VVOR and VORSup were recorded with both video-oculography and VHIT devices to quantify the oscillation (head or body) frequency and the eye movements.

Verbal consent was obtained from all subjects. However, since this study is a retrospective analysis of data that was already acquired during diagnostic testing, with adequate anonymity, the ethics committee considered that the consent could be waived.

No statistical analysis was conducted due to the small number of patients included in this study.

RESULTS

Five patients (0.11% of all) were included in this study. The main features are shown in Table 1. A global bilateral vestibular weakness was documented in all. All six canals showed severe reduction of the slow phase gain of the VOR accompanied by compensatory corrective saccades (Figure 1). No case had VOR gain for any canal in the normal range. The mean gain of all canals from the VORs was 0.26, which is about 25% of the normal range (normal gain: 1, SD: 0.2).

In four patients, cVEMP and oVEMP tests were obtained. Low-amplitude cVEMP responses were present; mean amplitude of patients: 30.26 mv (range 22-34) vs. lower limit in controls (fifth percentile) of 25 mv (range 25-188), without asymmetry in all four patients. On the other hand, the oVEMP responses were uniformly absent. Audiometry documented asymptomatic mild high frequent symmetrical hearing loss, consistent with age-related hearing loss.

Table 1. Main features of cases

Patient	Age	Sex	Years since symptoms onset	Main symptom	Nystagmus	Bithermal caloric test (bilateral)	VHIT (gain VORrs)			oVEMPS	cVEMPS (μV)		Brain MRI (vermal atrophy)	Horizontal		Follow up (years)
							LH/RH	LA/RA	LP/RP		R	L		Abnormal VVOR	Dynamic visual acuity (DVA)	
1	77	F	3	Imbalance	DBN	Hyporeflexia	0.14/0.19	0.28/0.21	0.26/0.18	-	-	-	+	+	10	3
2	75	F	8	Imbalance	DBN + GEN	Areflexia	0.15/0,14	0.09/0.12	0.26/0.14	Absent	22	24	+	+	10	10
3	62	M	4	Imbalance	DBN	Hyporeflexia	0.07/0.10	0.11/0.63	0.56/0.11	Absent	33.1	31	+	+	7	4
4	71	M	3	Imbalance	GEN	Areflexia	0.08/0.08	0.24/0.37	0.46/0.27	Absent	33.5	33.5	+	+	9	2
5	80	F	3	Vertigo + imbalance	DBN	Hyporeflexia	0.43/0.51	0.66/0.5	0.3/0.39	Absent	34	31	+	+	9	10

DBN: down beating nystagmus, GEN: gaze evoked nystagmus. Caloric test (Bithermal): Hyporeflexia total response (sum of all caloric irrigations) <20°/sec SPV. Areflexia: total response <5°/sec SPV. VHIT: Video head impulse test. VORrs: vestibulo-ocular reflex regression slope. VVOR: Visually enhanced VOR. LH and RH: Left and right horizontal canals, LA and RA: Left and right anterior canals, LP and RP Left and right posterior canals. DVA: Dropped line from the base line visual acuity on the standard Snellen chard.

DISCUSSION

CANVAS is a rare condition. Our patients exhibited global reduction of semicircular canal function. In a non-specific study, Tarnutzer and associates reported similar findings in five patients with CANVAS [11]. While this does not prove with certainty that they had a ganglionopathy, this is consistent with the conjecture that the vestibular ganglion is damaged. Generalized dorsal root ganglionopathies (DRG) are also called "ataxic neuropathies" as they often exhibit sensory ataxia of their limbs due to deafferentation of the cerebellum [12]. Thus, the DRG hypothesis also explains sensory ataxia, although it does not explain cerebellar disturbances involving systems with no sensory ganglia, such as visual tracking.

Our data as well as that of a case report of Rust and associates suggest that in patients meeting the clinical criteria for CANVAS, severely impaired canal function can co-exist with partial sparing of otolithic function [6], as reflected in the cVEMP responses. The patient reported by Rust and associates had a small (about 2 μv) oVEMP as well as a small (about 20 μV) cVEMP. The preservation of small cVEMP responses in some of our patients is against the hypothesis that CANVAS has a DRG mechanism, because it is thought that the saccular input for the cVEMP traverses through the vestibular ganglion [13].

To explain the preservation of the cVEMP in their case, Rust and colleagues suggested that the deficit in CANVAS might be on a vestibular nuclear level, rather than affecting the DRG [6]. This explanation is implausible as it fails to account for pathology showing damage to Scarpa's ganglion [4, 5]. Other explanation concerning the conservation of cVEMPs in otherwise severely affected vestibular end organ is the different embryologic origin of canals: utricule and saccule. The cochlea and saccule arise from the pars inferior of the inner ear, whereas the three semicircular canals and utricle have already developed from the pars superior. This embryologic difference has been associated to different vulnerability to age-related inner ear degeneration [14]. The intact hearing in patients with CANVAS supports this theory.

Another possibility is that cVEMP responses can be generated in persons with bilateral vestibular loss through pathways that do not require a functioning vestibular ganglion. The cVEMP is normally elicited by sound, which stimulates the saccule [15]. In vestibular disorders, non-vestibular inputs can sometimes replace vestibular input. For example, neck input can partially replace canal input in humans with bilateral vestibular loss [16, 17]. Rust et al pointed out that there are collections of patients with bilateral loss of caloric responses in the literature documenting sparing of VEMPs, including a large series from Agrawal et al [18]. While preserved VEMP testing in patients with bilateral canal loss was interpreted as sparing of otolithic input, another possible explanation is that in bilateral vestibular loss, perhaps due to sensory plasticity, cVEMP responses elicited by sound do not require a functioning vestibular ganglion or due to embryologic reason part of the saccular nerve runs within the cochlear nerve as was described above. However, the CANVAS is an independent biological model of bilateral vestibular loss, thought to be an isolated vestibular nerve loss instead of the hair cells involvement cases that previous studies had included [18]. Therefore, the features found in this study are considered as an original observation.

