A patient with neuropathy and ataxia: what do I have to consider?

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Purpose of review
An increasing number of peripheral neuro(no)pathies are identified as involving other components of the neurological system, particularly those that further impair balance. Here we aim to outline an evidence-based approach to the diagnosis of patients who present with a somatosensory disorder which also involves at least one other area of neurological impairment such as the vestibular, auditory, or cerebellar systems.

Recent findings
Detailed objective investigation of patients who present with sensory impairment, particularly where the degree of imbalance is greater than would be expected, aids the accurate diagnosis of genetic, autoimmune, metabolic, and toxic neurological disease.

Summary
Diagnosis and management of complex somatosensory disorders benefit from investigation which extends beyond the presenting sensory impairment.

Keywords
ataxia, ganglionopathy, neuronopathy, neuropathy, sensory

INTRODUCTION
Genetic, autoimmune, nutritional, and toxic disorders often involve several different parts of the nervous system. Somatosensory disorders are common [1] and most can be identified and characterized with a combination of the physical examination, neurophysiology and serum parameters. Imaging modalities such as Magnetic Resonance Imaging (MRI) and more recently ultrasound offer additional diagnostic value in a small subset of presentations [2]. However, making an exact and comprehensive diagnosis is more difficult where the somatosensory disturbance is accompanied by one or more other neurological focus of pathology, such as the vestibular apparatus or cerebellar impairment [3*]. This is compounded by the increasing number of diseases which are recognised as involving multiple etiological sources of imbalance and gait ataxia [3*]. Of note, a broad-based unsteady gait may be common to cerebellar, sensory and vestibular impairment, therefore more specific signs, and where available objective measures, are sought in order to identify or differentiate between these. In this work, we offer an evidence-based approach to such adult patients, which is not intended to enumerate an exhaustive list of differential diagnoses, but to proffer a clinically expeditious method and highlight some of the diagnoses that are more common or which we consider should not be overlooked.

A literature search of PubMed without date of publication limitation was undertaken in which the terms “ataxia” OR “cerebell” OR “neuropathy” OR “neuronopathy” OR “ganglionopathy” OR “polyneuropathy” OR “vestib” OR “auditory” were utilised and the results manually curated for relevance. Where appropriate, primary sources quoted in references were also retrieved and curated.

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* We use the term ‘somatosensory’ to include neuropathy and neuronopathy (or ganglionopathy).
Peripheral nerve and neuro-muscular junction disease

KEY POINTS

- An increasing number of peripheral neuro(no)pathies have been identified in which other components of the nervous system are affected.
- Patients presenting with peripheral sensory impairment and imbalance should be investigated for additional extra-sensory components such as peripheral vestibular dysfunction and cerebellar impairment.
- Defining the clinical phenotype of the patient aids formulation of differential diagnoses.
- With an expanded number of genetic causes that have been elucidated, inherited diseases should be given adequate consideration, as they may have prognostic and family planning implications.

In this study, we focused on the clinical diagnosis of adult-onset ataxia that presents with the combination of cerebellar and peripheral or cranial nerve pathology.

ESTABLISHING THE PRESENCE OF A SOMATOSENSORY DEFICIT

Clinical and neurophysiological assessment is generally adequate in establishing whether sensory loss is due to a neuropathy or neuronopathy, by determining if it is symmetric or asymmetric, length dependent or non-length dependent, axonal or demyelinating, large and/or small fiber. Additionally, the degree of motor and sensory involvement may be garnered. Whilst reduced or absent vibration and proprioception perception suggest large fiber involvement, paraesthesia, neuropathic pain, and burning sensations are suggestive of small fiber involvement.

Our standard nerve conduction study (NCS) protocol comprises unilateral antidromic median, ulnar, radial, sural, and superficial peroneal sensory studies with median, ulnar, fibular, and tibial motor studies. Bilateral studies are performed if clarification is required, for example, to determine symmetry and to confirm the distribution and pattern of involvement. We employ blink reflexes and mechanically activated massetter reflexes to help in distinguishing a cranial neuropathy from neuronopathy and to assess brainstem function. Neuropathy affects both tests, however in neuronopathy, the massetter reflex may not be affected as the cell bodies are located in the brainstem and not in the trigeminal ganglion [4]. This is of value in assessing for the presence of conditions which may manifest multiple cranial neuro(no)pathies.

