recordings in diseases such as critical illness polyneuropathy or myopathy or in obese patients. CMAP amplitude and latency differences in relation to diaphragm position (inspiratory versus expiratory pause) as well as right to left side differences of latencies are well known. This dependency has an important impact on phrenic nerve conduction studies in daily practice. The examiner should take special care to perform the examination during either inspiratory or expiratory pause. Under ICU conditions this can be achieved easily by halting the ventilator at the end of either the inspiratory or expiratory cycle to perform stimulation. In an earlier study we demonstrated that phrenic nerve conduction studies using esophageal CMAP recordings can be performed under ICU conditions in patients with critical illness polyneuromyopathy.

In conclusion, these results show that phrenic nerve conduction studies using the NAVA probe for recording can be performed reliably, and we establish normal values for healthy young adults.

REFERENCES


NEUROPHYSIOLOGICAL EVIDENCE FOR GENERALIZED SENSORY NEURONOPATHY IN CEREBELLAR ATAXIA WITH NEUROPATHY AND BILATERAL VESTIBULAR AREREFLEXIA SYNDROME

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ABSTRACT: Introduction: Cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome (CANVAS) is a recently described multisystem ataxia defined by the presence of cerebellar ataxia, bilateral vestibulopathy, and a somatosensory deficit. The characteristic clinical sign is an abnormal visually enhanced vestibular reflex. The somatosensory deficit contributes to a significant level of disability in CANVAS. Methods: This study was a neurophysiological investigation of 14 patients with CANVAS. Results: Findings revealed uniformly absent sensory nerve action potentials in all limbs, abnormal blink reflexes in 13 of 14 patients, and abnormal masseter reflexes in 6 of 11 patients. Tibial H-reflexes were absent in 11 of 14 patients. Somatosensory evoked potentials were abnormal in 10 of the 11 patients tested, and brainstem auditory evoked responses were abnormal in 3 of 8. Cutaneous silent period responses were abnormal in 7 of 14 patients. Conclusions: We suggest that a sensory neuronopathy should be sought in cerebellar and/or vestibular ataxias, particularly where the degree of ataxia is out of proportion to the clinically identified cerebellar and/or vestibular dysfunction. Muscle Nerve 51:600–603, 2015

Cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome (CANVAS) is a novel vestibulocerebellar ataxia that consists of the triad of cerebellar impairment, bilateral vestibular hypofunction, and a somatosensory deficit. Although there is a degree of overlap between the clinical features of sensory, vestibular, and cerebellar impairment (e.g., gait ataxia may be a result of any
of the 3), cerebellar dysarthria and central oculomotor abnormally are purely due to cerebellar pathology, whereas reduced vestibuloocular reflex (VOR) gain (e.g., an abnormal head impulse test) is isolated etiologically to vestibular dysfunction, and dysesthesias and allodynia are uniquely referable to somatosensory deficits. Our group has seen more than 70 patients with this condition. Clinically, the hallmark of CANVAS is an abnormal visually enhanced vestibuloocular reflex (VOR).\textsuperscript{2} We have previously described a consistent pattern of cerebellar atrophy together with multiple atrophic cranial sensory ganglia as the key underlying pathology in CANVAS.\textsuperscript{3} In addition, we recently demonstrated a dorsal root neuronopathy (ganglionopathy) on histopathologic assessment.\textsuperscript{3} In this work we assess the value of neurophysiological investigation to define neuronopathy in the appropriate context (i.e., the presence of combined cerebellar impairment and bilateral vestibulopathy) to aid in the diagnosis of CANVAS during life. The etiology of CANVAS is unknown, but we have previously reported 6 separate kindreds,\textsuperscript{4} suggesting a probable autosomal recessive inheritance. We have now identified a total of 13 kindreds, and there is no discernible phenotypic difference between the families.

Sensory neuronopathies are a group of disorders with distinct clinical presentations that reflect their anatomic localization. Their identification may aid in the diagnosis of an underlying disorder.\textsuperscript{5} The associated conditions are generally distinct from those associated with length-dependent axonal neuropathies and include paraneoplastic syndromes, non-paraneoplastic immune-mediated diseases (e.g., Sjögren syndrome), human immunodeficiency virus infection, drug-induced toxicity (e.g., platinum-based chemotherapy and pyridoxine toxicity), and inherited disorders such as Friedreich ataxia.\textsuperscript{6}\

**RESULTS**

All 14 patients had absent upper and lower extremity SNAPs bilaterally. Four had mildly delayed median terminal motor latencies (2 only unilaterally). Otherwise, the motor studies were normal. Three had retained tibial H-reflexes, but in 11 they were absent. Only 2 had normal blink reflexes with stimulation of the supraorbital and infraorbital nerves; 1 patient had intact supraorbital and abnormal infraorbital, and 2 had intact infraorbital but abnormal supraorbital reflexes. Seven of 11 patients had absent masseter reflexes, and 1 had delayed responses. Seven of the 9 studies had abnormal median SSEPs, and a further 2 had very low-amplitude responses (with the latencies delayed in 1). Two of 10 studied, both of whom were hearing impaired, had absent BAERs. Electromyographic sampling in a lower extremity was normal in all patients. CSP studies were abnormal in at least 1 limb in 7 of 14 patients.

