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ORIGINAL COMMUNICATION

Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome: a slowly progressive disorder with stereotypical presentation

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Abstract Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) is a newly described condition with onset in adulthood, characterized by progressive balance impairment and sensory disturbances in the lower limbs, which can severely affect patients' quality of life. Its pathogenesis remains obscure and the diagnosis challenging. We described four patients complaining of slowly progressive gait unbalance and sensory disturbances at the feet followed, after a period ranging 2–6 years, by cerebellar dysfunction. All patients showed gait and limb ataxia, positive Romberg sign, cerebellar dysarthria, gaze-evoked nystagmus, absent deep tendon reflexes, and impaired vibratory sensation. Nerve conduction studies revealed axonal sensory neuropathy, brain magnetic resonance imaging showed cerebellar atrophy, and otoneurological investigation demonstrated bilateral vestibular areflexia with impaired vestibulo-ocular reflexes. The diagnosis of CANVAS should be suspected on clinical ground based on homogeneous course of symptoms and signs, and addressed by video-oculography eye movement recording.

Keywords CANVAS · Sensory neuropathy · Cerebellar · Vestibular · Eye movements

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Introduction

Cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome (CANVAS) is a late onset disease characterized by the progressive impairment of the three neurological pathways responsible for balance: cerebellar, vestibular and sensory system. A syndrome with combined vestibular and cerebellar dysfunction was first described in the 1990s and defined as a distinct entity in 2004 [1, 2]. Its clinical features included cerebellar gait, limb ataxia and visually enhanced vestibulo-ocular reflex (VVOR) impairment due to the combined deficit of the three compensatory reflexes that are crucial in eyes' movement control: vestibulo-ocular reflex (VOR), smooth pursuit and optokinetic reflex (OKR). More recently, a syndrome with the acronym CANVAS was described [3]. It included axonal sensory neuropathy as a core feature in addition to cerebellar and vestibular failure, contributing significantly to unbalance and disability.

The diagnosis of CANVAS is challenging due to the slow progression of symptoms and the need of specific examinations on both smooth-pursuit eye movements and vestibulo-ocular reflexes, requiring slow head rotation and head impulse test, respectively [4]. Such symptoms and signs can be useful to address the diagnostic suspicion on clinical ground.

Case 1

A 70-year-old man complained for 5 years of slowly progressive gait unbalance and impaired sensation in the feet without painful symptoms. His family history was unremarkable, in particular for cerebellar and vestibular ataxic disorders and neuropathies. Two years after the onset of symptoms, slow speech and difficulty in fine hand

movements occurred. Neurological examination revealed gait and limb ataxia, positive Romberg sign, cerebellar dysarthria, horizontal bilateral gaze-evoked downbeating nystagmus, abnormal visually enhanced vestibulo-ocular reflex, absent deep tendon reflexes in all limbs and abolished vibratory sensation in the lower limbs (below the fifth percentile for age at the first metatarsal joints: 0/8 at 64 Hz Ryedel-Seiffer tuning fork). Otoneurological investigation with assessment of sinusoidal stimulation of smooth pursuit and head impulse test by video-oculography, demonstrated bilateral vestibular areflexia with reduced gain of smooth pursuit and impaired VVOR. Brain magnetic resonance imaging (MRI) revealed cerebellar vermian and hemispheric atrophy (Fig. 1). Nerve conduction study (NCS) showed severe axonal sensory neuropathy with absent sensory nerve action potentials (SNAPs) in all limbs, while motor conduction was normal except for decreased amplitude of right ulnar nerve compound motor action potential (CMAP) known after cubital tunnel surgery performed 4 years before (Table 1). Laboratory screening in serum and cerebrospinal fluid (CSF) including fasting glucose, protein electrophoresis, thyroid hormones, ANA, ENA, rheumatoid factor (RF), vitamin B12, anti-Yo, Hu, Ri, amphiphysin, Ma1, Ma2 and CV2 antibodies, and anti-GAD and CASPR2 antibodies, was negative. Other genetic causes were not consistent with the negative family history and the late onset.

