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PERIPHERAL NERVES ARE PATHOLOGICALLY SMALL IN CEREBELLAR ATAXIA NEUROPATHY VESTIBULAR AREFLEXIA SYNDROME (CANVAS): A CONTROLLED ULTRASOUND STUDY.

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ABSTRACT

BACKGROUND

Sensory neuronopathy is a cardinal feature of Cerebellar Ataxia Neuropathy Vestibular Areflexia Syndrome (CANVAS). Having observed that two patients with CANVAS had small median and ulnar nerves on ultrasound, we set out to examine this finding systematically in a cohort of patients with CANVAS, and compare them with both healthy controls and a cohort of patients with axonal neuropathy. We have previously reported preliminary findings in seven of these CANVAS patients and seven healthy controls.

METHODS

We compared the ultrasound cross-sectional area of median, ulnar, sural and tibial nerves of 14 CANVAS patients with 14 healthy controls and 14 age-and-gender matched patients with acquired primarily axonal neuropathy. We also compared the individual nerve cross-sectional areas of CANVAS and neuropathy patients with the reference values of our laboratory control population.

RESULTS

The nerve cross-sectional area of CANVAS patients was smaller than that of both the healthy controls and the neuropathy controls, with highly significant differences at most sites (p<0.001). Conversely, the nerve cross-sectional areas in the upper limb were larger amongst neuropathy controls than healthy controls (p<0.05). On individual analysis, the ultrasound abnormality was sufficiently characteristic to be detected in all but one CANVAS patient.

DISCUSSION

Small nerves in CANVAS probably reflect nerve thinning from loss of axons due to ganglion cell loss. This is distinct from the ultrasound findings in axonal neuropathy, in which nerve size was either normal or enlarged. Our findings indicate a diagnostic role for ultrasound in CANVAS sensory neuronopathy and in differentiating neuronopathy from neuropathy.

INTRODUCTION

Cerebellar Ataxia Neuropathy Vestibular Areflexia Syndrome (CANVAS) is a recently recognized slowly progressive disorder characterized by three cardinal features: cerebellar ataxia, bilateral vestibular areflexia and somatosensory deficits [1,2]. CANVAS is not uncommon in New Zealand, with an estimated minimum prevalence of ~ 1/100,000 [3]. Post-mortem studies in two CANVAS patients have shown gross atrophy of dorsal root ganglia with sub-total neuronal loss and severe loss of myelinated axons in the posterior columns [2]. A sural nerve sample has shown severe loss of axons with no active Wallerian degeneration or Schwann cell proliferation [1]. These findings characterise the somatosensory disorder of CANVAS as a sensory neuronopathy.

Having observed that two patients with CANVAS had small median and ulnar nerves on ultrasound, we set out to examine this finding systematically in a cohort of patients with CANVAS, and compare them with healthy controls and with patients affected by a non-genetic/non-inflammatory neuropathy that was primarily ‘axonal’on electrodiagnostic tests [4]. Axonal neuropathy has previously been reported to be associated with normal or, less commonly, enlarged nerves on ultrasound [5-9]. We have recently reported preliminary findings of upper limb nerve ultrasound in seven of these CANVAS patients and seven

healthy controls [10].

MATERIALS AND METHODS

The New Zealand Health Disability Ethics Committee and local ethics committees approved this study. All participants gave informed consent. The study included 14 CANVAS patients, 14 age-and-gender matched healthy controls and 14 age-and-gender matched patients with axonal neuropathy. Eleven of the 14 CANVAS patients were included in a previous study of autonomic dysfunction in CANVAS [3]. Subjects were recruited from three New Zealand centres: Tauranga (19), Wellington (14) and Auckland Hospital (9).

CANVAS patients

The diagnosis of CANVAS was based on the triad of progressive ataxia, bilateral vestibular failure and somatosensory impairment [1]. Ataxia was diagnosed by an experienced neurologist and supported in most cases (12/14) by typical vermian and crus1 changes in the cerebellum on MRI. Bilateral vestibular failure was diagnosed with the Halmagyi head impulse test [11] and video-oculography recording of the horizontal vestibular ocular reflex

gain. Sensory impairment in all patients was consistent with the suggested clinical and electrophysiological criteria for sensory neuronopathy [12] with nerve conduction studies showing absent or reduced sensory action potentials (SNAPs) in median, ulnar, radial and sural nerves. Other conditions in the differential diagnosis, such as triplet repeat SCAs, late-onset Friedreich ataxia, multiple system atrophy, and inflammatory disorders of the brain, had been excluded. We excluded CANVAS patients with diabetes or other co-morbidity potentially associated with peripheral neuropathy.

Most CANVAS patients were recruited using The New Zealand Neuromuscular Registry [13].

