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REPORT

Autonomic dysfunction is a major feature of cerebellar ataxia, neuropathy, vestibular areflexia 'CANVAS' syndrome

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Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) is a recently recognized neurodegenerative ganglionopathy. Prompted by the presence of symptomatic postural hypotension in two patients with CANVAS, we hypothesized that autonomic dysfunction may be an associated feature of the syndrome. We assessed symptoms of autonomic dysfunction and performed autonomic nervous system testing among 26 patients from New Zealand. After excluding three patients with diabetes mellitus, 83% had evidence of autonomic dysfunction; all patients had at least one autonomic symptom and 91% had more than two symptoms. We also found a higher rate of downbeat nystagmus (65%) than previously described in CANVAS. We confirmed that sensory findings on nerve conduction tests were consistent with a sensory ganglionopathy and describe two patients with loss of trigeminal sensation consistent with previous pathological descriptions of trigeminal sensory ganglionopathy. Our results suggest that autonomic dysfunction is a major feature of CANVAS. This has implications for the management of patients with CANVAS as the autonomic symptoms may be amenable to treatment. The findings also provide an important differential diagnosis from multiple system atrophy for patients who present with ataxia and autonomic failure.

Keywords: CANVAS syndrome; cerebellar ataxia; vestibular failure; neuronopathy; autonomic failure

Abbreviations: CANVAS = cerebellar ataxia, neuropathy, vestibular areflexia syndrome; SAS = Survey of Autonomic Symptoms; TIS = Total Symptom Impact Score

Introduction

In 1995, Rinne *et al.* reported the association of a progressive cerebellar disorder in 7 of 53 patients with bilateral vestibular failure; four of these patients also had sensory neuropathy. The co-occurrence of ataxia, vestibular failure and neuropathy has since been described in several cohorts (Migliaccio *et al.*, 2004; Zingler *et al.*, 2007; Wagner *et al.*, 2008; Kirchner *et al.*, 2011; Szmulewicz *et al.*, 2011, 2014). Szmulewicz *et al.* (2011) coined the term CANVAS (Cerebellar Ataxia, Neuropathy, Vestibular Areflexia Syndrome). They subsequently reported post-mortem histopathological findings in three patients: cerebellar atrophy, predominantly affecting the superior and inferior vermian Purkinje cell layers with preservation of the brainstem neurons; atrophy of the vestibular, geniculate and trigeminal ganglia; and atrophy of the sensory ganglia and dorsal columns (Szmulewicz *et al.*, 2014). The latter finding is consistent with the neurophysiological finding of complete loss of sensory action potentials rather than a length-dependent pattern of sensory loss.

In 2012, two of our patients with CANVAS were noted to have symptomatic postural hypotension. The combination of postural hypotension and progressive ataxia suggested that their diagnosis might have been multiple system atrophy, but the prolonged clinical course, absence of rapid eye movement sleep behaviour disorder, parkinsonism or brainstem atrophy on MRI, and the presence of vestibular failure were against this diagnosis.

We hypothesized that autonomic failure may be a feature of CANVAS itself and tested this hypothesis by assessing autonomic function in as many patients with CANVAS as we could identify. We also attempted to elucidate the neuroanatomical basis for downbeat nystagmus (Supplementary material).

Materials and methods

Patients

Neurologists throughout New Zealand were approached for patients diagnosed with CANVAS. The histories and examination findings were established retrospectively for each patient using hospital notes, supplemented where necessary with additional assessments by the authors. To fulfil the diagnosis of CANVAS patients had progressive cerebellar ataxia, bilateral vestibular failure and sensory neuropathy/neuronopathy without another cause for symptoms such as alcoholic cerebellar degeneration or aminoglycoside toxicity.

Vestibular failure had initially been diagnosed in all patients with a positive head impulse test (Weber *et al.*, 2008). Where available, vestibular failure was confirmed either by quantitative vestibulo-ocular reflex on video-oculography (Supplementary material) or caloric testing (Kim *et al.*, 2011), to avoid including patients with false positive head impulse test (Kremmyda *et al.*, 2012). Where quantitative testing was not available, vestibular failure was qualitatively confirmed if there was an impaired visually enhanced vestibulo-ocular reflex on video-oculography (Petersen *et al.*, 2013). Where no confirmatory laboratory test was available (two patients) the head impulse test was required to be unequivocally positive. Neuropathy was considered to be present when nerve conduction studies demonstrated reduced or absent sensory nerve action potentials.

