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Original Article

Variability in the Results of Vestibular Assessment in Patients with Genetically Confirmed Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome

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BACKGROUND: Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS) presents an unpredictable and uneven clinical development of cerebellar ataxia, neuropathy, and vestibular areflexia. The aim of this study is to report the variability of vestibular test results in genetically confirmed patients with cerebellar ataxia, neuropathy, and vestibular areflexia syndrome.

METHODS: Caloric testing, video head impulse test (vHIT), and rotatory chair testing were performed in 7 patients who presented pathogenic repeat expansions in the replication factor complex unit 1 gene related to cerebellar ataxia, neuropathy, and vestibular areflexia syndrome.

RESULTS: Reduced vestibulo-ocular reflex (VOR) gain was observed in 100% of the patients in rotatory chair testing. Three of them had bilateral areflexia in caloric testing while 2 showed unilateral hypofunction and 2 had no alterations in the test. Only 1 patient had bilateral abnormal vHIT with gains under 0.6 in both ears.

CONCLUSION: Genetic testing allows an early diagnosis of cerebellar ataxia, neuropathy, and vestibular areflexia syndrome, whereby the vestibular system may be affected to different degrees. Rotatory chair testing has a higher sensitivity for the detection of vestibular hypofunction in these patients. Caloric testing can provide additional information. vHIT might underdiagnose patients with mild-to-moderate vestibulopathy.

KEYWORDS: CANVAS, bilateral vestibulopathy, vestibulo-ocular reflex, video head impulse test, rotatory chair testing

INTRODUCTION

Cerebellar ataxia with sensory neuropathy and vestibular areflexia syndrome is an uncommon recently described genetic syndrome.[1-3] It provokes gait imbalance, which is caused by the impairment of 3 out of the 4 main props our body has to maintain balance (cerebellar, vestibular, and sensory). Vision is the only one that remains unaffected.[4] It is a progressive disabling cause of ataxia, which affects individuals differently and unequally and its diagnosis can be challenging. A long-standing history of chronic cough preceding the symptoms as well as autonomic dysfunction is present in most of the cases.[5,6]

Neuropathy is characterized by a large and small sensory fiber impairment, which has a non-length-dependent clinical presentation. Motor fibers are preserved. The pathophysiological mechanism underneath is dorsal root ganglionopathy.[7,8]

Cerebellar dysfunction causes ataxia, dysarthria, and dysphagia among others. Brain magnetic resonance imaging (MRI) shows cerebellar atrophy affecting Crus 1, which functionally takes part of the oculomotor cerebellum.[9]

Bilateral vestibulopathy (BVP) may cause oscillopsia and worsening of unsteadiness in uneven ground or darkness. The impairment of the VOR can be confirmed by vHIT, rotational chair testing, or caloric testing. The vestibular assessment shows reduced VOR on different frequencies of the vestibular stimulus. Patients with CANVAS have a deficient visuo-vestibular ocular reflex (VVOR) caused by the disability of the VOR, the optokinetic reflex, and the smooth pursuit.[10]

The clinical definition was proposed in 2016 by Szmulewicz et al,[12] which includes abnormal visually enhanced VVOR, cerebellar atrophy on MRI, neurophysiological evidence of a sensory neuronopathy, and exclusion of other genetic ataxias. Neuropathy seems

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to be the most constant one[11] and frequently the other 2 may not be present.

Biallelic intronic repeat expansion in the replication factor complex unit 1 (RFC1) gene was described in 2019, making possible the diagnosis of CANVAS in individuals lacking some of the clinical features.[11-14] Although the mechanism underlying neurodegeneration is still unknown, *RFC1* is a gene implicated in DNA replication and repair.

It is inherited in an autosomal recessive manner. The most common variant is a biallelic pentanucleotide repeat expansion (AAGGG) with more than 400 repeats in the intron 2 of the *RCF1* gene, although further pathogenic allelic configurations have also been reported.[10,12]

This late-onset ataxia is explained by a combination of sensory axonal neuropathy, cerebellar postural disorder, and vestibular hypofunction. However, the timing of onset and the progression of each of the different components may vary. The aim of this study is to analyze the variability in the vestibular responses in patients diagnosed with CANVAS genetically tested.

MATERIAL AND METHODS

This retrospective descriptive study was performed in the neurotology unit of an otolaryngology department of a third-level hospital.

