CANVAS is an Oligosymptomatic Disease

Dear Editor,

Cerebellar ataxia with sensory neuropathy and vestibular areflexia syndrome (CANVAS) is a rare, progressive and disabling cause of ataxia in adulthood.[1] Sporadic in most cases, it may also be associated with a biallelic expansion of an intronic AAGGG pentanucleotide in the *RFC1* gene.[2,3] An association with heterozygous missense mutations in *ELF2* gene has also been described.[4]

The cerebellum, vestibular system and peripheral nervous system are all involved in disturbance of balance in CANVAS, however, we frequently find that patients report few otovestibular and sensory complaints, making the diagnosis more difficult.

The aim of this work was to show how CANVAS, despite being a cause of disabling ataxia, manifests itself with few and elusive symptoms, especially at otovestibular and neuromuscular level, exemplifying it through a series of four patients.

We present a series of four patients who consulted in our hospital for long-term oligosymptomatic gait ataxia. All patients met the proposed diagnostic criteria for CANVAS.[5]

Anamneses, systemic and neurological examinations were performed. Otovestibular testing consisted in video-assisted cranial impulse test (vHIT), videooculogram and bone and air tone audiometry. Electrophysiological study consisted of nerve conduction studies (NCS) and sensory evoked potentials (SEP). Cranial magnetic resonance imaging (MRI) study and laboratory investigations were performed to rule out systemic conditions.

RFC1 gene mutation was studied in all four patients. Patients

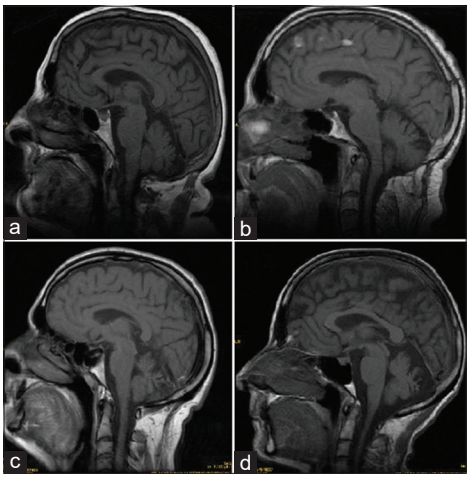

Figure 1: Magnetic resonance imaging study. Sagittal sections of the 4 patients (a) case I, (b) case II, (c) case III, (d) case (IV) show different degrees of atrophy of the cerebellar vermis

I and IV harbored abnormal expansions in *RFC1*, while cases II and III did not present the mutation.

Table 1 presents a summary of symptoms and exploratory findings in every study patient.

The initial symptom was spasmodic cough in cases I and IV, and it preceded unsteadiness by many years. It occurred in episodes arriving in bursts caused by strong odors, certain foods or vocal overexertion. Its frequency was variable,

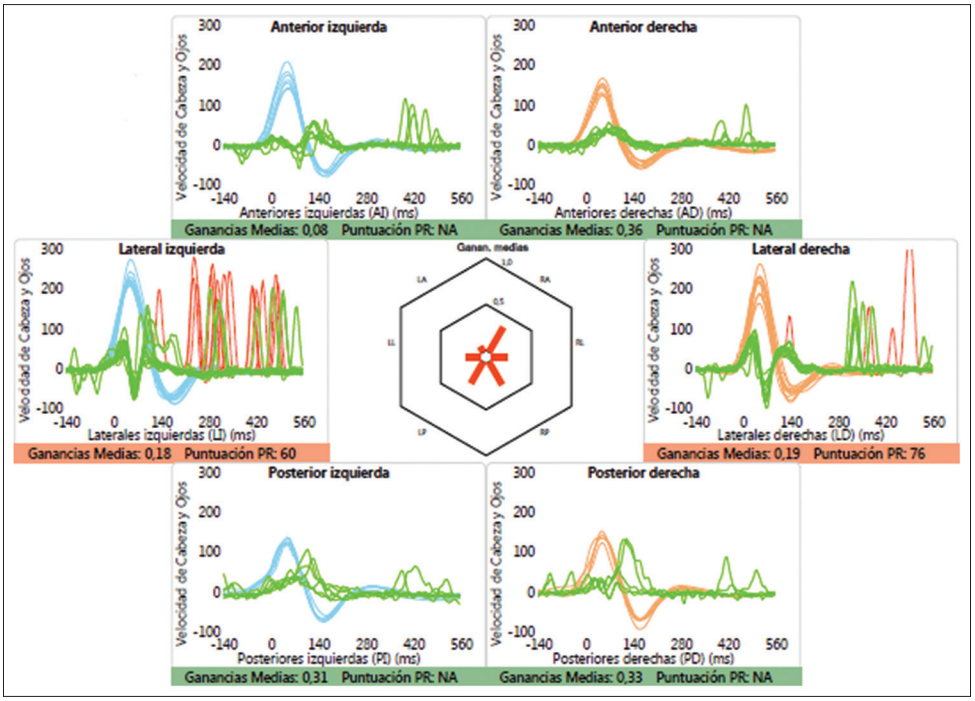

Figure 2: vHIT, case II (original). Reduced gain values are observed in every semicircular canal, together with presence of compensatory saccades. The blue (left) and orange (right) curves represent the speed of head movement. Eye movement speed is represented by the green curves, which appear superimposed on the head movement for comparison. Red lines represent saccades (compensatory eye movements) of pathological characteristics, (speed >100o/sec). Covert saccades appear during head movement, so they are not visible to the naked eye, and overt saccades appear after head movement