Imaging analysis

All patients had had MRIs. The images were reviewed by two experienced neuroradiologists to exclude other causes of ataxia and to compare the appearances with those previously described in CANVAS. In addition, the images were analysed for regional cerebellar atrophy, in an attempt to localize an anatomical correlate of downbeat nystagmus (Supplementary material and Supplementary Fig. 1).

Autonomic assessment

Autonomic assessment was performed prospectively using the same protocol in each centre. The Survey of Autonomic Symptoms (SAS) devised by Zilliox *et al.* (2011) was administered to all patients. The SAS is a questionnaire comprising 11 (for females) or 12 (for males) items, validated for assessing autonomic symptoms in patients with autonomic neuropathy. The Total Symptom Impact Score (TIS) derived by summating the rated severity of individual SAS scores was calculated. Results were compared with the published distribution of results in patients with and without neuropathy (Zilliox *et al.*, 2011).

Bedside cardiac autonomic tests were performed using the protocol developed for the diagnosis of diabetic autonomic neuropathy (Ewing and Clarke, 1982; Ewing *et al.*, 1985). Parasympathetic function was assessed by continuous ECG monitoring for heart rate variation during Valsalva manoeuvre, deep breathing and on standing. Sympathetic function was assessed by measuring blood pressure response to change in posture and handgrip. Each autonomic test (except the Valsalva ratio) has a defined normal, borderline and abnormal range (Ewing *et al.*, 1985). Assigning 0 for normal, 1 for borderline and 2 for abnormal, and with minor modification to the Ewing classification, we defined definite parasympathetic dysfunction as a score $\geqslant 4$ and definite sympathetic dysfunction as a score $\geqslant 2$. Details of the autonomic function test protocol are provided in the Supplementary material.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and approved online by the New Zealand Health and Disability Ethics Committee. All patients gave written consent for their data to be published in this manner.

Statistics

The data are described with standard descriptive statistics. Pearson's test was used to test potential correlations of autonomic symptom scores and autonomic function test subscores. Statistical analysis was performed using R version 3.01 (http://www.R-project.org/).

Results

Twenty-six patients with CANVAS were recruited from seven centres; Auckland, $n = 13$; Wellington, $n = 6$; Christchurch and Tauranga, $n = 2$ each; Dunedin, Hamilton and Whangarei, $n = 1$ each. The mean age at assessment was 65.8 years (range 49–84); mean age of symptom onset was 54.6 years (range 19–82) and mean duration of symptoms was 11.7 years (range 1–35). Two-thirds of the patients were female (Table 1). All patients had European ancestry; four also had New Zealand Maori ancestry and two had other Polynesian ancestry. Most patients (22/26) reported gait imbalance as their initial symptom; three presented with sensory symptoms in the distal extremities. Two patients