Case 2

A 63-year-old man reported slowly progressive gait unbalance and sensory disturbances in the distal lower limbs for 8 years. His family and personal medical history were negative, except for known occupational hearing loss due to his work in a textile industry for 25 years. Neurological examination showed gait and limb ataxia, positive Romberg sign, cerebellar dysarthria, bilateral gaze-evoked horizontal nystagmus, abnormal head impulse test, reduced vibratory sensation (below the fifth percentile for age at the first metatarsal joint: 4/8 at 64 Hz Ryedel-Seiffer tuning fork) and pin-prick sensory loss in the lower limbs with a distal-proximal gradient, absent deep tendon reflexes in lower limbs and normal in upper limbs. Laboratory screening including fasting glucose, protein electrophoresis, thyroid

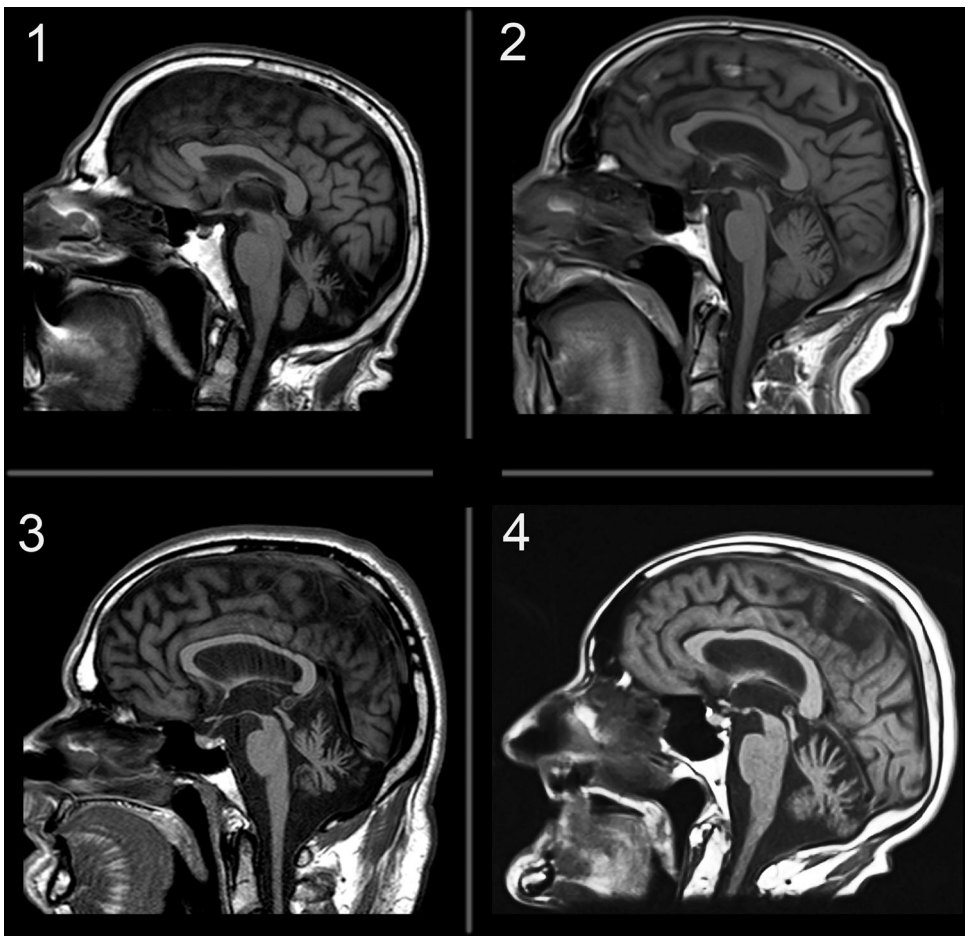

Fig. 1 T1-weighted sagittal brain magnetic resonance imaging in the four CANVAS patients showing cerebellar vermian atrophy

Table 1 Nerve conduction studies in the four patients reported showing the severe reduction or absence of SNAPs at all site recorded with spared motor nerve conductions

	Sensory NCV	SNAP (uV)	SCV (m/s)	Motor NCV	CMAP (mV)	MVC (m/s)	F-wave latency (ms)
Patient 1	Median	1 (nv ≥ 20)	51(nv ≥ 50)	Media	14.5 (nv ≥ 4)	55 (nv ≥ 49)	28
	Ulnar	– (nv ≥ 17)	– (nv ≥ 50)	Ulnar	12.4 (nv ≥ 6)	55 (nv ≥ 49)	27
	Radial	– (nv ≥ 15)	– (nv ≥ 50)	Tibial	10.8 (nv ≥ 2)	48 (nv ≥ 49)	48
	Sural	– (nv ≥ 6)	– (nv ≥ 40)				
Patient 2	Median	3.9	58	Median	13.3	52	27
	Ulnar	3.6	50	Ulnar	15	62	28
	Sural	2.7	46	Tibial	4.3 (nv ≥ 2)	43 (nv ≥ 41)	NR
				Peroneal	3.6 (nv ≥ 4)	39 (nv ≥ 44)	NR
Patient 3	Median	0.5	45	Median	21.3	52	27
	Radial	–	–	Tibial	24	44	51
	Sural	–	–				
Patient 4	Ulnar	–	–	Ulnar	15	52	25
	Radial	4.7	NR	Tibial	20	46	50
	Peroneal	– (nv ≥ 6)	–	Peroneal	7.3	47	47
	Sural	–	–				