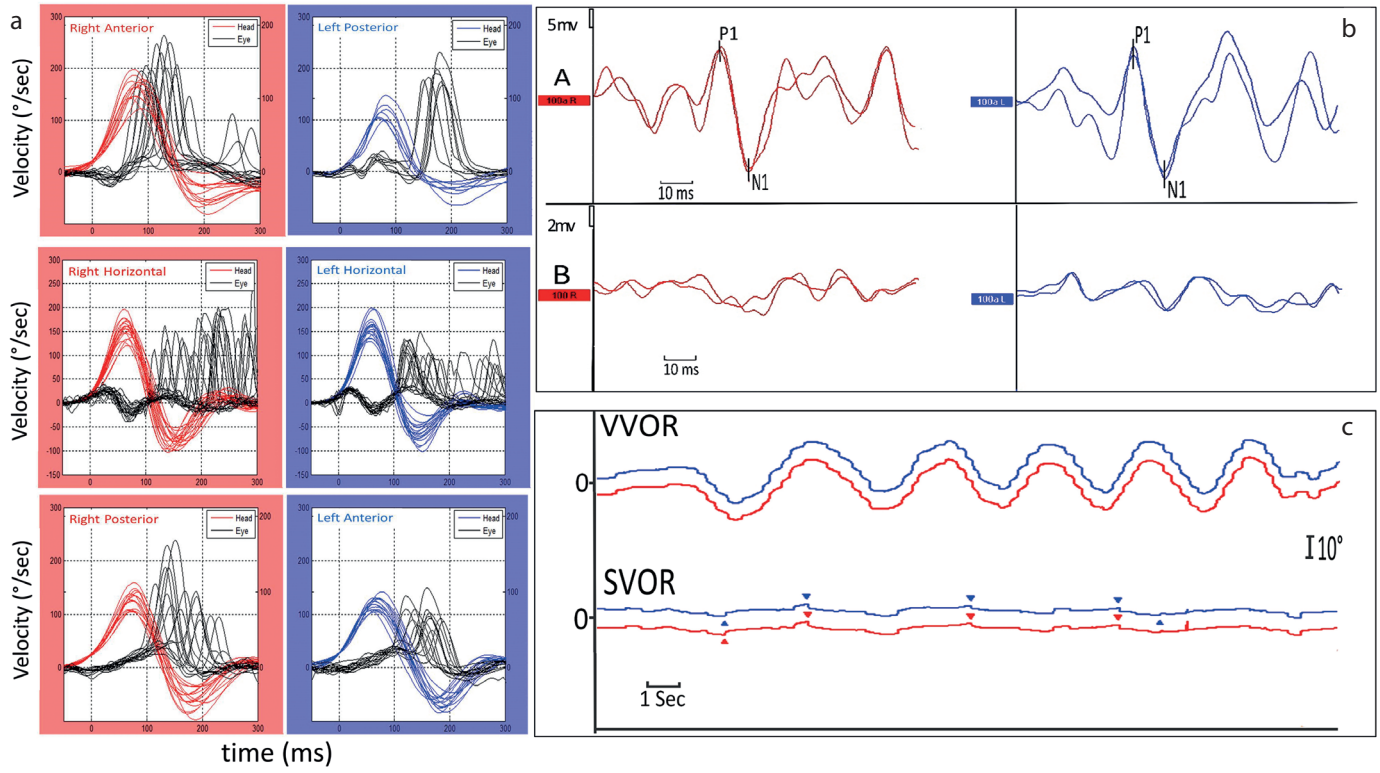

Figure 1. a, c. Representative case (Patient 2): (a) Left panel, the 6 canal VHIT shows global reduction of individual responses with systematic correctives saccades. (b) in the right upper panel are the VEMPS: cVEMPS are in A and oVEMPS in B. The right ear is shown in red, left in blue. Normal responses in cervical and absence in ocular VEMP in both sides. The right lower panel, (c) showing the abnormal VVOR with staircase eye movements during the head oscillation due to small catch up saccades. In contrast, the visual suppression of VOR was normal. Right eye is shown in red, left eye in blue.

Finally, there is a moderated possibility that the absence of oVEMP with preserved cVEMP were found by chance. The low number of patients prevents us to perform a more specific statistical analysis to rule out this statement.

CONCLUSION

We report here five patients that met the clinical criteria for clinically definite CANVAS. All of them had severe impairment of all canal input. In contrast, four subjects had preserved cVEMP responses, which suggests partial spared saccule function. Loss of all canal input is consistent with the hypothesis that the deleterious process in CANVAS is of the vestibular ganglion. However, the preservation of cVEMP responses is against this hypothesis, and would suggest that either the lesion is selective within the DRG or idiosyncratic natural resistance of the saccular pathway preserve its function. Another non-vestibular pathway of cVEMP responses that do not require a vestibular ganglion in patients with bilateral vestibular loss is alternative attractive theory.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of UA Dr. Cesar Milstein Hospital, Buenos Aires, Argentina.

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