Table 1 Summary of patient characteristics and results of autonomic evaluation

	Age	Gender	First symptom at onset	Duration of symptoms	MRI findings	Diagnosis of CANVAS Cerebellar ataxia	NCS	Vestibular failure: Gains R, L	Nystagmus	Autonomic symptom assessment SAS	TIS	Sympathetic dysfunction Postural SBP reduction (mmHg)	DBP response to handgrip (mmHg)	Para-sympathetic dysfunction HR response to deep breathing	Valsalva ratio	HR response to standing (30:15 ratio)
1	75	Female	Sensory alteration legs	12 years	2013 Moderate vermian atrophy Mild Crus I atrophy	Gait ataxia, limb ataxia, dysarthria	2013 Absent SNAPs (arm + leg). Normal Motor study	Quantitative VOR 0.20, 0.12 VVOR	Downbeat	2	2	42	4	4.7	1.09	1.01
2	73	Female	Gait ataxia	23 Years	2010 Moderate vermian atrophy. Mild Crus I atrophy	Gait ataxia, limb ataxia, dysarthria	2013 Absent SNAPs Reduced CMAPs, increased distal latency	Head Impulse Test	Downbeat	4	9	30	24	10.0	1.12	1.00
3	62	Male	Gait ataxia	15 years	2010 Moderate dorsal and severe ventral vermian atrophy. Severe Crus I atrophy	Gait ataxia, limb ataxia, dysarthria	2013 Absent SNAPs Reduced CMAPs.	Quantitative VOR 0.06, 0.04	Downbeat, rotatory	8	21	+2	5	30.7	1.97	1.55
4*	58	Male	Gait ataxia	21 years	2011 Severe vermian atrophy. Severe Crus I atrophy	Gait ataxia, limb ataxia, dysarthria	2013 Absent SNAPs arms/legs. Normal motor study	Quantitative VOR 0.31, 0.38 Calorics, VVOR	No	6	18	30	6	7.2	1.09	1.00
5	68	Female	Gait ataxia	13 years	2009 Moderate ventral and severe dorsal vermian atrophy. Moderate Crus I atrophy	Gait ataxia, dysarthria	2011 Absent SNAPs. Mild widespread motor neuropathy	Quantitative VOR 0.07, 0.10	Downbeat	4	8	+6	12	9.2	1.18	1.08
6**	72	Male	Gait ataxia	17 years	2011 Mild dorsal vermian atrophy. Moderate Crus I atrophy.	Gait ataxia, limb ataxia, dysarthria	2013 Absent SNAPs. Mild length dependent axonal motor neuropathy	Quantitative VOR 0.19, 0.11	Gaze evoked horizontal nystagmus	5	8	8	− 8	32.3	1.72	1.33
7	67	Male	Gait ataxia	7 years	2012 Mild dorsal vermian atrophy. Moderate Crus I atrophy.	Gait ataxia, limb ataxia, dysarthria	2013 Absent SNAPs. Normal motor study	Quantitative VOR 0.21, 0.21	Gaze evoked nystagmus	3	7	36	7	24.1	1.37	1.56
8	76	Male	Gait ataxia, sensory loss legs	4 years	2010 Mild Crus I atrophy	Gait ataxia, limb ataxia, dysarthria	2011 Absent SNAPs. Normal motor study	Quantitative VOR 0.23, 0.11	Downbeat	2	4	53	9	15.4	1.19	1.03
9**	69	Female	Gait ataxia	9 years	2013 Mild ventral and dorsal vermian atrophy. Mild Crus I atrophy.	Gait ataxia, limb ataxia, dysarthria	2012 Absent SNAPs. Normal motor study	Quantitative VOR 0.16, 0.15	Gaze evoked horizontal nystagmus	4	8	10	7	3.6	1.39	1.00
10	56	Male	Gait ataxia and numbness feet	1 year	2013 Mild ventral vermian atrophy. Mild Crus I atrophy.	Gait ataxia, limb ataxia, dysarthria	2013 Absent SNAPs. Normal motor study	Quantitative VOR 0.22, 0.21 VVOR	Downbeat	1	2	+4	18	11.1	1.07	ND
11	66	Female	Gait ataxia	13 years	2004 Mild ventral vermian atrophy. Moderate Crus I atrophy	Gait ataxia, limb ataxia, dysarthria	2003 Absent SNAPs. Normal motor study	Quantitative VOR 0.55, 0.57 Dynamic VA	Downbeat	5	10	65	5	11.2	1.24	1.05
12#	61	Female	Gait ataxia	10 years	2013 Mild vermian and Crus I atrophy	Gait ataxia, limb ataxia, dysarthria	2004 Absent SNAPs. Normal motor study	Quantitative VOR 0.03, 0.34	Downbeat	4	12	41	5	12.4	1.45	1.08
13#	57	Female	Gait ataxia	5 years	2011 Mild dorsal atrophy. Mild Crus I atrophy.	Gait ataxia, dysarthria	2011 Absent SNAPs. Normal motor study	Quantitative VOR 0.57, 0.50 Dynamic VA	None	5	15	24	7	5.0	1.07	1.05
14	80	Female	Gait ataxia	24 years	2000 Mild dorsal and moderate ventral vermian atrophy. Mild Crus I atrophy	Gait ataxia, limb ataxia, dysarthria	2000 Absent SNAPs. Normal motor study	Quantitative VOR 0.11, 0.30 Calorics	Horizontal	6	14	5	2	NR	1.92	1.43
15	58	Female	Gait ataxia	5 years	2008 Mild ventral vermian atrophy. Mild Crus I atrophy.	Gait ataxia, ataxia,	2009 Absent or reduced SNAPs. Normal motor study	Calorics, Dynamic VA	Downbeat	6	9	3	3	8.0	1.29	1.08
16	54	Female	Gait ataxia, 'spastic gait'	35 years	1998 Normal	Gait ataxia, limb ataxia, dysarthria	1999 (age 39) Low sural SNAPs, normal motor and sensory studies elsewhere	Calorics, Dynamic VA	Downbeat, horizontal	10	27	+12	15	16.5	1.28	1.00

(continued)