In patient 2, ulnar left CMAP amplitude was reduced after surgery for cubital syndrome

SNAP sensory nervous action potential, *SCV* sensory conduction velocity, *CMAP* compound motor action potential, *MCV*, motor conduction velocity, *NR* not recorded, *nv* normal value, – absent,

hormones, ANA, ENA, RF, vitamin B12, anti-sulfatide antibodies tested in serum was negative. Anti-Yo, Hu, Ri, amphiphysin, Ma1, Ma2, and CV2 antibodies, and anti-GAD and anti-CASPR2 antibodies were absent in serum and CSF. Otoneurological examination demonstrated bilateral vestibular areflexia with reduced gain of smooth pursuit and altered VVOR. Brain MRI demonstrated cerebellar atrophy (Fig. 1). NCS revealed axonal sensory-motor neuropathy characterized by a predominant reduction of SNAP than CMAP amplitude in all limbs (Table 1).

Case 3

A 43-year-old man complained of mild and slowly progressive gait unbalance for about 10 years. Symptoms worsened 6 years after the onset, when he reported slow speech and inability to perform sports activities. Neurological examination revealed gait and limb ataxia, positive Romberg sign, cerebellar dysarthria, horizontal gaze-evoked nystagmus, broken up smooth visual pursuit, reduced vibratory sensation (below fifth percentile for age at the first metatarsal joint: 2/8 at 64 Hz Ryedel-Seiffer tuning fork), pinprick and light touch sensory loss with a length-dependent distribution at lower limbs, and normal deep tendon reflexes. Brain MRI demonstrated cerebellar atrophy (Fig. 1). Celiac disease, ANA, ENA, FR and anti-GAD antibodies were negative. Genetic assay for spinocerebellar ataxia (SCA) type 1, 2, 3, 6, 15, 17, 28, Friedreich's ataxia and vitamin E deficiency was negative. NCS showed reduced SNAP and normal CMAP in all four limbs (Table 1). Somatosensory-evoked potential were absent after stimulation of both upper and lower limbs. Blink reflex examination showed normal early ipsilateral R1 and late bilateral R2 responses, demonstrating that the trigeminal-facial pathway was unaffected. Genetic and muscle biopsy analyses ruled out mitochondrial POLG-related disorders (e.g. MIRAS, SANDO), including those dominated by sensory neuropathy [11]. Otoneurological examination with video-oculography revealed bilateral vestibular areflexia, abnormal broken up smooth visual pursuit, reduced gain of horizontal smooth pursuit (gain 0.33, normal range 0.69–1) and VVOR.

Case 4

An 84-year-old woman, with no family history of neurological diseases, complained of slowly progressive gait imbalance and sensory disturbances in the feet for about 6 years. She described a worsening of symptoms in the last 2 years while she developed a severe imbalance resulting in several falls. The neurological examination showed a severe gait more than limb ataxia, positive Romberg sign, broken up smooth visual pursuit, bilateral gaze-evoked down beating nystagmus, altered head impulse test, pinprick and light touch sensory loss at four limb with a length-dependent distribution, absent vibratory sensation at

malleolus and first metacarpal joint (64 Hz Ryedel-Seiffer tuning fork), absent deep tendon reflexes at lower limbs and distal upper limbs with symmetrically reduced bicipital and tricipital reflexes. The strength was normal and there were no pyramidal signs. Laboratory screening including fasting glucose, protein electrophoresis, thyroid hormones, vitamin B12, vitamin E, ANA, ENA, FR, anti-sulfatide antibodies, anti-Yo, Hu, Ri, amphiphysin, Ma1, Ma2, CV2, anti-GAD and anti-CASPR2 antibodies in serum was negative. Celiac disease and Sjogren syndrome have been ruled out. Brain MRI scans revealed a mainly vermian cerebellar atrophy (Fig. 1). NCS showed severe axonal sensory neuropathy with absent SNAPs at all limbs (except for severe decrease of right radial SNAP amplitude) and normal CMAPs (Table 1). Otoneurology examination demonstrated low gain (<0.5) of smooth visual pursuit, spontaneous down beating nystagmus and bilateral vestibular areflexia.

Discussion

CANVAS results from the impairment of cerebellar, vestibular and sensory functions leading to progressive and severe balance impairment. The first description of a syndrome characterized by late onset axial and limb ataxia in patients with bilateral vestibular deficit with impaired visually enhanced VVOR, and cerebellar dysfunction did not include peripheral neuropathy [2]. More recently, sensory or sensorimotor axonal neuropathy has been included as an integral part of the CANVAS' clinical picture.