Genetic Study

Genomic DNA extraction was performed from peripheral whole blood. A TP-PCR was carried out to assess the presence of an expanded AAGGG repeat in the *RFC1* intron 2 region. When confirmed expansion, electrophoresis of PCR and TP-PCR products were carried out. Finally, PCR amplification and Sanger sequencing of SNPs rs11096992 (AA) and rs2066790 (AA) were completed to determine the presence of the disease-associated haplotype. In 2 related cases, sequencing of the *RFC1* gene in which the AAGGG expansion was detected in heterozygosis allowed the discovery of a nonsense variant.

Other genetic ataxias including Friedreich's ataxia, multiple system atrophy, and the most common spinocerebellar ataxias were genetically tested negative in this cohort.

Patients

The following information was collected for the 7 cases: Sex, family history, age and age of symptom onset, pure tone audiometry, clinical evidence of sensory neuropathy, cerebellar dysfunction, vestibular areflexia, and the presence of additional typical features such as dry cough and dysautonomia. Data obtanied from neurological evaluation, results of MRI and nerve conduction studies was included. Written informed consent was obtained from patients participating in the study. The study was approved by the Ethics Committee of the Hospital 12 de Octubre (22/485).

Methods

Vestibular assessment of the 7 patients was carried out to demonstrate bilaterally reduced or absent VOR and VVOR. They were documented by the following tests. Each of these tests allows us to study vestibular impairment in different frequencies.

To carry out caloric testing, the lateral semicircular canal of each ear was irrigated with cold (30ºC) and warm (44ºC) water. Eye movements were recorded after each irrigation and the maximal slow-phase velocity of caloric-induced nystagmus was measured. All patients underwent caloric testing using Ulmer VNG VideoNystagmoGraph. Bilateral hypofunction was proved when the sum of the bithermal maximum peak slow phase velocity on each side was <6º/seg.[15] Unilateral hypofunction was considered when unilateral weakness was higher than 20%.[16]

Rotatory chair testing permits the evaluation of VOR and VVOR. It allows quantification of VOR in response to stimulation of both horizontal semi-circular canals at low-to-middle frequencies. All patients underwent a rotatory sinusoidal harmonic acceleration test using Ulmer VNGVideoNystagmoGraph SYNAPSYS MED4 rotatory chair. In order to establish pathological values of VOR and VVOR, Ulmer VNG Normative data was used. The VOR under 0.4 and VVOR under 0.89 values were considered pathological.

The VOR velocity gain was quantified by vHIT. They were all assessed by Otometrics ICS Impulse. It was used for high-frequency vestibular assessment. Unpredictable, passive, and impulsive (10º-10º amplitude, 150-300º/s acceleration) head turns were delivered by the examiner in the plane of the lateral semicircular canal in both directions (right and left), while subjects were required to stare at a fixed target at eye level. According to the Barany Society, a value under 0.6 in the horizontal angular VOR was considered as the threshold for vestibular hyporeflexia.

All of them were performed by the same examiners.

All descriptive statistical analyses were performed using Excel database and Statistical Package for Social Sciences version 18.0 (SPSS Inc.; Chicago, IL, USA)

MAIN POINTS

- CANVAS is a genetic syndrome that involves uneven development of cerebellar ataxia, sensory neuropathy and vestibular areflexia.
- In cases where there is clinical suspicion, genetic testing enables an earlier diagnosis and therefore patients may have not develop bilateral hypofunction.
- In our study, rotatory chair testing demonstrates greater sensitivity in identifying vestibular hypofunction among these patients whilst vHIT may potentially underdiagnose mild to moderate vestibulopathy.

RESULTS

Genetic Testing

Five patients presented the biallelic AAGGG repeat expansion in *RFC1*, with more than 400 repeats. The 2 sisters have a recently discovered variant associated with CANVAS. They present a nonsense c724C>T p.(Arg242*) variant in compound heterozygosity with the pathogenic repeat expansion in the *RFC1* gene.[17]

Patients

The clinical features of all 7 patients appear summarized in Table 1. Cases 5 and 6 were sisters. The others were sporadic cases. There