Peripheral Neuropathy Controls

The neuropathy was due to diabetes in ten, idiopathic in three and thought probably due to vasculitis in one. The patients with diabetic and idiopathic neuropathy presented clinically with large fibre sensory deficits in a glove-and-stocking distribution. Nerve conduction studies confirmed a length-dependent axonal neuropathy with reduced or absent sural SNAP, normal or reduced median, ulnar and radial SNAPs, and normal or slightly reduced conduction velocities [4]. In ten patients, the amplitude of the compound muscle action

potentials in the lower extremities was also reduced, with normal or slightly prolonged distal motor latency. The patient with vasculitis had sensory and motor signs and electrodiagnostic evidence of axonal loss in a generalized, but asymmetric multifocal distribution.

Healthy Controls

The 14 healthy controls were subjects who attended outpatient clinics for non-neurological conditions with no personal or family history of neurological disorders and no symptoms or signs of peripheral neuropathy.

Clinical assessment of sensory deficit

Sensory signs were graded with the Inflammatory Neuropathy Cause and Treatment Sensory Sumscore (ISS) [14], which ”ranges from 0 (normal sensation) to 20 (most severe sensory deficit)”. It is scored by examining five components: upper limb pinprick; lower limb pinprick; upper limb vibration; lower limb vibration and upper limb two point discrimination, each of which is rated 0 to 4 based on specific criteria [14].

Nerve Ultrasound

A single ultrasonographer (LP) performed all ultrasound studies using the SonoSite Edge system (Fujifilm SonoSite Inc., Bothel, WA, USA) with a 6-15 MHz linear array transducer. In the study period when all CANVAS patients were assessed, the ultrasonographer was blinded to whether the patients had CANVAS, neuropathy or were healthy controls. In the latter stages the ultrasonographer was aware of the diagnosis in seven neuropathy and five healthy control subjects.

The cross-sectional area of the median and ulnar nerves was measured unilaterally at mid-forearm and mid-humerus level; sural nerve at the lower calf and tibial nerve at the popliteal fossa. These nerves were chosen because median and ulnar were where we first observed the cross-sectional area difference, sural might be expected to be most affected as it's a purely sensory nerve, and tibial to include a larger proximal nerve as that might have more scope for observing atrophy. The nerves were measured using the trace function on the ultrasound device with manual tracing within the hyperechoic rim surrounding the nerve. Three measurements were made at each site and the transducer was lifted between each measurement. The mean values were taken.

Statistical analysis

We used ANOVA to compare the demographics (age, male/female ratio, height, weight), ISS and ultrasound findings between the CANVAS, neuropathy control and healthy control groups. Where ANOVA showed a significant difference, we did post-hoc comparisons to see whether individual groups differed significantly from each of the other groups. The TukeyHSD algorithm was used to correct for multiple comparisons within these post-hoc analyses and all *p* values are quoted after this correction. We also compared the individual nerve cross-sectional areas of each nerve with the reference values obtained in our control population before this study (our laboratory defines abnormality by the mean ± 2 SD. See Supplementary Table 1 for lower and upper limits).

RESULTS

There were no significant group differences in age, gender, height or weight (Table 1). Sensory examination ISS scores were different across the three groups ($p<0.001$). Scores were twice as high in the CANVAS patients (15.6 ± 3.2) than in the neuropathy controls (7.0 ± 2.7) and both were much higher than the healthy controls (0.6 ± 1.1); ($p<0.001$ for all post-hoc intergroup comparisons).

The nerve cross-sectional areas were significantly different across the groups at all six sites. There was a consistent group finding at all sites that CANVAS patients' nerves were smaller than both the healthy controls' and the neuropathy controls'. This was particularly the case in the upper limbs where the CANVAS patients' nerves were, overall, half the size of healthy control patients' and about a third the size of peripheral neuropathy patients' (p<0.001 for all comparisons) (Table 2, Figs. 1 and 2). Relative to our reference population, the nerve cross-sectional area of CANVAS patients was significantly reduced at two or more sites in 13/14 patients and four or more sites in nine/14 (Supplementary Table 1).

In contrast to the CANVAS patients' small nerves, the neuropathy patients' nerves in the upper limb were about a third larger than the healthy controls (p<0.03 for all comparisons; Table 2, Figs. 1 and 2). This was not as consistent a finding as in the CANVAS patients with just seven/14 patients having abnormalities at two or more sites and three/14 at four or more (Supplementary Table 1). Six of the seven neuropathies with nerve enlargement at two or more sites were diabetic and one idiopathic. Two additional neuropathies (one diabetic, one idiopathic) had nerve enlargement at just one site.

The ulnar nerve was the most often affected in both the CANVAS patients (12/14 at both mid-forearm and mid-humerus) and the neuropathy controls (eight/14 at mid-humerus), followed in CANVAS patients by the median at mid-forearm (11/14) and mid-humerus (ten/14) (Supplementary Table 1).