Somatosensory loss such as is seen in neuropathy and neuronopathy may manifest with a broad-based gait, although this may also be high stepping. It is important to note that such a gait may be the result of impairment in three key balance systems, namely somatosensory, vestibular and cerebellar [5,6]. Additionally, disturbance in any of these systems is not mutually exclusive and we recognize an increasing list of disorders that effect two or all three of these [3]. Whilst an ataxic gait and imbalance are common to both sensory and vestibular impairment, symptoms such as vertigo or motion induced oscillopsia would indicate vestibular and/or cerebellar involvement [7]. It then follows that in the patient with a broad-based gait and a somatosensory deficit, the patient should be screened for vestibular and cerebellar involvement.

WHAT DO I DO IF MY PATIENT HAS A SOMATOSENSORY DEFICIT WITH VESTIBULAR AND/OR AUDITORY INVOLVEMENT?

Vestibular involvement in diseases that may present with a somatosensory deficit may be due to a cranial neuropathy or neuronopathy [8,9]. In most neurological diseases the exact pathology remains unclear given the dearth of published temporal bone pathology. Diagnosis of a vestibular component reduces the number of differential diagnoses. In addition, vestibular rehabilitation would add to the standard-of-care neurologic rehabilitation for an isolated somatosensory deficit [10]. Assessment of vestibular function may be performed by a facility that offers formal vestibular function testing, and the modalities that are available to assess semicircular canal function (involved in the perception of radial acceleration of the head) are the video head impulse test (vHIT), rotational chair and bithermal caloric irrigation. The otolith organs (utricle and saccule) which are concerned with linear acceleration of the head and may be assessed using vestibular-activated myogenic potentials (VEMP) or the subjective visual vertical (or horizontal) test [11]. It should be noted that the vHIT offers several advantages over the clinical HIT (cHIT) including abrogation of false-negative results due to the so-called ‘covert corrective saccades’, which are imperceptible to the clinician during the cHIT but clearly recorded by the vHIT [12].

Despite only a modest degree of published scientific enquiry, there is evidence to support frequent involvement of the vestibular nerve or ganglia in somatosensory disorders [8,9]. Diseases, where vestibular involvement has been shown to be common include demyelinating neuropathies such as Guillain-Barre Syndrome [13] and Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) [14]. In a study of Charcot-Marie Tooth...
(CMT) disease, vestibular impairment was seen in 60–70% of subjects, and it was proffered that cVEMPs may be more sensitive (75%) than the vHIT [15].

Auditory neuropathy may also be present in cases of peripheral neuropathy [16,17] with or without concomitant vestibular involvement [9]. The importance here, is that reduced hearing may be an independent factor in compromised balance and its sequelae, including increased risk of falls and impaired mobility [18]. Auditory neuropathy has been reported in tandem with a peripheral neuro (no)pathy in diseases including CMT [19], CIDP [20], diabetes mellitus type 1 [17], Friedreich ataxia (FA) [21] and Refsum’s disease [22].

In X-linked Fabry’s disease there is commonly a painful length-dependent small fiber neuropathy affecting the Aδ and C fibers. There is little evidence to suggest any large fiber involvement. Therefore, vibration sense and position sense are mostly normal but there may be abnormalities in pain and temperature sensation. Despite this lack of large fiber involvement, Carmona et al. [23] found evidence of objective vestibular dysfunction in approximately half of their patient cohort, and similarly approximately 60% had evidence of hearing loss on pure tone audiogram. In the aggregate, 70% of subjects had combined cochlear and vestibular dysfunction. The exact site of the pathology is unknown. Malignancy and its treatments not uncommonly result in peripheral as well as vestibular neuropathy, and particularly in males are associated with increased all-cause mortality [24].

We recommend that all patients with a somatosensory deficit, particularly if the degree of imbalance is greater than expected, undergo vestibular function and auditory testing. At a minimum, we suggest that vestibular testing involve a vHIT and VEMP’s. Auditory neuropathy is diagnosed on the basis of an abnormal ABR and normal otoacoustic emissions [22]. Where vestibular and/or an auditory neuropathy is present, further etiological testing (e.g., CMT gene testing) will be guided by the results of the NCS and other factors such as family history.

WHAT DO I DO IF MY PATIENT HAS A SOMATOSENSORY DEFICIT WITH CEREBELLAR INVOLVEMENT?