Table 1: Summary of symptoms and semiological findings

	Case I	Case II	Case III	Case IV
Sex and age of patient	M, 66 years.	F, 84 years.	F, 73 years.	F, 62 years
Age at onset	40 years	55 years	50 years	44 years
Inaugural symptom	Cough	Instability	Instability	Cough
Vertigo	-	-	-	-
Hearing loss	-	-	-	-
Tinnitus	-	-	-	-
Saccades and smooth pursuit eye movements	Impaired	Impaired	Impaired	Impaired
Downbeating nystagmus	Gaze-evoked	Spontaneous	Spontaneous	Gaze-evoked
Constipation	-	-	-	+
Gait	Wheelchair	Wheelchair	Wheelchair	Bilateral support
Dysarthria	++	+	+	+++
Limb dysmetria	++	+	+++	+++
Dysphagia	Slight	-	Moderate	-
Saccadic HIT	+	+	+	+
Ankle reflex	Absent	1/4	Absent	Absent
Other tendon reflexes	1/4	2/4	1/4	2/4
Romberg sign[1]	+	+	+	+
Vibratory sense	Abolished distal to iliac crests	Abolished distal to iliac crests	Abolished distal to iliac crests	Abolished distal to iliac crests
Orthostatic hypotension	-	-	+	-

F, female; HIT, head impulse test; M, male. [1]Although the patients required bilateral support or a wheelchair to move, the positive sign was interpreted as a worsening of standing stability with eyes closed

becoming almost daily. In no case was an alternative cause found. Although its pathophysiology remains unclear, it could be due to hypersensitivity to denervation in the upper respiratory tract.[2,6]

Unsteadiness of gait was the inaugural symptom in cases II and III. The median age at onset of gait instability in the series was 47 years (range 40--59). Progression was constant, which prevented independent walking 10 years after onset in all cases.

Cerebellar involvement was corroborated by the finding of limb dysmetria, gait ataxia, spontaneous downbeat and bilateral gaze-holding nystagmus and slurred speech. Furthermore, sagittal brain MRI sections showed different degrees of vermian-predominant cerebellar atrophy in each case [Figure 1].

The absence of cortical sensory responses and of sensory action potentials in superficial peroneal and median nerves, together with normal motor action potentials was consistent with a sensory neuronopathy in all patients.

Opposite to what would be expected in a generalized sensory neuronopathy, tendon reflexes were preserved in every study case, except for absent ankle reflexes (preserved in one case). This phenomenon could be due to a selective respect of Ia fibers. Contrariwise, loss of Ib fibers would justify the vibratory and arthrokinetic hypoesthesia found on examination.[6,7] No patient perceived pain, numbness or tingling, which could indicate respect of the small diameter nerve fibers.

Vestibular hypofunction was suspected due to impaired smooth pursuit and saccadic eyes movements and also due to loss of visual tracking with compensatory saccades during the head-impulse test in all patients, in whom the v-HIT demonstrated bilateral vestibular dysfunction, with reduced gains of the vestibulo-ocular reflex bilaterally, along with overt corrective saccades [Figure 2].

The absence of vertigo and other otovestibular symptoms was striking. This phenomenon could be due to the symmetry in the reduction of gain values demonstrated by vHIT; and to the slow disease progression which could allow the development of compensatory mechanisms. No tinnitus or sensorineural hearing loss was found, a fact consistent with histopathological findings, in which the vestibular nerve was affected, while the cochlear nerve was spared.[8]

Dysautonomia is due to a postganglionic lesion of the autonomic nervous system in CANVAS, and is recognized as part of the neuromuscular spectrum in this disease.[9] Orthostatic hypotension and chronic constipation revealed dysautonomia in cases III and IV, respectively. No other dysautonomic manifestations were found, so this neuromuscular phenotypic expression was also subtle, as mentioned above.

In summary, we found that the patients explained few symptomatic complaints beyond gait instability. The clinical manifestations were not very expressive, except for those derived from cerebellar involvement. The scarce expressiveness of vestibular and neuromuscular involvement was striking. All this despite the significant disability they presented and the severe alteration of the different ancillary tests performed.

This highlights the need to stay one step ahead of the patient's symptoms and include a v-HIT study in the vestibular examination to demonstrate bilateral vestibular areflexia and to perform an ad hoc electrophysiological study to define sensory neuronopathy once we have this entity in mind.

Postural imbalance in CANVAS is due to the impairment of multiple systems. Cerebellar, proprioceptive and vestibular involvement can be inferred from a detailed clinical examination. However, this represents a diagnostic challenge, because symptoms and signs are often few, subtle and misleading. A high degree of clinical suspicion, along with performing detailed neurological examinations, electrophysiological and vestibular tests, are all necessary to identify CANVAS. This probably makes CANVAS an underdiagnosed entity. Further research is needed to define the phenotypic spectrum of the disease and its physiopathology.

Ethics approval

This study complies with the agreements of the Declaration of Helsinki and the institutional ethics committee.

Consent to participate and consent to publish

Informed consents were obtained for every test performed, and for the use of their results in this publication**.**

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Conflicts of interest

There are no conflicts of interest.

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