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](image)

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1. Ampar N, Mehta A, Mahale RR, Javali M, Pradeep R, Acharya P, et al. Electrophysiological evaluation of audiovestibular pathway dysfunction in Parkinson’s disease and its correlates: A case control study. Ann Indian Acad Neurol 2021;24:531-5.

2. Gordis L. Epidemiology. 6th ed. Philadelphia, PA: Elsevier Saunders; 2019.

3. Park K. Incidence in Park’s Textbook of Preventive and Social Medicine. 24th ed. Banaridas Bhanot Publishers; 2017. p. 74-8.
Table 1 presents a summary of symptoms and exploratory findings in every study patient.

| 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 | + | + | + | + |
| Vibratory sense | Abolished distal to iliac crest | Abolished distal to iliac crest | Abolished distal to iliac crest | Abolished distal to iliac crest |
| Orthostatic hypotension | - | - | - | - |

F, female; HIT, head impulse test; M, male. 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.

The initial symptom was spasmotic 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,
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.\[2,4\]

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 areflexia, 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.\[8\]

Dysautonmia 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 dysautonemia 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.

**FINANCIAL SUPPORT AND SPONSORSHIP**
Nil.

**CONFLICTS OF INTEREST**
There are no conflicts of interest.

**REFERENCES**

1. Szmulewicz DJ, Waterston JA, Halmagi GM, Mossman S, Chancellor AM, Melean CA, et al. Sensory neuropathy as part of the cerebellar axasia neuropathy vestibular areflexia syndrome. Neurology 2011;76:1903.

2. Cortese A, Tozza S, Yau WY, Rossi S, Beecroft SJ, Jaunmukfane Z, et al. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RFC1 repeat expansion. Brain 2020;143:480-90.

3. Transcutt A, Cortese A, Reich S, Dominik N, Faber J, Jacobi H, et al. History, phenotypic spectrum, and discriminative features of multisystemic RFC1 disease. Neurology 2021;96:1369-82.

4. Ahmad H, Requena T, Frejo L, Cobo M, Gallego-Martinez A, Martin F, et al. Clinical and functional characterization of a missense ELF2
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5. Szmulewicz DJ, Roberts L, McLean CA, MCDougall HG, Halmagyi GM, Storey E. Proposed diagnostic criteria for cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS). Neurol Clin Pract 2016;6:61-8.
6. Infante J, García A, Serrano-Cárdenas KM, González-Aguado R, Gazulla J, de Lucas EM, et al. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) with chronic cough and preserved muscle stretch reflexes: Evidence for selective sparing of afferent Ia fibres. J Neurol 2018;265:1454-62.
7. Szmulewicz DJ, McLean CA, Rodriguez ML, Chancellor AM, Mossman S, Lamont D, et al. Dorsal root ganglionopathy is responsible for the sensory impairment in CANVAS. Neurology 2014;82:1410-5.
8. Szmulewicz DJ, Merchant SN, Halmagyi GM. Cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome: A histopathologic case report. Otol Neurotol 2011;32:e63-5.
9. Wu TY, Taylor JM, Kilfoyle DH, Smith AD, McGuinness BJ, Simpson MP, et al. Autonomic dysfunction is a major feature of cerebellar ataxia, neuropathy, vestibular areflexia ‘CANVAS’ syndrome. Brain 2014;137:2649-56.

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