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CANVAS an update: Clinical presentation, investigation and management

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Abstract.
BACKGROUND: Cerebellar Ataxia with Neuropathy and bilateral Vestibular Areflexia Syndrome (CANVAS) is a multi-system ataxia which results in cerebellar ataxia, a bilateral vestibulopathy and a somatosensory deficit. This sensory deficit has recently been shown to be a neuronopathy, with marked dorsal root ganglia neuronal loss. The characteristic oculomotor clinical sign is an abnormal visually enhanced vestibulo-ocular reflex.
OBJECTIVE: To outline the expanding understanding of the pathology in this condition, as well as diagnostic and management issues encountered in clinical practice.
METHODS: Retrospective data on 80 CANVAS patients is reviewed.
RESULTS: In addition to the triad of cerebellar impairment, bilateral vestibulopathy and a somatosensory deficit, CANVAS patients may also present with orthostatic hypotension, a chronic cough and neuropathic pain. Management of falls risk and dysphagia is a major clinical priority.
CONCLUSIONS: CANVAS is an increasingly recognised cause of late-onset ataxia and disequilibrium, and is likely to be a recessive disorder.

Keywords: Cerebellar ataxia, vestibulopathy, neuronopathy, ganglionopathy

1. Introduction

Cerebellar Ataxia with Neuropathy and Vestibular Areflexia Syndrome (CANVAS) is a slowly progressive ataxic disorder characterised by the combination of bilateral vestibular, cerebellar and somatosensory impairment [44]. An abnormal visually enhanced vestibulo-ocular reflex (VVOR) reflects a compound deficit of the three compensatory oculomotor reflexes: the vestibulo-ocular reflex (VOR), the optokinetic reflex, and smooth pursuit [30]. Hence, an abnormal VVOR (see Fig. 1) is seen in patients with CANVAS [32,44] reflecting cerebellar and bilateral vestibular dysfunction (see Figs 2–4) [1,4,30,38,44,45,49]. An impaired VVOR can be demonstrated clinically by turning a patient's head slowly (at approximately 0.5 Hz) while the patient visually fixates upon an

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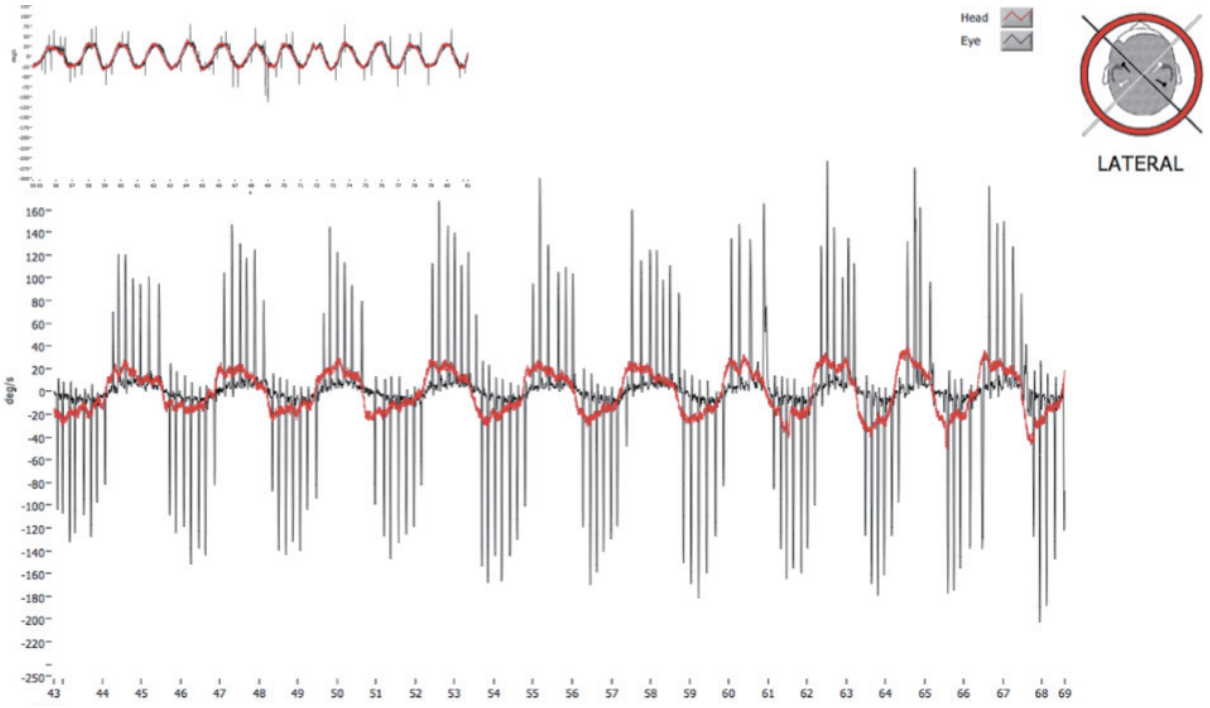