Somatosensory impairment is a reasonably common accompaniment of cerebellar disease [25]. In addition to the aforementioned neurophysiological protocol for aid in differentiating a neuropathy from a neuropathy, evidence of cerebellar impairment may be gathered from a number of clinical domains including oculomotor, speech, appendicular, gait, and cognition and affect [26]. Whilst cerebellar structural abnormalities may be objectively assessed with imaging, demonstration of dysfunction (i.e., cerebellar ataxia) is largely subjective and reliant on the physical examination. The exception is oculomotor measurement, which can be performed with a range of widely available video-oculography systems [27]. Commonly seen oculomotor abnormalities include saccadic (or broken-up) pursuit; saccadic vestibulo-ocular suppression; gaze-evoked nystagmus; dysmetric, latent, or slow saccades to target; and saccadic intrusions [28]. Clinical features which are seen in cerebellar disease but are less than specific, particularly in isolation, include reduced speech intelligibility (e.g., neuromuscular disease or apraxia of speech), motion-induced or spontaneous oscillopsia (seen in peripheral vestibular disease), and decreased dexterity (e.g., proximal limb weakness or somatosensory impairment). Gait disturbance, imbalance, and falls are nonspecific and may be caused by pathology affecting a number of other systems [6]. For these reasons it is important to accurately define the nature of the clinical abnormalities (e.g., cerebellar dysarthria versus hypernasal speech).

Peripheral neuropathy is frequently found in Spinocerebellar Ataxia (SCA) types 1, 2, and 3 [29]. Despite some disagreement in the literature, a somatosensory deficit is unlikely to be a feature of SCA6 [30]. Other inherited causes of combined somatosensory and cerebellar impairment include Ataxia with Vitamin E Deficiency (AVED) [31], Cerebrotendinous xanthomatosis [32,33], Polymerase Gamma-Related Ataxia [33], a variant of CMT which is associated with cerebellar disease [34] and Ataxia with Oculomotor Apraxia types 1 and 2 [35**]. Fragile X-Associated Tremor Ataxia Syndrome (FXTAS) is commonly associated with an axonal neuropathy. This affects males more often than female carriers of the FMR1 gene permutation [36]. A length-dependent neuropathy is an integral part of Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) [37].

The association of cerebellar ataxia and sensory neuronopathy (ganglionopathy) may be seen in autoimmune disease including biopsy proven coeliac disease, sarcoidosis, Sjogren’s and Crohn’s diseases, and antiglutamic acid decarboxylase antibodies associated cerebellar ataxia. Malignancy (ovarian, bowel, multiple myeloma, uterine, melanoma, and possibly prostate), paraneoplastic and subsets of immunoglobulin M paraproteinemic disease may also manifest this dual pathology, whilst a number of toxic syndromes including amiodarone toxicity [38].
Peripheral nerve and neuro-muscular junction disease

WHAT DO I DO IF MY PATIENT HAS A SOMATOSENSORY DEFICIT WITH VESTIBULAR AND CEREBELLAR INVOLVEMENT?

The pathology of FA involves the dentate nuclei of the cerebellum, a dorsal root ganglionopathy [39,40], vestibular and cochlea nerve and ganglia as well as vestibular and cochlea nuclei atrophy, whilst the respective end organs remain uninvolved [41,42]. Similarly, the underlying somatosensory deficit in cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) is a dorsal root ganglionopathy [43], a vestibular ganglionopathy [44] whilst the cerebellar pathology is more diffuse [43]. Although in CANVAS the facial and trigeminal ganglia are also involved, the auditory system is unaffected [45,46]. A biallelic pentamer expansion in RFC1 has recently been identified [46,47]. SCA3 may also present with the triad of cerebellar, somatosensory and vestibular impairment [48,49]. Klockgether et al. showed that the severity of the neuropathy in SCA3 is not related to CAG repeat length, age of onset, or disease duration, but primarily correlates with the time period over which the disease exerts its effect [49]. MSAs may vary present with vestibular dysfunction [50], autonomic and large fiber somatosensory impairment [51].

In addition to the clinical features referable to somatosensory, vestibular and cerebellar dysfunction discussed in the preceding sections, a very useful bedside test is that of an abnormal (saccadic) visually enhanced vestibulo-ocular reflex (VVOR), which confirms the presence of combined bilateral vestibular hypofunction and cerebellar oculomotor dysfunction [52]. An abnormal VVOR can be demonstrated by turning a patient’s head slowly from side-to-side, while the patient’s gaze is directed at an earth-fixed target (e.g., a coloured dot on a wall) and observing that the ensuing eye movements are broken-up rather than smooth. The VVOR is a simple, brief and reproducible bedside test [53].