Table 1 Continued

	Age	Gender	First symptom at onset	Duration of symptoms	MRI findings	Diagnosis of CANVAS		Nystagmus	Vestibular failure: Gains R, L	Autonomic symptom assessment		Sympathetic dysfunction		Para-sympathetic dysfunction		
						Cerebellar ataxia	NCS			SAS	TIS	Postural SBP reduction (mmHg)	DBP response to handgrip (mmHg)	HR response to deep breathing	Valsalva ratio	HR response to standing (30:15 ratio)
17+	76	Female	Gait ataxia	17 years	1999 Mild ventral vermian atrophy. Mild Crus I atrophy	Gait ataxia, limb ataxia, dysarthria	1998 Absent SNAPs. Normal motor study	Downbeat, horizontal	Quantitative VOR 0.12, 0.24	9	27	+5	34	10.5	1.27	**1.00**
18+	63	Female	Gait ataxia	15 years	2011 Mild ventral vermian atrophy. Mild Crus I atrophy.	Gait ataxia, limb ataxia, dysarthria	2011 Absent SNAPs. Normal motor study	Horizontal	Quantitative VOR 0.09, 0.03 Dynamic VA	4	5	24	**2**	**4.0**	**1.08**	1.10
19$	69	Female	Gait ataxia	17 years	2006 Mild vermian atrophy. Mild Crus I atrophy.	Gait ataxia, dysarthria	2006 Absent SNAPs Normal motor study	Horizontal	Calorics Dynamic VA	1	1	+1	4	19.5	NR	0.95
20	68	Female	Paraesthesia limbs, mild ataxia	2.5 yr	2011 Normal	Gait ataxia, limb ataxia	2013 Reduced upper and lower limbs SNAPs Reduced lower limb CMAPs	Gaze evoked horizontal nystagmus	Quantitative VOR 0.50, 0.50 Calorics	7	23	31	12	**1.5**	1.14	1.13
21	71	Male	Paraesthesia limbs	8 yrs	2011 Moderate ventral vermian atrophy. Moderate Crus I atrophy.	Gait ataxia, limb ataxia, dysarthria	NCS 2009 Absent SNAPs Normal motor study	Downbeat	Calorics VVOR	5	14	35	7	13.0	**1.08**	**1.00**
22*	53	Female	Gait ataxia	12 years	2006 Mild dorsal and moderate ventral vermian atrophy Mild Crus I atrophy.	Gait ataxia, limb ataxia, dysarthria	2002 Absent sural SNAPs, reduced digital SNAPs. Reduced CMAPs	Downbeat	Vestibulo-oculographic VVOR	5	17	21	**2**	**3.3**	1.37	**1.00**
23	52	Male	Gait ataxia	5 years	2012 Moderate ventral vermian atrophy. Mild Crus I atrophy.	Gait ataxia, limb ataxia, dysarthria	2010 Absent SNAPs. Normal motor study	Downbeat	Vestibulo-oculographic VVOR	4	5	10	**10**	18.0	1.37	1.06
24	84	Male	Gait ataxia	1.5 years	2013 Global cerebellar atrophy	Gait ataxia, limb ataxia, dysarthria	2013 Low or absent digital SNAPs. Normal hand motor study.	Downbeat	Quantitative VOR 0.23, 0.28	6	14	+27	4	15.9	1.33	0.99
25	49	Female	Chronic cough	7 years	2011 Mild dorsal and severe ventral vermian atrophy. Moderate Crus I atrophy	Gait ataxia, limb ataxia, dysarthria	2013 Absent SNAPs Normal motor study	Downbeat	Quantitative VOR 0.38, 0.38 Dynamic VA	4	10	22	2.7	5.2	2.14	0.95
26	73	Female	Gait ataxia	4 years	2013 Mild dorsal vermian atrophy. Mild Crus I atrophy	Gait ataxia, limb ataxia	2010 Absent SNAPs. Reduced lower limb CMAPs	Downbeat	Head Impulse Test	6	16	23	ND	NR	**1.08**	1.16

*, **, #, + denote sibling pairs.

$ part of sibling pair but sister is deceased.

Gains = ratio (velocity of eye movement)/(velocity of head movement) 80 ms after onset of head impulse.

Interpretation of autonomic test results adapted from Ewing et al. (1985).

Valsalva ratio: normal ≥ 1.22, abnormal ≤ 1.21.

Heart rate variation during deep breathing: normal ≥ 15, borderline 11–14, abnormal ≤ 10.

Heart rate response to standing (30:15 ratio): normal ≥ 1.04, borderline 1.01–1.03, abnormal ≤ 1.0.

Postural systolic blood pressure decline: normal ≤ 10 mmHg, borderline 11–29 mmHg, abnormal ≥ 30 mmHg.

Diastolic blood pressure response to sustained handgrip: normal ≥ 16 mmHg, borderline 11–15 mmHg, abnormal ≤ 10 mmHg.

In bold = abnormal; underlined = borderline, otherwise normal.