Fig. 1. Abnormal horizontal visually-enhanced vestibulo-ocular reflex (VVOR) in a patient with CANVAS. Head rotation stimulus is shown in red; eye movement response is shown in black. Inset: normal horizontal VVOR gain (∼1), recorded using portable rapid video-oculography equipment. Main panel: diminished VVOR gain followed by salvos of compensatory saccades. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/VES-140536)

earth-fixed target and observing that the compensatory eye movements are saccadic rather than smooth (see Fig. 1). Hearing is unaffected. We have seen 80 patients, including thirteen kindreds with this not uncommon condition [42] (from a population of approximately 10 million people). Our understanding of this disorder has deepened as we uncover the clinical [44], pathological [43–45] radiological [45], neurophysiological and genetic [46] details of this condition.

The timing of the onset of the various components of CANVAS may vary. Where the patient presents with the triad of: bilateral vestibulopathy, cerebellar dysfunction and a somatic sensory deficit (having ruled out other possible causes including spinocerebellar ataxia type 3 [5,6,12,20,40,47] and Friedreich's ataxia [8,11,21,35] the diagnosis may be relatively straightforward. However, in those patients where a significant delay in the manifestation of all three cardinal features exists, diagnosis may be more challenging (see Table 1). In our experience the onset of the final component of the diagnostic triad may take more than 10 years, such that a patient with cerebellar ataxia and bilateral vestibulopathy (CABV) (or any other combination of two of the three cardinal features of CANVAS) should have baseline investigations, and then be reviewed at regular intervals to ascertain whether they had indeed initially presented with CANVAS *in evolution*.

Amongst our CANVAS patients, there are three to date with no clinical signs of a peripheral sensory deficit (for example, diminished sensory perception and abnormal deep tendon reflexes), who yet have decreased or absent sensory nerve action potentials (SNAPs) on neurophysiological testing. For this reason, and to document baseline testing in those who may have CANVAS in evolution, we routinely perform nerve conduction studies on all patients with CABV.

We have previously delineated a differential pattern of cerebellar atrophy that preferentially affects the anterior and dorsal vermis (lobules VI, VIIa, and VIIb) and laterally, predominantly affecting crus I [44] (see Fig. 5). Additionally, a multiple cranial nerve neuronopathy (ganglionopathy) affecting cranial nerves V, VII and the vestibular portion of VIII has been demonstrated [43,46]. Selective atrophy of the vestibular nerves and marked diminution of the number of Scarpa's ganglion cells with atrophic peripheral and central axons is seen, whilst the auditory nerve and