**DISCUSSION**

A limitation of this study is that we performed distal orthodromic sensory studies in the upper
extremities and distal antidromic studies in the lower extremities. Although this could possibly result in failure to detect a length-dependent process, markedly abnormal blink reflex results in 12 of 14 subjects confirmed a generalized sensory abnormality consistent with a neuronopathy.

Our initial description of CANVAS suggested that the somatic sensory deficit was most likely a length-dependent process, although a neuronopathy could not be excluded because of the widespread sensory deficit in some patients. In autopsy studies we subsequently established that there are pathological changes in cranial nerve and dorsal root ganglia (DRG). Macroscopic postmortem examination of the spinal cord showed globally atrophic DRG with histological evidence of DRG neuronal loss and marked loss of myelinated axons in the posterior columns. The anterior horns and lateral columns showed a normal neuronal population.

Neurophysiological investigation was carried out in all subjects because of the known association of vestibulocerebellar disease with somatosensory deficit in several disorders, including CANVAS, Friedreich ataxia, and spinocerebellar ataxia type 3 (SCA3). A sensory neuronopathy is suggested by non-length-dependent symptoms, signs, and neurophysiological sensory testing, without motor involvement. All our patients had widespread absent SNAPs and fulfilled these criteria, although 1 patient did not have any sensory symptoms or signs. The pathophysiological implication of a sensory neuronopathy is that the primary abnormality is the loss of DRG neurons with secondary loss of myelinated axons in the posterior columns and peripheral neuronal degeneration as a consequence of diminished trophic factor production in the DRG. This has been confirmed in reports of pathological examinations in CANVAS patients. Clinically, the presence of a sensory neuronopathy is reflected in the manifestation of patchy to global sensory impairment.

The presence of tibial H-reflexes in 3 of 14 patients and absence of masseter reflexes in 6 of 11 were unexpected findings. Sensory neuronopathy is associated with a loss of peripheral reflexes (that involve ganglion cells) and retention of masseter reflexes that do not involve ganglion cells. There is no evidence to support that the retained H-reflexes were due to upper motor neuron involvement or selective sparing of spindle cell sensory neurons. However, for patients in whom the sensory neuronopathy is anatomically subtotal (manifested clinically as patchy sensory impairment), this may be a factor.

In the patients we have described, the only common motor abnormality was a slight delay in the median terminal motor latencies (4 of 14) of uncertain clinical significance. This may represent asymptomatic superimposed median nerve entrapment at the wrists, although the patients had no relevant symptoms. Abnormal median terminal motor latencies have been described in spinocerebellar ataxia type 1 (4 of 12 patients), but the patients in this study had negative tests for the SCA1 gene mutation.

The utility of blink and masseter reflexes has increased in the post-MRI era, and these tests have helped to further characterize the sensory deficit in CANVAS. Auger showed that the blink reflex was normal in all 17 patients with paraneoplastic sensory neuronopathy tested and abnormal in 20 of 43 with non-paraneoplastic neuronopathy. This is consistent with our findings of frequently abnormal blink reflexes, and of trigeminal ganglion involvement in a patient at postmortem, but an absence of an association of CANVAS with neoplasia.

The CSP results indicate Aβ fiber involvement in CANVAS. These findings have been described previously in only 1 patient with sensory neuronopathy, but the pattern of involvement described here is consistent with a small-fiber neuronopathy. This requires further investigation. No alternative etiology was present.

We suggest that neurophysiological assessment to diagnose a sensory neuronopathy should be considered in patients with cerebellar and/or vestibular impairment particularly in whom the degree of ataxia is out of proportion with the clinically apparent cause(s) of ataxia. The combination of abnormal VVOR, non-vertiginous ataxia, slowly progressive symptoms, clinical evidence of somatosensory impairment, and lack of a family history to suggest dominant spinocerebellar ataxia are factors that should suggest a diagnosis of CANVAS.

In view of our findings, an efficient screening approach would be to assess digital and lower extremity SNAPs. If the SNAPs are absent or of low amplitude, a more detailed study should be performed to exclude motor involvement. If excluded, abnormal blink reflexes may be sought. Because 1 of the patients had a normal sensory examination and no sensory symptoms, we could not identify a dependable clinical analog as a substitute for neurophysiological studies.

Camdessanché et al. proposed diagnostic criteria for possible or probable acquired sensory neuronopathies. Using these criteria, CANVAS would be classified as a possible acquired sensory neuronopathy despite these clinical and neurophysiological features, as only paraneoplastic, cisplatin, and Sjögren neuronopathies are considered likely, even though the clinical and
neurophysiological features may be the same.

Given the pathological evidence of a sensory neuronopathy that we have shown previously, and the neurophysiological findings presented in this study, we suggest that CANVAS be incorporated into the classification system as a fourth cause of probable neuronopathy along with onconeural antibodies or a cancer within 5 years, cisplatin treatment, or Sjögren syndrome.

The present findings, combined with the neuropathological data reported previously, suggest that sensory neuronopathy may be an integral part of CANVAS. In addition, when a patient with disequilibrium is found to have cerebellar and bilateral vestibular impairment, the neurophysiological protocol suggested here can aid in the diagnosis of CANVAS.

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