DBP = diastolic blood pressure; ND = not done; NR = no result (Patient 14 had frequent atrial ectopics, Patients 19 and 26 had frequent pauses during this part of the test to render result uninterpretable); SBP = systolic blood pressure; SNAP = sensory nerve action potential; VOR = vestibulo-ocular reflex; VVOR = visually enhanced vestibulo-ocular reflex; R = right; L = left; NCS = nerve conduction studies; HR = heart rate; CMAP = compound muscle action potential; VA = visual acuity.
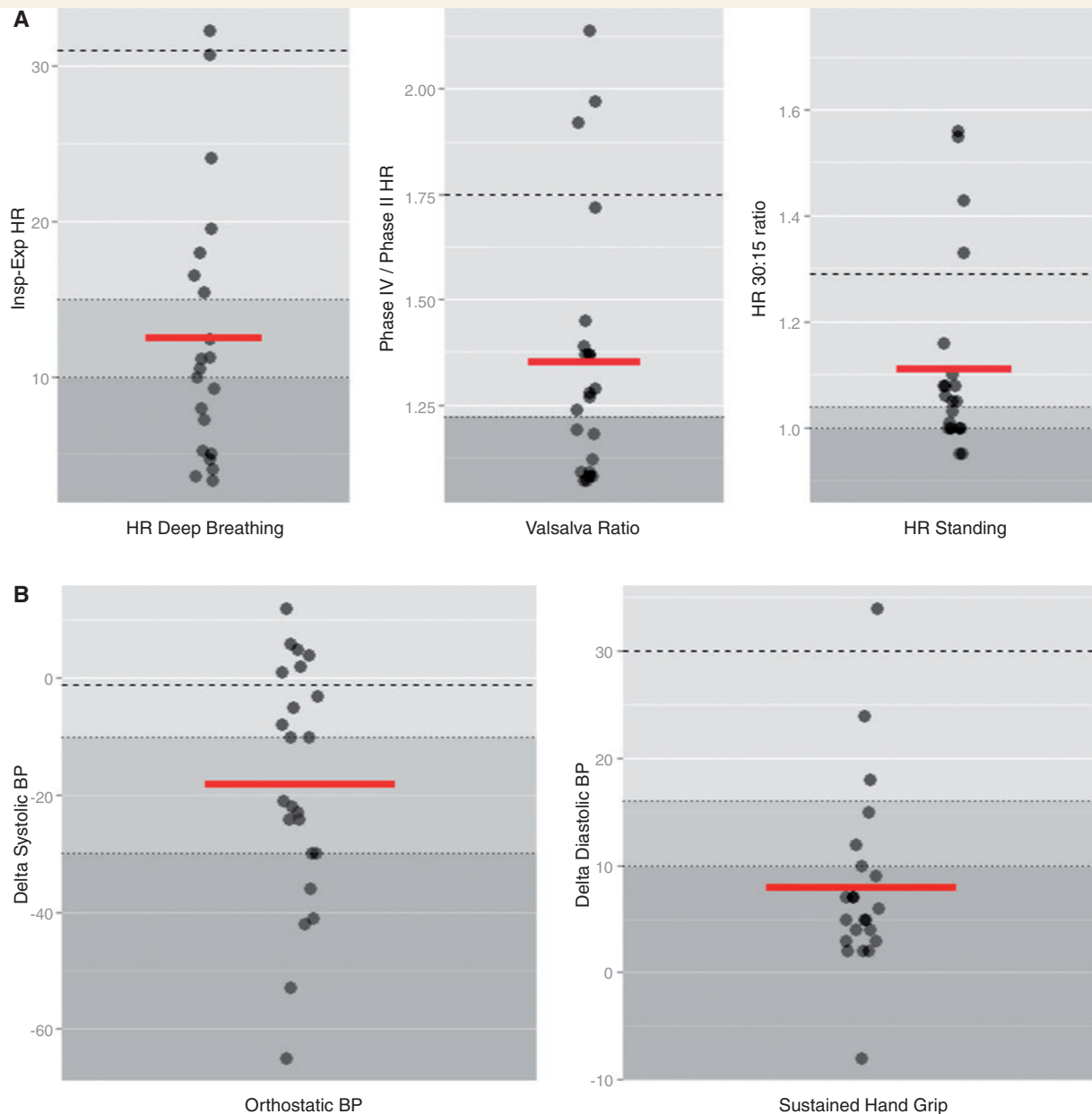
Figure 1 Distribution of autonomic function test scores. The dark grey shaded area represents abnormal results, light grey represents borderline results and pale grey represents normal results. The dashed line represents mean normal values derived from Ewing *et al*. (1985). The solid red line represents the median test value. (**A**) The three parasympathetic test results; and (**B**) the two sympathetic test results. Insp-Exp = inspiration-expiration; HR = heart rate; BP = blood pressure.

described chronic cough and in one patient this was the initial symptom, 5 years before the onset of ataxia. On examination, all had gait ataxia whereas 23 (88%) patients also had dysarthria and/or limb ataxia. Twenty-four (92%) had nystagmus, 17 of whom (65%) had downbeat nystagmus. Two patients had absent pinprick appreciation on the face. Three patients had diabetes mellitus; we excluded their autonomic assessments from our analysis.