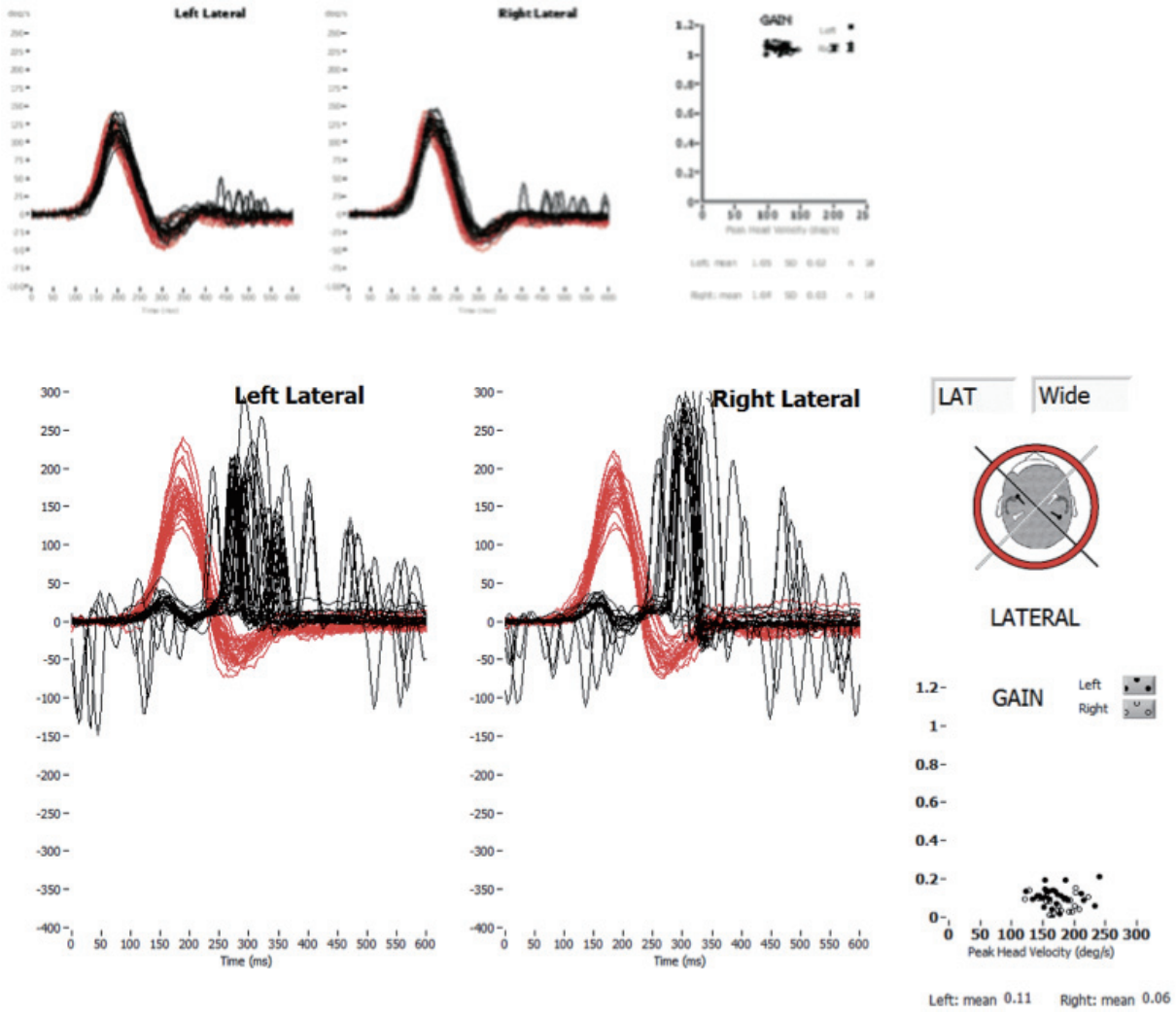

Fig. 2. Bilateral vestibulopathy demonstrated on video head impulse testing of a patient with CANVAS. Head rotation stimulus is shown in red; eye movement response is shown in black. Inset: normal bilateral horizontal VOR gain (∼1). Main panel: profound bilateral VOR gain deficit (peak VOR gain $<$ 0.2), followed by compensatory saccades. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/VES-140536)

end-organ are unaffected (Fig. 6). The cristae and maculae show a normal population of hair cells and supporting cells [43]. We have now uncovered the third focus of pathology: marked atrophy of the dorsal root ganglia with resultant posterior column atrophy [46]. Sub-total neuronal loss in the dorsal root ganglia is seen. Consequentially, posterior columns show severe loss of myelinated axons with normal anterior and lateral horns. Similarly, secondary peripheral neuronal degeneration is seen in the sural nerve (Fig. 7). Hence, the somatic sensory deficit seen in CANVAS is a 'neuronopathy' rather than a 'neuropathy', as we previously believed [44] (see Table 1 for details of the clinical somatosensory deficit) and this presents another target of diagnostic investigation in the clinical assessment of the ataxic patient.

Amongst our patients we have 13 kindreds, which vary from sibling pairs to multiple affected family members over greater than one generation. Our efforts at identification of the culprit genetic mutation are progressing, and at present it appears that inheritance is most likely to conform to an autosomal recessive model, although an autosomal dominant pattern with markedly decreased penetrance is possible. Of course, the possibility of phenocopies cannot be excluded until the culprit gene is isolated and routine testing is applied. Additionally, the variability in presentation (for example the predominance of vestibular over cerebel-