All our patients showed a similar clinical picture, characterized by slowly progressive gait ataxia and sensory disturbances in the feet as presenting features, followed by mild cerebellar dysarthria that occurred after 2–6 years. The course of the disease observed in our patients, similar to those previously reported [5], suggested that the diagnostic suspicion of CANVAS can be based on the neurological examination.

The most remarkable aspect leading to patients' disability was the severe and progressive balance impairment. This could be explained by cerebellar and vestibular dysfunctions, proprioceptive impairment caused by a non-length dependent sensory neuropathy and VVOR impairment. These latter components seem to be the prototypical abnormality in CANVAS patients. On clinical ground, they presented with gaze-evoked horizontal or downbeating nystagmus associated with saccadic breakdown of smooth pursuit and abnormal head impulse test, whose alteration is also seen in "doll's head reflex". In suspected cases, disrupted vVOR can be detected by a video-oculography that, using high-speed video camera mounted on goggles, can reveal corrective saccades during a slow passive head movement on horizontal plane while the patient gaze is kept on an earth-fixed target. VVOR impairment results from altered gain of smooth pursuit eye movements and vestibulo-ocular reflex which are physiologically redundant at low (<1 Hz) stimulus frequencies. The "doll's head reflex", typically examined in comatose patients but almost ever in awake patients, is dependent upon the integrity of vestibular, oculomotor and abducens nerves and nuclei, and the medial longitudinal fasciculus. This reflex stabilizes images on the retina during head movements, most efficiently at high-input velocities, by producing an eye movement in the direction opposite to head movement. Impairment of this reflex may be visible at bedside in CANVAS patients. Smooth pursuits, which are complementary to the vestibular ocular reflex system in stabilizing the retinal image, are more efficient at low target velocities. They are normal in chronic peripheral vestibular, whereas can appear broken by saccadic intrusions at the neurological examination in dorsolateral pontine nucleus and cerebellar-flocculus lesions [6].

In CANVAS, peripheral neuropathy appeared dominated by large and small sensory fiber impairment, whose length-dependent (distal prevalent) clinical presentation diverged from the non-length-dependent (distal and proximal) distribution of NCS abnormalities. Motor nerve conduction was almost completely preserved. This pattern suggests that CANVAS may be associated with a primary damage of dorsal root ganglion neurons rather than a dying-back axonal neuropathy [7]. Indeed, histopathologic examination of one case [8] demonstrated a severe neuronal loss in the Scarpa's ganglion and in the geniculate and trigeminal ganglia. This has been confirmed by a pathological study in two CANVAS patients [9] and is consistent with recent neurophysiological findings on a cohort of 14 patients revealing the absence of SNAPs in all limbs and abnormal blink reflexes in 13 of 14 patients, and abnormal masseter reflexes in 6 of 11 patients studied [10]. Brain MRI demonstrated cerebellar vermian and hemispheric atrophy ranging from minimal to severe, with spared supratentorial structures.

Similar to other cases described in previous papers [2–5], we did not find any extra-neurological involvement after screening of systemic immune-mediated disorders and malignancies. CANVAS should be therefore considered a pure neurological syndrome. The diagnostic work-up of CANVAS should rule out treatable conditions such as nutritional deficits, immune-mediated disorders, and paraneoplastic syndrome related to underlying malignancies. Moreover, some features could raise the suspect of specific genic or acquired disorders. SCA type 3 is characterized by

VVOR dysfunction, sensory neuropathy and cerebellar ataxia, its dominant inheritance pattern is a useful clue for for the differential diagnosis with CANVAS. Friedreich's ataxia (FRDA), Wernicke's encephalopathy and cerebellar type of multiple system atrophy (MSA-C) should also be considered as major differential diagnoses. Nevertheless, a late onset is very unusual in FRDA that, moreover, shows spinal cord atrophy at MRI. Wernicke's encephalopathy typically presents with sub-acute onset related to vitamin B1 deficiency that has been reported as normal in CANVAS patients. MSA-C causes cerebellar dysfunction but does not include vestibulopathy or sensory neuropathy.

The association between peripheral neuropathy and cerebellar atrophy should prompt to the differential diagnosis of mitochondrial diseases, among which some show predominantly sensory neuropathy or neuronopathy and early ataxia, such as in POLG1 and C10ORF2 mutations [11]

The report of two siblings affected by CANVAS suggested a possible autosomic recessive inheritance of this disorder [3], which pathogenesis is still not clearly defined.

In conclusion, CANVAS appears as a stereotyped syndrome that should be suspected in patients with prominent balance impairment, sensory neuropathy symptoms, early mixed ataxia, and eye movement abnormalities suggesting cerebellar and vestibular dysfunction. Focused examination of eye movement at patient bedside can address the appropriate diagnostic work-up.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest

Ethical standard The study has been approved by the appropriate ethics committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

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