In 22 subjects, the presence of bilateral vestibular failure was confirmed by quantitative testing: 18 subjects by quantitative video-oculographic head impulse testing, and four by bithermal caloric tests. The diagnosis was confirmed with abnormal visually

enhanced vestibulo-ocular reflex tests recorded with video-oculography in two patients; only two subjects were diagnosed on the basis of bilateral unequivocally positive clinical head impulse tests.

The degree of vestibular failure was marked with the average gain on video-oculography being 0.24 [standard deviation (SD) 0.16, range 0.03–0.57, normal >0.79]. The results for both sides were similar within an individual, the average absolute difference in gain between the two sides being 0.07 (correlation coefficient 0.8, $P = 0.0001$).

The pattern of the nerve conduction tests pointed to a sensory neuronopathy with absent sensory action potentials in 21 of the 23 (91%) non-diabetic patients.

Genetic and vitamin E testing

Eighteen patients had been tested for spinocerebellar ataxia 1, 2, 3, 6 and 7; nine of these had also been tested for spinocerebellar ataxia 17; five for dentatorubral-pallidoluysian atrophy and two for *SPG7*, which has been described in a patient with ataxia and vestibular failure (Roxburgh *et al.*, 2013). Serum vitamin E levels had been measured in 13 patients, all results were normal.

Brain imaging

Of the 25 MRI scans available for review, two were normal, one showed generalized cerebellar atrophy and 22 had some degree of vermian and crus I atrophy as previously described in CANVAS (Szmulewicz *et al.*, 2011). No patient had brainstem or upper cervical cord atrophy. Twenty-three scans were available for assessment of focal atrophy. Crus I atrophy was associated with increased disease duration ($P < 0.001$) but not with patient age. No specific association with downbeat nystagmus was found (Supplementary material).

Survey of autonomic symptoms

All patients reported at least one SAS autonomic symptom and 21 patients (91%) reported at least two (Table 2). The median SAS score was 4 (range 1–10). The median TIS score was 9 (range 1–27). The distribution of these scores was significantly different from the historical controls [SAS 95% confidence interval (CI): 0.58–1.69, TIS 95% CI: 1.51–5.02) (Fig. 2) (Zilliox *et al.*, 2011). Cold feet (78%), light-headedness (65%), constipation (65%) and dry mouth or eyes (52%) were the most common symptoms. Additionally, 78% (seven of nine) of the males had erectile dysfunction. Symptom severity was similar to that reported in patients with diabetic autonomic neuropathy (Fig. 2B) (Zilliox *et al.*, 2011).

There was a modest linear correlation of increasing SAS (rho = 0.41) and TIS (rho = 0.48) scores with disease duration ($P = 0.04$ and 0.02, respectively) but not with age (Fig. 2).

Autonomic function results

Parasympathetic testing

An abnormal heart rate response to deep breathing was noted in 10 (48%) patients, and to standing in 8 patients (36%). Valsalva ratio was abnormal in 9 patients (41%). Nine (39%) patients had definite parasympathetic dysfunction, as defined by our pre-specified criteria (Fig. 1A).

Sympathetic testing

Seventeen (77%) patients had an abnormal diastolic response to handgrip and seven (30%) patients had orthostatic hypotension. Eighteen (78%) patients had definite sympathetic dysfunction (Fig. 1B). Nineteen (83%) patients had either definitely abnormal parasympathetic or sympathetic function, or both. There was no clear correlation between the two in individual patients. There was no correlation between the individual autonomic test results and either disease duration or increasing age. At the time of the autonomic tests, two patients were taking a beta-blocker; one of these patients had abnormal diastolic blood pressure response to

Table 2 Prevalence of autonomic symptoms from the SAS

Autonomic symptoms	%
Lightheadedness	65
Dry mouth/eyes	52
Pale or blue feet	39
Feet colder than rest of body	78
Reduced feet sweating compared to rest of body	48
Reduced feet sweating during exercise or warm weather	35
Increased sweating in hands compared to rest of body	0
Nausea, vomiting or bloating after a small meal	26
Persistent diarrhoea	4
Persistent constipation	65
Leakage of urine	39
Erectile dysfunction	78

handgrip, and the other had two abnormal parasympathetic and one borderline sympathetic tests.