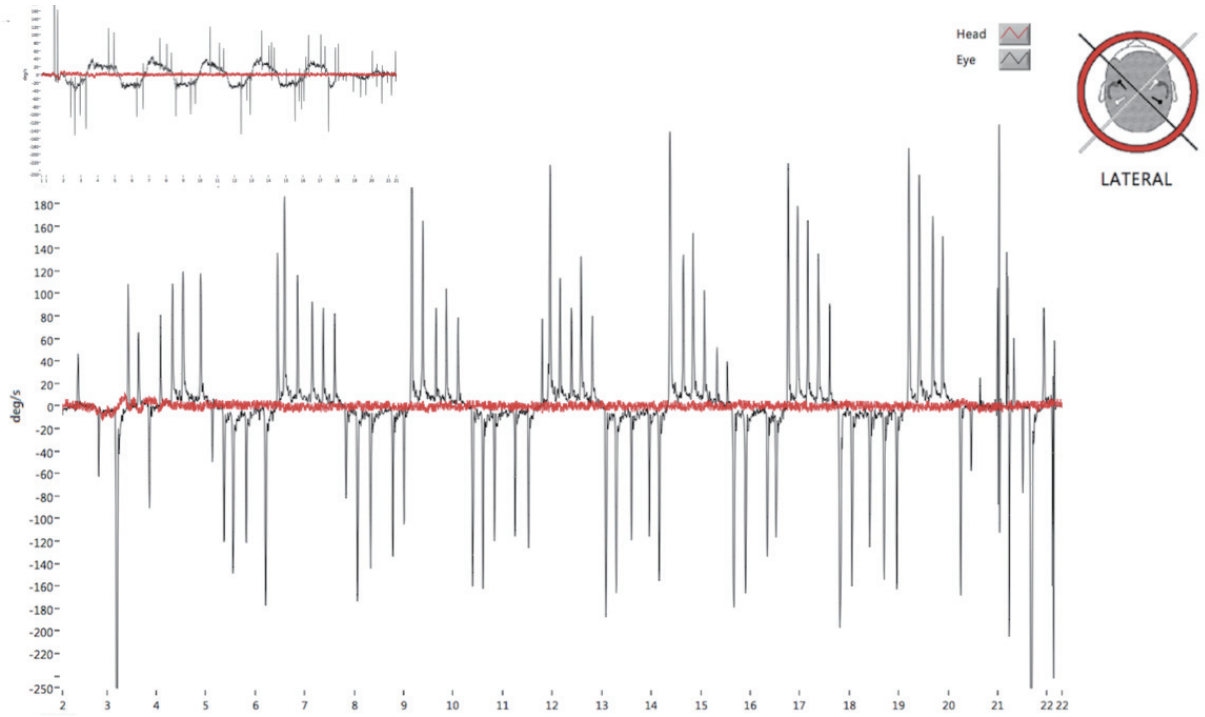

Fig. 3. Saccadic smooth pursuit in a CANVAS patient. Inset: head is stationary (red trace), whilst patient is visually tracking a horizontally moving target (0.66 HZ) and eye movement is shown in black. Main panel: note the numerous, high amplitude corrective saccades that result in 'broken-up' smooth pursuit. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/VES-140536)

lar impairment or the presence of small (Aδ) fibre peripheral nerve involvement in some) particularly between families, may be due to heterogeneity (phenotypic, genotypic or allelic).

We screen all potential CANVAS patients for spinocerebellar ataxia (SCA) type 1, 2, 3, 6 and 7 as there is considerable variability in their presentation [39] and these genetic tests are generally available. Of these, it is particularly SCA3, which may result in cerebellar ataxia, a bilateral peripheral vestibulopathy [5,6,12,47] and a sensory neuropathy [20,40]. Adult onset Friedreich's ataxia may also result in the combination of cerebellar impairment [21] a bilateral vestibulopathy [8,11] and a sensory neuronopathy [22,35], and so we also perform a Friedreich's ataxia gene test gene prior to diagnosing CANVAS.

We have found chronic cough and autonomic dysfunction to be variable features of CANVAS. Many patients report a relatively long-standing chronic, non-productive cough that may have preceded the onset of imbalance and somatosensory impairment. The cause of this cough is yet to be elucidated but may be the sequela of a vagal neuronopathy and denervation hypersensitivity of the upper airways and oesophagus [41]. Clinical features referable to autonomic dysfunction may be seen in CANVAS patients, and most commonly includes hypohidrosis and orthostatic hypotension. Orthostatic hypotension is a sustained reduction of systolic blood pressure of at least 20 mmHg (or diastolic blood pressure of 10 mmHg) within 3 minutes of standing (or head-up tilt to at least 60 degrees on a tilt table) [10]. Small (Aδ) fibre sensory nerve involvement may be demonstrated neurophysiologically, but where limited specialty investigation is available, we find that the combination of examination of the patient's socks for the absence of moisture and accurately performed lying and standing blood pressure measurements to be acceptable indicators of autonomic dysfunction, which may reflect possible small fibre pathology. Management of postural hypotension is of the utmost importance as part of a comprehensive approach to falls prevention. Whilst imbalance is not a useful clinical clue to the presence of orthostatic hypotension in a patient with CANVAS, we have found that specific questioning about light headedness on sitting up from lying or standing from sitting, to be relatively reliable indicators for the need to perform formal autonomic investigations. We have generally found that the combination of avoiding drug-induced orthostatic hypotension (see Table 2) and adequate hydration (particularly

