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Normal tendon reflexes despite absent sensory nerve action potentials in CANVAS: a neurophysiological study

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ABSTRACT

CANVAS is a recently defined progressive ataxic syndrome with impairment of vestibular, somatosensory and cerebellar function due to atrophic degeneration of dorsal root ganglia and dorsal columns, of cranial nerve somatosensory ganglia, of vestibular ganglia and vestibular nerves and of cerebellar Purkinje cells. While all patients eventually develop sensory impairment in a non-length dependent pattern and lose sensory nerve action potentials, some retain their tendon reflexes. Here we study 5 CANVAS patients with absent sensory nerve action potentials but intact, even brisk Achilles tendon reflexes and, in 4, preserved H reflexes in the upper and lower limbs. These findings imply that dorsal root ganglion neurons subserving cutaneous afferents more vulnerable than those subserving muscle afferents. Our findings have a clinical message: preservation of the Achilles tendon jerk does not exclude a large fibre peripheral neuronopathy.

1. Introduction

CANVAS (Cerebellar Ataxia, Neuronopathy, Vestibular Areflexia Syndrome) is a sensory ganglionopathy with cerebellar degeneration. There is atrophic degeneration of dorsal root ganglia (DRG) and of dorsal columns, of cranial nerve somatosensory ganglia, of vestibular ganglia and vestibular nerves and of cerebellar Purkinje cells, but sparing of vestibular receptors, of the peripheral auditory system and of the corticospinal tracts [1,2]. Clinically CANVAS manifests as a progressive ataxia with impairment of vestibular, somatosensory and cerebellar function [3–5]. Some patients also have autonomic involvement causing orthostatic hypotension, constipation, impotence, impaired sweating and chronic cough [6,7].

As expected, the sensory loss is accompanied by loss of cutaneous sensory nerve action potentials [1,3,4,7–11], but in some patients tendon reflexes are preserved, even brisk [3,4,8]. This paradoxical clinical finding has recently been confirmed in single cases from Italy [9] and Japan [11].

In order to clarify the paradox of preserved tendon reflexes with absent sensory nerve action potentials (SNAPs), we re-studied 5 of our CANVAS patients with intact or brisk tendon reflexes, 3 of whom (A, B and D in Table 1) were included in a previous report [3], focussing on the sensory neuronopathy. We now document in more detail this dissociation between the function of large myelinated cutaneous afferents and that of group Ia muscle afferents and discuss its implications.

2. Methods

2.1. Patients

Here we report our clinical and neurophysiological findings in 5 of our own CANVAS patients with brisk or normal tendon reflexes. Each patient had presented to one of us (GMH) with progressive impairment of stance and gait over many years and on examination had the typical clinical signs of CANVAS [5], namely: (a) impaired horizontal and vertical smooth pursuit; (b) impaired horizontal and vertical vestibulo-ocular reflexes on impulsive testing; (c) impaired horizontal and vertical visually enhanced vestibulo-ocular reflexes; (d) gaze-evoked nystagmus; (e) positive Romberg test; (f) sensory impairment (4/5) or sensory symptoms (1/5). In addition each patient had the atypical finding of normal or brisk tendon reflexes, including the Achilles tendon reflex.

2.2. Nerve conduction studies

Each patient had 2 sets of nerve conduction studies, first for diagnosis and then for monitoring, 6 months to 12 years apart (Table 2), with little difference in findings. One or both of these studies were done by one of us (DB). H reflexes were recorded in patients A–D. The H reflex is a short-latency spinal reflex produced by electrical stimulation of group Ia muscle afferents in the parent nerve, exciting α motoneurons in the spinal cord through a largely monosynaptic pathway

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Table 1
Clinical features.

Patient	A	B	C	D	E
Age at onset	57	46	53	42	43
Age when NCS	65	46	57	60	64
Current age	69	60	57	69	Died 75
Achilles tendon reflexes	Normal	Brisk	Normal	Brisk	Brisk/normal
Tactile/vibration/position sensation	Impaired to toes	Impaired to hips	Intact	Impaired to knee	Impaired hands/ft
Pain/temperature sensation	Intact	Impaired on feet	Intact	Impaired to waist	Impaired limbs, trunk
Nystagmus	Horizontal gaze-evoked	Horizontal gaze-evoked, rebound, downbeating	Downbeating	Horizontal gaze-evoked, downbeating	Horizontal gaze-evoked
Vestibulo-ocular reflexes	Absent	Absent	Absent	Absent	Absent
Visually enhanced vestibulo-ocular reflexes	Impaired	Impaired	Impaired	Impaired	Impaired
Romberg's sign	Positive	Positive	Positive	Positive	Positive
Gait ataxia (heel-toe)	Present	Present	Present	Present	Present
Limb ataxia	UL,LL	LL	LL	LL	UL,LL
Autonomic features	Cough	Cough, orthostatic hypotension	Nil	Cough	Cough
MRI cerebellar atrophy	Vermis	Vermis > hemispheres	Mild	Mild lateral lobe	Mild
Sural nerve biopsy	Not done	Severe axonal	Not done	Not done	Severe axonal

Table 2
Nerve conduction.