Table 1. Summary of Clinical Data

	Sex	Age/ Onset	Initial Symptoms	Cerebellar Atrophy	Romberg	Peripheral Neuropathy	Cough	Family History	Electroneuromyography	Pure-Tone Average	
										RE	LE
1	F	50/30	Lower limb neuropathy	No	+	Yes	Yes	No	Sensory axonal neuropathy	13	13
2	F	51/30	Dry cough	No	+	Yes	Yes	No	Sensory axonal neuropathy	9	10
3	F	68/59	Lower limb neuropathy	No	+	Yes	No	No	Sensory axonal neuropathy	25	25
4	F	66/59	Lower limb neuropathy	No	–	Yes	No	No	Sensory axonal neuropathy	30	32
5	F	56/30	Dry cough	No	–	Yes	Yes	Yes (sibling of case 6)	Sensory axonal neuropathy	40	44
6	F	50/45	Lower limb neuropathy	No	+	Yes	Yes	Yes (sibling of case 5)	Sensory axonal neuropathy	27	19
7	M	77/40	Lower limb neuropathy	Yes	+	Yes	Yes	No	Sensory axonal neuropathy	20	10

F, female; LE, left ear; M, male; RE, right ear.

were 6 women and 1 man. The age of the patients ranged from 50 to 77 years (median 56) with an age of symptom onset between 30 and 70 years (median 45).

Five patients presented with a dry cough while for 2 of them, it was their first symptom, antedating the appearance of an imbalance in 2 decades. None of the patients had clear symptoms of dysautonomia. Pure-tone average at the frequencies of 500, 1000, 2000, and 4000 Hz was normal for age.

Neurological Findings

All 7 patients underwent a 4-limb conducted study that showed non-length-dependent sensory polyneuropathy. Patient 7 had also other sensory alterations probably due to diabetes. Neuropathic pain was present in all patients. Neuropathy was the first symptom in 5 of them (1, 3, 4, 6, 7), preceding the rest of the symptoms between 5 and 30 years. Clinical signs of cerebellar dysfunction including positive Romberg, dysarthria, or dysphagia were present in 5 patients (1, 2, 5, 6, 7). The MRI results only showed cerebellar atrophy affecting Crus I in patient 7.

Vestibular Findings

All cases presented a history of imbalance and unsteadiness especially when walking or standing, which worsened in darkness, uneven ground, or during head motion. Just patient 7 needed gait support. None of them had wheelchair bound.

Abnormal findings in caloric testing were found in 5 patients. Three of 7 (42.9%) cases had bilateral dysfunction and 2 of 13 (29%) had unilateral hypofunction. The sum of bithermal maximum peak slow phase velocity on each side was <6º/seg in cases 1, 5, and 7. Cases 3 and 6 presented unilateral dysfunction. Unilateral weakness was 48% left in case 3 and 32% right in case 6. Cases 2 and 4 did not show lateral semicircular canal hypofunction. Rotatory chair testing demonstrated hypofunction in 5 of the cases with VOR gain results under 0.4. Two patients had 0.4 gain values, just on the edge of vestibular hypofunction definition and therefore were considered pathological. Five of 7 patients had VVOR gain under 0.89. Video head impulse test exhibited abnormal bilateral VOR gain under 0.6 in patient 7 (right VOR and left VOR were under 0.2). The rest of the patients showed normal VOR gains over 0.8. Vestibular data are summarized in Table 2.

DISCUSSION

Cerebellar ataxia, neuropathy, and vestibular areflexia are the main clinical manifestations of CANVAS. Patients can have mild or moderate clinical expression and although sensory neuropathy seems to be the most frequent symptom,[10] the rest of the clinical signs are often few and misleading. Nowadays, t's simpler to classify these patients with the confirmation of their diagnosis through molecular genetic testing. Most of our patients did not have a complete clinical CANVAS therefore genetic testing was essential to reach a correct diagnosis.[5] All 7 patients had genetic testing confirmation with the biallelic AAGGG repeat expansion in *RFC1*. Even though the dry cough is not considered part of the cardinal features, its relationship with limb dysesthesia guides the suspicion of the syndrome.[12] In our series, 5 of 7 patients presented dry cough and its presence was key to their diagnosis.

The median age of our patients was 56 years, which is lower than in other studies.[18] It may be the reason why some of them have not yet developed severe vestibular dysfunction or cerebellar atrophy.