Table 1
Clinical evaluation of the potential CANVAS patient

Component of the CANVAS triad	Abnormality	Clinical examination finding	Suggested/Preferred investigative modalities
Bilateral vestibulopathy	Decreased VOR gain bilaterally Abnormal VVOR	Bi-directionally abnormal horizontal head impulse test. Saccadic bedside VVOR	Rapid video-oculography [3] (see Fig. 2), video nystagmography or rotational chair testing
Cerebellar impairment	Cerebellar atrophy	N/A	MRI evidence of anterior and dorsal vermal atrophy, and laterally, hemispheric atrophy predominantly affecting crus I (see Fig. 6)
	Cerebellar dysarthria	Dysarthric speech	Formal speech therapy (speech pathology) assessment, including swallow assessment where clinically indicated
	Appendicular ataxia	For example, evidence of upper and lower limb dysmetria, intention tremor & dyssynergia	N/A
	Dysphagia of cerebellar origin	N/A	Video fluoroscopy
	Cerebellar oculomotor abnormalities	Impaired smooth pursuit and *VOR suppression; gaze-evoked nystagmus; dysmetric saccades to target; rebound nystagmus, pure vertical or torsional nystagmus	Rapid video-oculography [3], video nystagmography, rotational chair testing (see Figs 3 and 4)
Somatosensory impairment	Neurophysiological evidence of a neuronopathy	Sensory deficit in one or more of light touch, pin prick, vibration or proprioception.	Neurophysiological studies demonstrating reduced or absent SNAPs in a pattern indicative of a neuropathy or neuronopathy
Additional requirement	Exclusion of genetic ataxias able to be gene tested, particularly SCA3 and Friedreich's ataxia		

*NB: where VOR gain is markedly reduced, VOR suppression may appear to be relatively normal as there is little VOR activity to suppress; N/A: not applicable.

Table 2
Select common causes of drug-induced orthostatic hypotension [49]

Pharmacological class	Drug examples
Diuretics	frusemide, hydrochlorothiazide
Alpha adrenoreceptor antagonists	alfuzosin, tamsulosin
Beta adrenoreceptor antagonists	propranolol, labetalol
Antidepressant agents	imipramine, mianserin
Angiotensin-converting enzyme inhibitors (ACEI)	captopril, lisinopril
Phosphodiesterase type 5 (PDE5) inhibitor	sildenafil, tadalafil
Nitrates	glyceryl trinitrate (nitroglycerine), isosorbide dinitrate

important in warmer climates), wearing elastic stockings [28] and fludrocortisone at a dose of 0.1 to 0.2 mg/day [7,29] to be adequate management. Occasionally, the addition of the vasopressor midodrine is required at doses of 5–10 mg three times daily (as duration of action is short (2 to 4 hours)) [9,16,24]. Dosing should occur no later than 3 to 4 hours before bedtime because of the risk of supine hypertension. In order to minimise adverse medication effects, we recommend frequent monitoring of serum potassium, a diet high in potassium and regular measurement of supine blood pressure (especially where dual therapy is undertaken) [7, 29].

Particularly where a clinical suspicion of autonomic dysfunction exists, investigation for a possible small fibre neuropathy or neuronopathy may be indicated. We employ the combination of sudomotor or so called 'sweat tests' (we have used the QSART system), tilt table testing and measurement of the cutaneous silent period (CSP) in the upper and lower limbs [24]. The material risks to the longevity in CANVAS patients centre on the sequelae of aspiration and falls. For this reason we have a very low threshold for formal swallow assessment, which in our institutions involves referral to a speech therapist and video fluoroscopy. Although yet to be definitively elucidated, CANVAS pa-