Given the remarkable consistency of our results which are in no way independent of each other (cross-sectional area in one nerve correlates closely with the cross-sectional area in the same nerve at another site in the same patient, and the cross-sectional area of other nerves in that patient) we did not consider it necessary to adjust for multiple testing at six different sites.

DISCUSSION

This study confirms our preliminary findings that the nerves of CANVAS patients are significantly smaller than the nerves of age-and-gender matched healthy controls [10]. Additionally, this study shows that CANVAS patients' nerves are significantly smaller than those of patients with axonal loss from peripheral neuropathy, at all measurement sites in the upper and lower limbs. There were no significant differences in age, gender, height or weight to account for the group differences in the nerve size.

Previous pathological studies of CANVAS patients have demonstrated atrophy of the dorsal root ganglion, with sub-total neuronal loss and secondary posterior column atrophy, and complete absence of axons with replacement fibrosis and no active Wallerian degeneration or Schwann cell proliferation in sural nerve [1,2].

The clinical and electrophysiological pattern of abnormality in our CANVAS patients was consistent with the diagnostic criteria suggested for sensory neuronopathy [12] and with a recent electrophysiological study [15], so it is very likely that the reduced nerve size in CANVAS corresponds to the severe loss of axons previously demonstrated in nerve biopsy. Plausibly, sensory axon loss secondary to dorsal ganglion cell death results in nerve thinning, reflected in reduced nerve cross-sectional area on ultrasound.

When checked against our reference control population, the abnormal nerve size in individual CANVAS patients was sufficiently severe to be detected at multiple measurement sites, in all but one patient. Accordingly, nerve sonography could justifiably be proposed as a diagnostic tool for neuronopathy in CANVAS.

The ulnar and median nerves were the most affected. For reasons that are unclear, the lower limb nerves were less often affected. Potentially, this discrepancy reflects a preferential

involvement of the sensory afferents to the fasciculus cuneatus and, possibly also the cuneocerebellar tract, in this neuronopathy, but this remains to be demonstrated.

No previous systematic nerve ultrasound studies of sensory neuronopathy exist for comparison. Interestingly, two studies have shown smaller nerve cross-sectional areas in patients with amyotrophic lateral sclerosis (ALS) than controls [16,17]. This was explained as motor neurone loss resulting in atrophy of the nerve [16]. While the differences in nerve cross-sectional area was statistically significant between the ALS and control groups, the absolute differences were not "obvious enough to assist in the diagnosis" [16] due to a significant overlap between patients and controls [17]. By contrast, in our study, the ultrasound changes were sufficiently severe to be classified as abnormal in all but one patient.

Our study confirmed that in contrast to the CANVAS patients, the nerve cross-sectional areas of patients with axonal neuropathy were either comparable to or larger than those of the healthy controls. Most of our neuropathy patients had diabetes. Our findings are consistent with recent nerve ultrasound studies in diabetes showing nerve enlargement both at compression sites and non-compression sites [9,18-19]. It has been proposed that the nerve enlargement may be due to impaired axonal flow with accumulation of materials within the axon [9,20], oxidative stress, microangiopathy and/or nerve ischemia with associated neuro-

inflammation [9,21-22]. However, other studies have reported no difference in nerve size between patients with diabetes and healthy controls (6,23). The conflicting reports in the literature regarding whether diabetic nerves are enlarged or not could be partly accounted for by variation in the 'normal ultrasound values' in different laboratories, possibly relating to differences in image acquisition techniques, resolution and population demographic.

Nerve enlargement has also been reported in vasculitic neuropathy. Epineural oedema, perivascular haemorrhage and focal inflammation have been suggested as possible mechanisms [5,24].

Reduced nerve size on ultrasound has not been reported in peripheral neuropathy, supporting the argument that the underlying pathophysiological mechanisms in CANVAS and axonal neuropathy are quite distinct.

Electrodiagnostic tests provide information about large diameter nerve fibres; the small myelinated and unmyelinated nerve fibres and the non-neurological nerve components are not assessed. In 'pure' ganglionopathy, the loss of neurones without additional abnormality at peripheral nerve level triggers nerve thinning, which is expressed by reduced sensory amplitudes on electrophysiology and reduced nerve size on ultrasound. However, neuronopathies and severe axonal neuropathies may be indistinguishable on

neurophysiological tests. Nerve ultrasound helpfully discriminated CANVAS neuronopathy from axonal neuropathy, with reduced and increased nerve sizes, respectively.

Our findings apply to CANVAS, but might also be applicable to other forms of sensory neuronopathy, where nerve sonography could be a valuable additional tool to diagnose this condition with potentially higher specificity than nerve conduction studies. It would be interesting, in future studies of CANVAS and other neuronopathies, to also compare the ultrasound of the peripheral nerves with spinal root, posterior spinal column and cerebellar imaging.