This study shows the importance of a complete vestibular assessment in patients with CANVAS. Bilateral vestibular hypofunction is considered one of the key features of the syndrome. Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome is one of the etiological differential diagnoses of bilateral vestibular pathology.[19] We assessed vestibular pathology using the different equipment in our otoneurological laboratory which included vHIT, caloric testing, and rotatory chair testing. The main purpose of this was to assist reduced VOR in different frequencies and show that they can be unequally affected. Visuo-vestibular ocular reflex is relevant in these patients because it provides information on peripheral and central vestibular function.[20]

The gold standard for identifying bilateral vestibular hypofunction is rotatory chair testing.[21,22] As in other studies, all 7 cases presented

Table 2. Summary of Vestibular Data

	Caloric Testing					vHIT		Rotatory Chair Testing	
	Total Reflectivity	Unilateral Weakness	Sum of Bithermal Mean Peak of Slow Phase Eye Velocity (°/sec)		Lateral Semicircular Canal Hypofunction	RE	LE	VOR	VVOR
			RE	LE					
1	3.3 left	1% right	3.3	3.3	Bilateral	1	0.8	0.27	0.77
2	22.4% right	9% left	22.4	18.9	–	1	0.9	0.29	0.77
3	10.7% right	48% left	10.8	3.5	Unilateral	0.9	0.9	0.39	1.42
4	19% right	2% left	19.2	18.1	–	1	0.9	0.22	0.47
5	5.1% left	69% right	1.5	5.1	Bilateral	0.9	0.8	0.40	0.9
6	24.6% left	32% right	12.7	24.6	Unilateral	1.3	0.9	0.40	0.55
7	10.4% left	89% right	2.9	3.3	Bilateral	0.2	0.2	0.19	0.42

LE, left ear; RE, right ear; VOR, vestibulo-ocular reflex; VVOR, visuo-vestibular ocular reflex.

reduced values of VOR. Nowadays VVOR can be evaluated with a bedside clinical test as well as with vHIT or Rotatory chair testing.

Pathological VVOR appears even in patients where cerebellar atrophy is not visible in MRI. Visuo-vestibular ocular reflex has clinical applications in patients with vestibular and neurological dysfunctions. Five of 7 patients had reduced VVOR, but only case 7 had clearly cerebellar atrophy in MRI.

Our results showed that low-frequency stimulation with caloric testing can give us adequate information about the vestibular impairment. We had 3 patients (1, 5, and 7) that showed bilateral dysfunction, while patients 3 and 6 only had unilateral hypofunction. There are not many studies where patients with CANVAS show unilateral hypofunction in caloric testing. In our case, as they were diagnosed earlier, it can give us information about how quickly they develop complete BVP. It also proves that vestibular nerve ganglionopathy affects differently each frequency and is established at different times in both ears.

Video head impulse test can serve as an initial vestibular test for identifying patients with bilateral hypofunction. It has been demonstrated that there is a disagreement between vHIT and rotatory chair testing when bilateral pathology is not severe. Judge et al[23] showed that lower vHIT gains are consistent with having severe BVP, especially when average VOR gains are under 0.46. Our patient 7 was the only case having VOR gain under 0.4. He was the only one with severe vestibular pathology and balance impairment needing gait support. This patient was also the only one that clearly showed cerebellar atrophy in the MRI and therefore met the clinical criteria of CANVAS. Video head impulse test alone may not be the best test to study bilateral vestibular hypofunction.[24] Many of the otoneurological centers assess vestibular dysfunction only by using vHIT and this might underdiagnose CANVAS patients that have mild or medium bilateral dysfunction.

We did not perform VEMP(Vestibular Evoked Myogenic Potential) as it has been demonstrated in previous works that otoliths remain intact and they show normal results.[25] Computerized Dynamic Posturography and the Sensory organization test can help evaluate sensory inputs that influence the maintenance of balance,[26] which is a key aspect of CANVAS. Vestibular rehabilitation may be useful in these patients despite controversial results in patients with BVP.[27] Further vestibular assessment of these patients in the future may show deterioration of VOR and VVOR as the syndrome progresses.

The most important limitation of our study is the reduced number of patients included. It limits the ability to generalize our results to all patients with this syndrome. Other limitations may be due to the cross-sectional nature of the study. Further, longitudinal studies are needed to better understand the evolution of these patients.

Since the discovery of the genetic cause of CANVAS, even lacking some of the defining clinical features, patients can be diagnosed earlier. This is important in order to understand the evolution of their vestibular impairment as they are not always going to have severe bilateral hypofunction at diagnosis. Rotatory chair testing offers a greater sensitivity to diagnose BVP. Caloric testing allows to classify patients according to whether they present bilateral or unilateral vestibular hypofunction in low frequencies. Finally, vHIT may underdiagnose patients with mild or moderate vestibular hypofunction. If we can assess these patients properly and perform vestibular rehabilitation such as home exercises and sessions of computerized dynamic posturography, they may improve their symptoms and therefore their quality of life.

Ethics Committee Approval: This study was approved by the Ethics Committee of Hospital 12 Octubre (Approval No: (22/485)., Date: November 15, 2022).

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

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