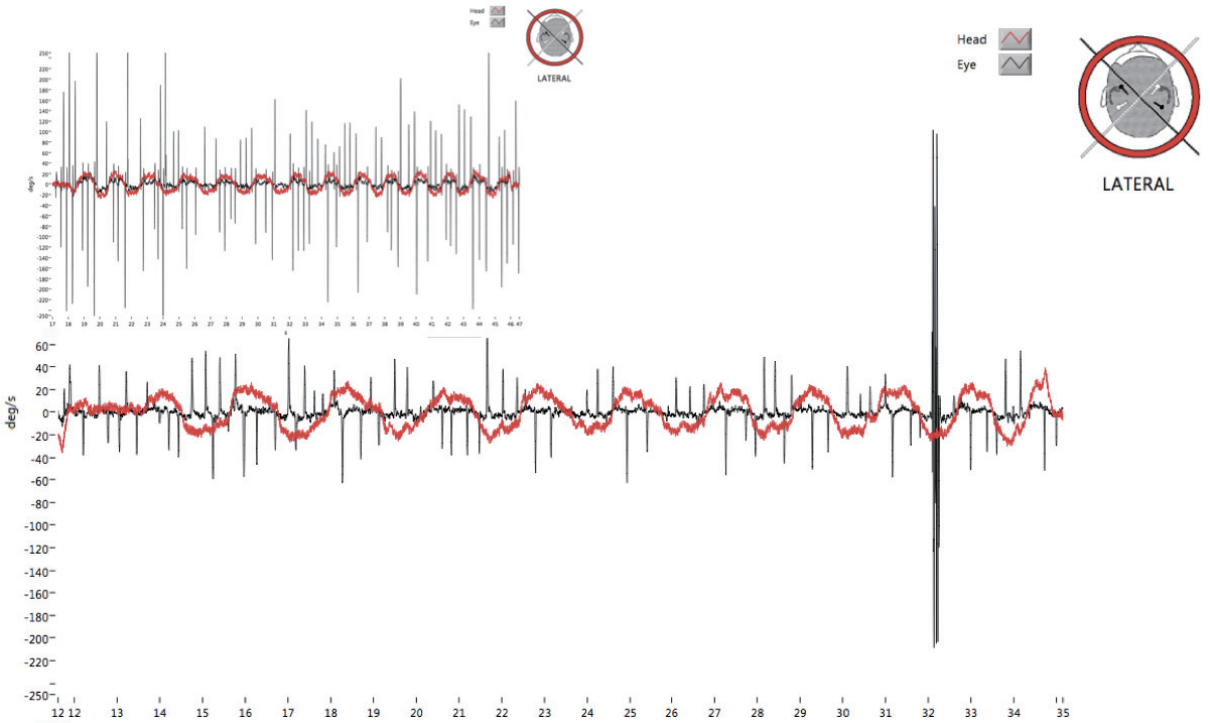

Fig. 4. Normal vestibulo-ocular reflex suppression (VORS). Head rotation stimulus is shown in red; eye movement response is shown in black. Inset: a patient with a pure cerebellar syndrome visually tracking a head fixed target during slow (0.5 HZ) sinusoidal head movements in the yaw plane, many high amplitude corrective saccades are seen. Main panel: CANVAS patient, the VORS is paradoxically normal (only occasional, low amplitude saccades are seen) as there is minimal VOR gain to suppress. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/VES-140536)

tients may be dyspahagic as a result of pharyngeal incoordination (as seen in patients with pure cerebellar syndromes) and/or sensory impairment (for example reduced trigeminal, chorda tympani, glossopharyngeal and pharyngeal branch of the vagus nerve input). Our experience is that most CANVAS patients with dysphagia respond to so called indirect strategies – involving behavioural techniques such as the chin-tuck position (which decreases the space between the base of the tongue and the posterior pharyngeal wall) thus functioning to increase pharyngeal pressure on the food and hence, aid its passage through this region [33,34]. Very few of our patients have required modification of their food consistency (such as the addition of thickening agents).

2. Falls and their sequelae

In terms of loss in disability-adjusted years for people aged 50 years or older, hip fracture ranks in the top 10 causes [34]. Particularly with increasing age, the sequelae of hip fracture include very substantial impacts on mortality and morbidity. The 1 year mortality rate for a fractured neck of femur is between 20 and 35 per cent [18,37,48]. Potential sources of morbidity associated with hip fractures include deep vein thrombosis, post-operative infection and loss of mobility [3]. There is no published data on the incidence of falls in CANVAS patients, but our experience is that these patients are at an increased risk of multiple falls when compared to their unaffected peers. We routinely perform dual-energy X-ray absorptiometry (DEXA bone densitometry) scans for evidence of osteopenia or osteoporosis [2,27] (which are treated with bisphosphonates or strontium ranelate) and even in the absence of these diagnoses, advise ongoing treatment with calcium and vitamin D supplementation to reduce fracture risk [25]. For all but our most mildly affected patients we advise comprehensive assessment at a multi-disciplinary community falls and balance clinic, which includes a home-based occupational therapy assessment in order to identify potential falls risks in the patient's home, to advise on bathroom modifications, placement of grab rails, etcetera.