Discussion

This is the first report to document autonomic symptoms and autonomic function in a large cohort of patients with CANVAS. We have demonstrated a high prevalence of autonomic dysfunction, confirming our hypothesis that autonomic failure is an important feature of this condition. This is consistent with a recent report of a sibling pair of patients with CANVAS who had histopathological evidence of sweat gland denervation (Umeh *et al.*, 2013).

The major differential diagnosis in a patient with progressive ataxia and autonomic dysfunction is multiple system atrophy (Wenning *et al.*, 1994), and indeed two of our patients had been incorrectly diagnosed with multiple system atrophy. There are several important features that distinguish CANVAS from multiple system atrophy. Bilateral vestibulopathy rarely, if ever, occurs in multiple system atrophy. Anderson *et al.* (2008) reported bilaterally impaired vestibular function in just 1 of 30 patients with probable multiple system atrophy. The authors considered that this patient may have had another diagnosis and we postulate that the patient in fact, had CANVAS. Furthermore, in another series of 255 patients with bilateral vestibular failure, just three patients were diagnosed with multiple system atrophy (Zingler *et al.*, 2007). The non-length dependent sensory neuronopathy, characteristic of CANVAS, as confirmed in this study, is a second feature of the syndrome that distinguishes it from multiple system atrophy; although peripheral neuropathy has occasionally been described in patients with multiple system atrophy, this has been a predominantly motor axonopathy (Gawel *et al.*, 2012). Downbeat nystagmus may also favour a diagnosis of CANVAS. Downbeat nystagmus has been reported in multiple system atrophy (Anderson *et al.*, 2008), but in a series of 117 patients with downbeat nystagmus, only one patient had multiple system
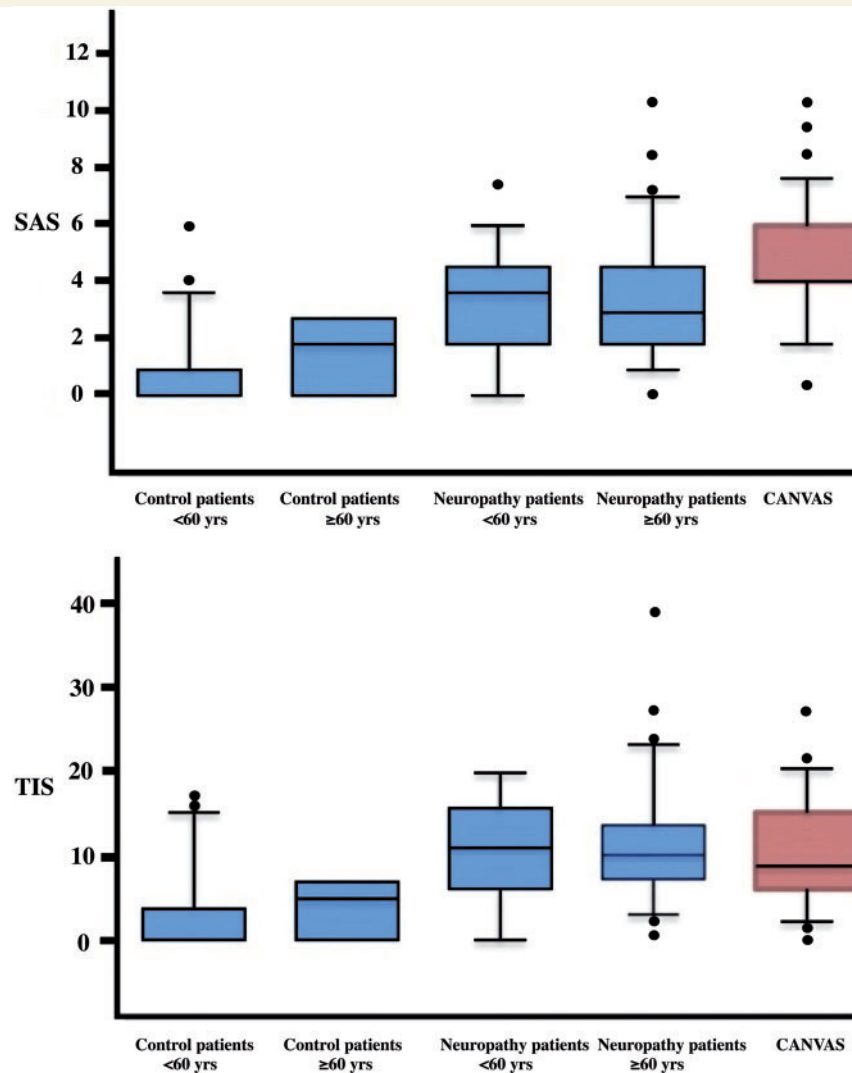
Figure 2 The SAS (**A**) and TIS (**B**) for historical controls and patients with diabetic neuropathy from Zilliox *et al*. (2011) (blue) compared with CANVAS patients (red). The box represents 25th to 75th centiles, the median is the horizontal line within the box, the whisker with error bars extends to the 10th and 90th centiles and the dots are the outliers. Figures are adopted from Zilliox *et al*. (2011) with permission from the authors.