Our neuropathy group included patients with different pathologies and less severe sensory deficits (as assessed by the ISS scores) than the CANVAS population. This may represent a bias when comparing the ultrasound findings in the two groups.

The high ISS score in the CANVAS group is consistent with a generalized severe neuronopathy. The death of the ganglion cells with secondary degeneration of their centripetal axons and spinal segmental branches, is likely to cause a significant disruption of the spinal and supraspinal processing of proprioceptive inputs. This may play a significant role in the unsteadiness and ataxia of the CANVAS patients.

In spite of the high ISS score, CANVAS patients do not particularly complain of sensory symptoms, while the opposite was true for the neuropathy patients. This observation is also true for patients with genetically determined neuropathies such as Charcot-Marie-Tooth [25]

and, in conjunction with the striking uniformity of the ultrasound abnormalities, may support a genetic basis for CANVAS.

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FIGURE LEGENDS

Figure 1. Nerve cross-sectional areas in 14 CANVAS, 14 healthy controls (HCONT) and 14 neuropathy patients (PNCONT)

The dotplots show the nerve cross-sectional area of each patient in each group at six recording sites. The horizontal line is the mean cross-sectional area in each group. CSA = Nerve cross-sectional area.

Figure 2. Group images of median nerve ultrasound at mid-forearm and mid-humerus level.

Each image is a superimposition of 14 individual median nerve images in each group. The superimposition was achieved by reducing the opacity of each original image by 80% and then sliding the nerve images on top of each other. The group nerve contour (bright grey line) was then re-traced, keeping midway between the widest and the narrowest individual nerve CSAs, approximating the mean CSA in each group. Some of the individual CSA

measurements are still visible underneath (pale little crosses) on either side of the 'group' line.

CSA = Cross-sectional Area; HCONT = Healthy controls; PNCONT = Neuropathy controls

List of abbreviations

CANVAS = Cerebellar Ataxia Neuropathy Vestibular Areflexia Syndrome

HCONT = Healthy controls

ISS = Inflammatory Neuropathy Cause and Treatment Sensory Sumscore

PNCONT = Neuropathy controls

SNAP = sensory nerve action potential

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Table 1. Group Demographics and Sensory Examination Scores

	Age (Years)	Females (n)	Height (cm)	Weight (kg)	ISS mean (SD)
CANVAS	65.6	10	167.2	63.5	15.6 (3.2)
Neuropathy controls	67.1	10	167.6	74.9	7.0 (2.7)
Healthy controls	67.1	10	169.6	75.4	0.6 (1.1)

Each group had 14 patients; all groups had 10 women. There were no significant inter-group differences for age ($p=0.93$), gender ($p=1.0$), height ($p=0.82$) or weight ($p=0.07$). ISS scores between groups were significantly different ($p<0.001$). Post hoc analysis showed that CANVAS patients' ISS scores were significantly higher than both neuropathy controls and normal controls, and neuropathy controls' mean ISS was also higher than normal controls ($p<0.001$ for all two-way group comparisons). ISS = Inflammatory Neuropathy Cause and Treatment Sensory Sumscore.

Table 2. Comparison of Nerve Cross-sectional Area across Patient Groups

	MF	MH	UF	UH	SC	TK
CANVAS	2.36 (1.0)	4.35 (1.9)	3.02 (1.0)	2.79 (0.8)	1.83 (0.8)	29.29 (5.7)
Healthy controls	5.73 (1.1)	8.86 (2.0)	6.03 (1.1)	5.96 (1.1)	3.62 (1.0)	37.35 (6.0)
Neuropathy controls	7.61 (2.4)	11.38 (3.2)	7.72 (2.2)	8.85 (3.1)	4.36 (2.0)	40.79 (11.7)
Post-hoc Comparisons						
CANVAS-Healthy controls	<.001	<.001	<.001	<.001	.0068	.0437
CANVAS-Neuropathy controls	<.001	<.001	<.001	<.001	<.001	.0023
Neuropathy controls-Healthy controls	.013	.028	.018	.0013	.38	.542

Group mean (SD) for the nerve cross-sectional area (mm^2) and post-hoc comparison for each nerve site measurement in the three groups.

There were significant differences for all CANVAS patients' nerves at all sites (ANOVA $p < 0.001$ at all upper limb sites and $p < 0.05$ at lower limb sites). The nerves of CANVAS patients were approximately half the size of healthy controls and about a third of neuropathy controls at upper limb sites. The nerves of neuropathy controls were demonstrably larger than healthy controls' in the upper limbs.

MF = Median Nerve Mid-Forearm; MH = Median Nerve Mid-Humerus; UF = Ulnar Nerve Mid-Forearm, UH = Ulnar Nerve Mid-Humerus; SC = Sural nerve lower calf and TK = Tibial nerve Popliteal Fossa