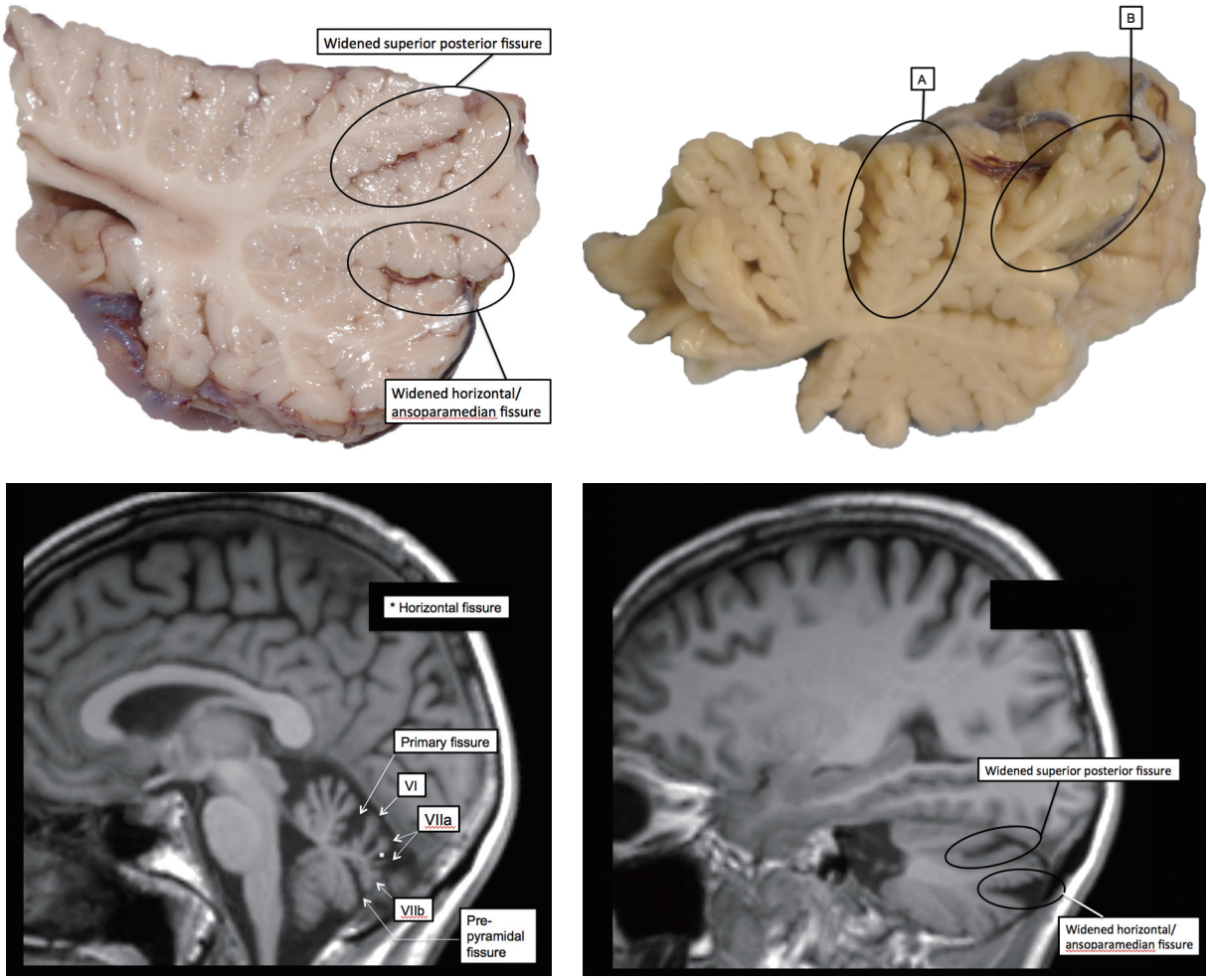

Fig. 5. Cerebellar atrophy in CANVAS. First panel: cerebellar atrophy is evident by widening of the superior posterior and horizontal fissures in a parasagittal macroscopic section; Second panel: anterior (A) and dorsal (B) cerebellar vermal atrophy (dorsal vermis corresponds to vermal lobules VI, VIIa and VIIb); Third panel: parasagittal view displaying widening of the superior posterior and horizontal fissures as a result of atrophy (T1-weighted MRI brain of a 46 year old CANVAS patient); Final panel: midsagittal view shows anterior and dorsal vermal atrophy (the latter relates to vermal lobules VI, VIIa and VIIb). (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/VES-140536)

3. Vestibular rehabilitation

Whilst evidence exists for the utility of intensive neurological physiotherapy in the management of cerebellar disease [14,15] and similarly vestibular rehabilitation in the treatment of bilateral peripheral vestibulopathies [13,23,36], there does not appear to be any published data on the combination of these two therapies in the management of patients with compound deficits of cerebellar, vestibular and somatosensory impairment. Anecdotally, we find significant benefit in referring our patients for individualised combination neurological and vestibular rehabilitation, which are performed regularly by the patient and reviewed periodically by a specialist physiotherapist.

4. Pain

Neuropathic pain, dysaesthesia and allodynia may be particularly troubling for those patients with CANVAS. This most likely reflects a degree of small fibre involvement in their somatosensory impairment. We have found membrane stabilising agents to be singularly useful in controlling these symptoms. Pregabalin may be extremely effective and in our experience is generally well tolerated. We begin treatment with a dose of 75 mg twice daily and up-titrate the dosage in 75 mg aliquots, as required, to a maximum dose of 300 mg daily. It may take several weeks to achieve maximal effect with pregabalin. Where a positive and sustained treatment response has occurred,