atrophy (Wagner *et al*., 2008). In contrast, downbeat nystagmus was a common feature (65%) in our cohort, higher than the 28% observed by Szmulewicz *et al*. (2011). Long disease duration is another feature favouring CANVAS over multiple system atrophy. In our study, the median duration from first symptoms was 12 years, whereas the average time from first symptoms to death in multiple system atrophy is 9.3 years (Wenning *et al*., 1994). Conversely, there are features of multiple system atrophy that are not present in CANVAS: rapid eye movement sleep behaviour disorder, parkinsonism, and brainstem atrophy on MRI (Brooks *et al*., 2009). Our study confirmed that in CANVAS, MRI changes were confined to the cerebellum. Vermian and crus I atrophy increased with disease duration, supporting this as an integral feature of CANVAS.

The severity and range of autonomic symptoms and signs also differ between multiple system atrophy and CANVAS. In patients with multiple system atrophy assessed with Ewing's protocol,

postural hypotension (85%) was more common than abnormal diastolic blood pressure response to handgrip (38%) (Plaschke *et al*., 1998) whereas we found the reverse (30% and 77%, respectively). Urinary symptoms are more prevalent (up to 83%) and more bothersome in multiple system atrophy (Metzler *et al*., 2013) than in CANVAS (39%, low symptom impact score). Autonomic failure is a major cause of morbidity in multiple system atrophy (Lipp *et al*., 2009) whereas all but one of our patients remain ambulant and, even then, this was due to ataxia.

We hypothesize that autonomic dysfunction in CANVAS is part of a primary ganglionopathy involving the autonomic, vestibular, facial, trigeminal and sensory ganglia (Szmulewicz *et al*., 2014). Supportive evidence comes from the markedly reduced sweat gland nerve fibre density in the skin biopsies of two siblings with CANVAS (Umeh *et al*., 2013). This localizes the lesion at least to the 'post-ganglionic' autonomic nervous system, though not distinguishing between a lesion of the ganglion itself or the

emanating unmyelinated axons. This is, potentially, a further differentiation from multiple system atrophy in which the autonomic dysfunction is preganglionic (Lipp et al., 2009).

CANVAS is reasonably common with 26 cases found in New Zealand (population 4.5 million) within 2 years of knowing that the condition existed. Thirteen patients were diagnosed in Auckland (population 1.5 million) giving a minimum prevalence of 0.87/100 000. It is likely that CANVAS is under-diagnosed in patients presenting with ataxia in whom vestibular function is not examined. Likewise it has been estimated that 30% of patients with 'idiopathic' bilateral vestibulopathy have CANVAS (Strupp et al., 2013), but the diagnosis might not be considered if ataxia and neuropathy are not deliberately sought and the clinical entity recognized.

The strength of our study is the prospective examination of autonomic function using validated autonomic assessments in a substantial cohort of CANVAS patients. We recognize the limitation of comparing autonomic assessments with historical controls, but the consistency of our results across the centres lends them credibility. While we are exposed to the inherent limitations of retrospective ascertainment of patient data to confirm the diagnosis, determine rate of downbeat nystagmus and perform imaging analysis, we are confident of the clinicians' abilities to diagnose ataxia, and vestibular failure and neuropathy were verified with physiological testing in most patients.

We conclude that autonomic dysfunction is a central feature of CANVAS providing an important differential diagnosis to multiple system atrophy when encountering patients with combined ataxia and autonomic dysfunction. Downbeat nystagmus is also more common in CANVAS than previous reported and if present should prompt the clinician to look for the other features of CANVAS. Neurologists should be more aware of this syndrome as it is a relatively common cause of ataxia. A head impulse test should be a routine part of the examination of every patient presenting with ataxia.

Supplementary material

Supplementary material is available at Brain online.

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