We routinely perform MRI imaging of the brain and spinal cord in a person presenting with features of cerebellar ataxia to evaluate cerebellar, brainstem dorsal column or cortico-spinal tract involvement. There are a range of conventional MRI abnormalities associated with certain ataxic diseases, noting that few are particularly specific. In FA it is not uncommon to find an absence of cerebellar atrophy or only mild regional atrophy effecting the superior vermis – global cerebellar atrophy is rarely seen in very advanced disease [54]. The primary imaging abnormality is a decrease of the antero-posterior diameter of the medulla oblongata and the cervical spinal cord, consistent with degeneration of the ascending posterior columns [55]. In AVED, cerebellar atrophy is usually absent [56], although mild hemispheric atrophy may occasionally be visualized. In contrast to FA, no cervical spine abnormalities are seen [57]. In MSAs, atrophy of the putamen (signal decrease on iron-sensitive sequences), middle cerebellar peduncle, pons, or cerebellar atrophy as well as the ‘hot cross bun’ sign may all be seen [58]. The two key MRI findings in FXTAS are white matter lesions in the middle cerebellar peduncles and the splenium of the corpus callosum, although neither of these is specific for the diagnosis [59]. In CANVAS the clinical MRI findings are that of anterior and dorsal vermis atrophy (the latter involving vermal lobules VI, VIIa, and VIIb) and hemispheric atrophy principally affecting crus I [60].

IDENTIFYING EXTRASENSORY INVOLVEMENT

Autonomic involvement should be enquired after, and it is particularly important to identify orthostatic intolerance as it is an independent and treatable cause of falls [61]. Other symptoms of autonomic dysfunction include temperature intolerance, and bladder, gastrointestinal tract, and erectile dysfunction. Formal testing with modalities such as tilt table testing and other tests of cardiac responsiveness, quantitative sweat analysis find value in confirming the presence of autonomic dysfunction [61]. Autoimmune autonomic ganglionopathy is uncommon and principally a postganglionic disorder believed to be due to antibodies targeting the nicotinic acetylcholine receptor. These antibodies may be idiopathic or part of a paraneoplastic process [62]. Dysautonomia is often a feature of MSAc [58*] and may be seen in SCA1, 2, 3 [63], 27B [reference: Rafehi H, Read J, Szmulewicz DJ, et al. An intronic GAA repeat expansion in FGF14 causes the autosomal-dominant adult-onset ataxia SCA50/ATX-FGF14. Am J Hum Genet. 2023 Jan 5;110 (1):105-119.] FA [64] and CANVAS [65,66] amongst others. In the appropriate clinical context, enquiring regarding a chronic cough may help in the diagnosis of CANVAS as this can precede other symptoms by many years to decades [67,68].

Similarly, other clinical features such as extrapyramidal signs, skeletal abnormalities, cognitive and psychiatric features may all be of value to the diagnostic process, however are beyond the scope of this paper.

b Quantitative or volumetric MRI is not addressed as it remains a research tool which is as yet clinically available.
GENETIC TESTING

The approach to genetic assessment will be influenced by the presenting clinical features, available family history and access to genetic testing. Of note, an absence of family history should not exclude consideration of inherited disease, particularly given the relatively late onset of certain disorders such as multiple variants of CMT, most commonly MME (encoding the metalloprotease nephrilysin) also known as ‘MME-related neuropathies’ [69]; SCA6 [70] and 27B [reference: Rafehi H, Read J, Szulwicicz DJ, et al.]. An intrinsic GAA repeat expansion in FGF14 causes the autosomal-dominant adult-onset ataxia SCAS0/ATX-FGF14. Am J Hum Genet. 2023 Jan 5;110(1):105-119.] and CANVAS [46,47,71]; and inheritance patterns which may lead to sparsely populated pedigrees and de novo mutations. Mitochondrial diseases such as Neuropathy, Ataxia and Retinitis Pigmentosa, and Maternally Inherited Leigh Syndrome should also be considered, and testing undertaken as is clinically appropriate [72**].


CONCLUSION

In addition to detailed electrophysiology, we advise vestibular function testing and cerebellar assessment in all individuals with a broad-based gait, but in particular where the imbalance is greater than would be expected for an isolated somatosensory impairment. Where clinically indicated a range of other testing should be considered and includes an audiogram, autonomic testing, imaging (particularly MRI) and genetic testing. Management options include genetic counselling, neurological and vestibular physical therapy, occupational therapy, and neuropathic pain medications.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


A clinically orientated guide to the patient who presents with cerebellar ataxia and somatosensory and/or vestibular dysfunction.


Peripheral nerve and neuro-muscular junction disease

36. A very instructive introduction to oculomotor abnormalities, how to identify them, their localization value and those more likely to be seen in certain diseases.
42. An excellent summary of the recessive cerebellar ataxias.