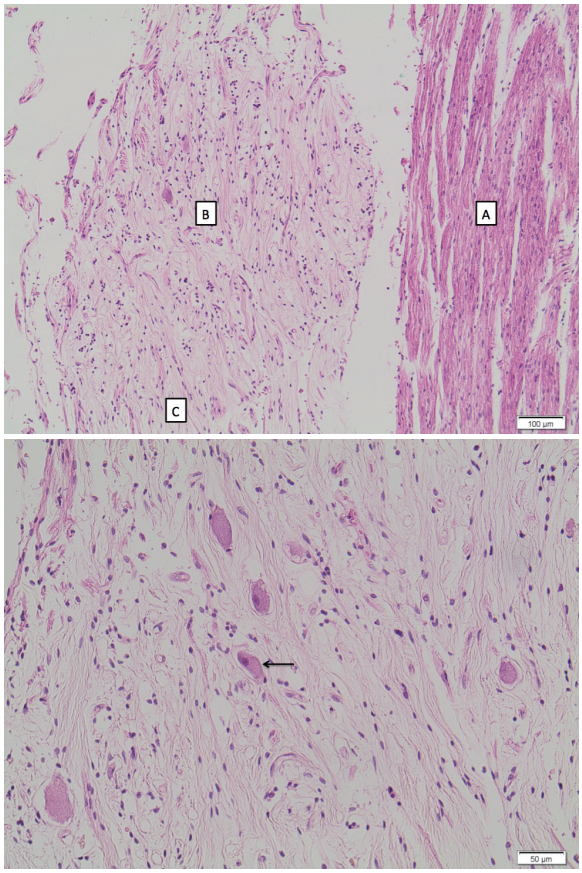

Fig. 6. Scarpa's (vestibular) ganglion. Top panel: normal myelinated auditory nerve (A) and atrophic Scarpa's (vestibular) ganglion (B) (atrophic vestibular nerve can be seen entering the ganglion in the lower portion of the image (C)); low power, haematoxylin and eosin (H&E); Lower panel: atrophic Scarpa's ganglion with scant residual neurones (arrow); high power, H&E. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/VES-140536)

consideration is given to gradually reducing the dose over time [32]. We have also used amitriptyline in this setting, but have found pregabalin to be more effective and better tolerated by our patients.

5. Conclusion

CANVAS is an increasingly recognised cause of late-onset ataxia and disequilibrium. It offers a fascinating physiological and pathological insight into the multi-system nature of human balance. Whilst cure is an omnipresent goal, management options exist and are increasing, as we learn more about this complex disorder.

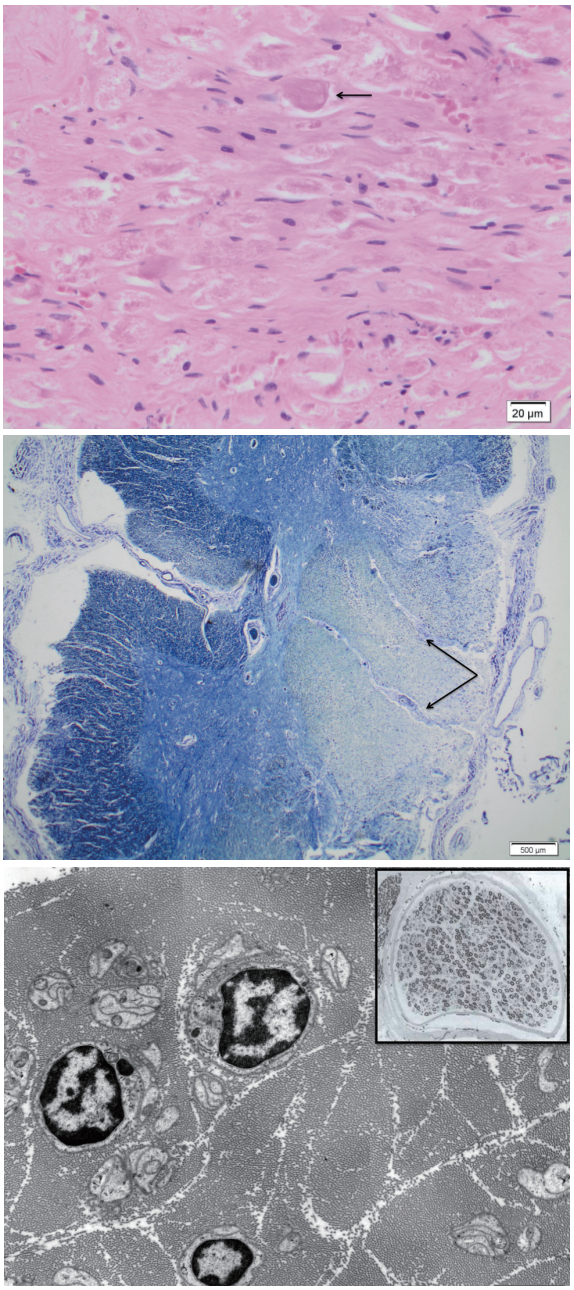

Fig. 7. Pathology underlying the somatosensory deficit seen in CANVAS. Upper panel: dorsal root ganglion showing severe loss of neurones (arrow); high power, H&E; Middle panel: Cross-section of cervical spinal cord showing demyelination of the posterior columns (arrows) secondary to dorsal root ganglion neuronal loss; low power, Luxol fast blue; Lower panel: cross section sural nerve showed complete absence of axons with replacement fibrosis. No active wallerian degeneration or schwann cell proliferation was seen, electron microscopy; inset: normal sural nerve, electron microscopy. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/VES-140536)

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