Patient	Sural SNAP	Median SNAP	Ulnar SNAP	LL motor	UL motor	Thenar F waves	Soleus H
	μV, m/s	μV, m/s	μV, m/s	mV, ms, m/s	mV, ms, m/s	ms	ms
A	0	0	0	8.2/3.9/38	8.3/3.5/38	33.2	34.1[a]
B	0	0	0	8.5,5.1,41	7.4/3.9/47	31.2	32.6
C	0	0.5/49	0	6.9,5.0,36	6.6/3.7/50	31.1	34.7[a]
D	0.5/41	0.9/46	0.6/52	13.0/5.5/50	6.9/3.6/51	27.6	28.1[a]
E	0	0	0.4/36	2.5/4.8/42	10.2/3.4/57	Not tested	Not tested
Laboratory normal	≥ 6/≥ 40	≥ 8/≥ 45	≥ 6/≥ 45	> 4.0/ < 6.0/≥ 40 tibial	> 3.0/ < 5.0/≥ 48 median	Age, height[b]	Age, height[c]

Tests were often performed bilaterally (only right-sided values tabulated), and repeated (only latest results tabulated).
LL motor = peroneal or tibial; UL motor = ulnar or median (if both done, tibial and median).
For sensory studies, values are [SNAP amplitude/conduction velocity] and for motor studies, values are [CMAP amplitude/distal latency/conduction velocity].
[a] H reflex appeared below threshold for the M wave.
[b] Equation: APB minimal F wave latency = 3.62 + 0.12 * Height + 0.04 * Age (years) ± 1.3 [Ref. 32].
[c] Equation: Soleus H reflex = 3.00 + 0.1419 * Height (cm) + 0.0643 * Age (years) ± 1.47 [Ref. 33].

[13,14]. Patients (A), (B) and (D) had another set of neurophysiological studies, included in the group data of a previous report [8].

SNAPs were recorded using surface electrodes, antidromically for the sural nerve, and orthodromically for the median and ulnar nerves following stimulation of digits 2 and 5, respectively [12]. In the lower limbs, motor conduction was recorded for the posterior tibial nerve, recording the compound motor action potential (CMAP) over abductor hallucis, and/or the peroneal nerve, recording the CMAP over extensor digitorum brevis. In the upper limbs, motor conduction was assessed for the median nerve, recording the CMAP over abductor pollicis brevis in 4 patients and for the ulnar nerve, recording the CMAP over abductor digiti minimi in one patient. The fastest F wave was documented for these nerve/muscle combinations. Skin temperature was monitored using a surface probe and kept above 32 °C.

H reflexes were recorded at rest from soleus in 4/5 patients and in 3 of them also from flexor carpi radialis (at rest), from tibialis anterior (during a steady voluntary contraction) and abductor pollicis brevis (during a steady voluntary contraction). The techniques are fully described elsewhere [13,14].

The procedures had the approval of the appropriate institutional review committee, and all studies were performed with fully informed consent, in accordance with the Declaration of Helsinki, initially for clinical management and with written informed consent for the specific purposes of this report.

3. Results

The symptoms, signs and relevant investigations are summarized in Table 1. The patients were all over 40 years, one female (D). All developed slowly progressive deficits of vestibular and cerebellar function, particularly affecting posture and gait. Sensory symptoms were relatively mild and 1 patient had no sensory deficit at all. None of our patients had signs of corticospinal dysfunction, such as weakness, spasticity, clonus or extensor plantar reflexes. In 2 patients, sural nerve biopsy revealed only changes expected with a ganglionopathy: severe loss of myelinated fibres, no infiltrates and no evidence of vasculitis [1]. Muscle biopsy in one of these revealed only early neurogenic changes: mild variation in fibre size with internal nuclei in some fibres, and fibre type grouping but no grouped atrophy, and no evidence of other diagnoses such as mitochondrial myopathy.

There was severe impairment of sensory nerve conduction in all 5 patients, with absent or just detectable SNAPs with normal or near-normal conduction velocities where a pathologically small SNAP could be recorded (Table 2). In contrast there were only minor motor conduction abnormalities. CMAP amplitudes were preserved, as were distal latencies, and there was no evidence of conduction block across the tested segments (Fig. 1A). Motor conduction velocities, and F waves studies on upper and lower limb nerves, assessing the full length of the motor axon, were all normal or near-normal (Fig. 1B,C; Table 2). The motor conduction abnormalities in this select group of patients were less prominent than we reported in larger series [3,8].

H reflexes were assessed as present or absent and by latency,