Idiopathic sensory ataxia - literature review

Samenvatting

Ataxie

Ataxie is een neurologisch syndroom dat kan ontstaan door cerebellaire, vestibulaire en sensorische aandoeningen. Cerebellaire ataxie komt het meeste voor. Sensorische ataxie is vaak moeilijker vast te stellen, maar wel van belang omdat het gaat om een ander pathofysiologisch proces.

Ataxie kent zeer veel verschillende vormen, elk met een eigen genetische of moleculaire etiologie. Ze zijn te verdelen in drie groepen: 1) verworven ataxie, 2) erfelijke ataxie en 3) niet-erfelijke degeneratieve ataxie. Omdat het hier gaat om een aandoening die al dan niet door blootstelling in het werk is ontstaan, is verder vooral gekeken naar de eerste groep van de verworven ataxie. In grote lijnen gaat het dan om

- Vasculaire accidenten: beroerte, bloeding, vasculaire aandoening in de hersenen
- Na anoxie, hyperthermie, trauma
- Bij chronische epilepsie
- chronisch alcoholmisbruik,
- ataxie als para neoplastisch fenomeen bij een tumor,
- als begeleidend verschijnsel van een auto-immuunziekten (reuzencel arteritis, lupus, schildklier, darmziekten)
- ten gevolge van vitaminedeficiëntie (B1, B12 of E),
- bij superficiale siderose (een ijzerstapelingsziekte),
- bij chronische infecties van het centrale zenuwstelsel (syfilis, HIV, Lyme, Whipple) of
- ten gevolge van toxische blootstelling aan medicamenten (5-FU, cytosine arabinoside, carbamazepine, lithium, fenytoine, anti-immuun medicatie)
- tgv blootstelling aan andere stoffen: oplosmiddelen (tolueen, met name snuiven), acrylamide, pesticiden en zware metalen (organo-lood, kwik, tin, anorganisch bismuth, kwik, thallium).

Sensorische ataxie kan secundair optreden aan perifere neuropathie. Dit kan acuut/subacuut zijn of chronisch. Bij de acute vormen is er vaak sprake van een voorafgaande infectieuze aandoening of een auto-immuunziekte. Bij chronische vormen is soms sprake van onder meer paraproteinaemieen, van vitaminedeficiëntie of ijzerstapeling, of van begeleidende ziekten als diabetes of coeliakie.

Perifere neuropathieën komen voor bij blootstelling aan oplosmiddelen. Al in de jaren zeventig werd onder onderhoudspersoneel van vliegtuigen onder meer een verhoogd voorkomen van polyneuropathie gevonden, onder meer door blootstelling aan vliegtuigbrandstof. En ook in 2011 werd nog in een groot cohort in Australië vastgesteld dat bij blootstelling aan oplosmiddelen tijdens het onderhoud van vliegtuigen meer perifere neuropathie voorkomt dan bij niet-blootgestelden.

Er zijn echter geen artikelen gevonden die een verband aantonen tussen vastgestelde idiopathische sensorische ataxie en blootstelling aan oplosmiddelen.

Overview of types of ataxia

(Klockgether 2010) (Barsottini et al. 2014)
Ataxia literally means “absence of order” and denotes a clinical syndrome of incoordination. It is estimated that there are at least 50 (and possibly up to 100) different ataxias, each of which has a distinct genetic or molecular aetiology. Ataxias can be subdivided into three major groups: (1) acquired ataxias, which are due to exogenous or endogenous non-genetic causes; (2) hereditary ataxias; and (3) non-hereditary degenerative ataxias.

Acquired ataxias

- Alcoholic cerebellar degeneration: Alcoholic cerebellar degeneration (ACD) is a chronic cerebellar disease that occurs mainly in middle-aged men with a history of chronic alcohol abuse.
- Ataxia due to other toxic causes: In addition to alcohol, other compounds can cause chronic cerebellar damage. Clinically, the most relevant are lithium, phenytoin, amiodarone, toluene (abusers), and the anti-cancer drugs 5-fluorouracil and cytosine arabinoside. Ataxia can also occur as a result of poisoning with heavy metals, including organo-lead compounds, mercury, and thallium.
- Paraneoplastic cerebellar degeneration: Paraneoplastic cerebellar degeneration (PCD) is an immune-mediated degenerative disorder of the cerebellar cortex that can occur in association with almost every tumour, most commonly small-cell lung cancer, cancer of the breast and ovary, and Hodgkin’s lymphoma.
- Other immune-mediated ataxias: Ataxia can be part of a polyglandular endocrine autoimmune syndrome in patients with circulating antibodies to glutamic acid decarboxylase (GAD). Anti-GAD ataxia is more common in women than in men, and is often associated with insulin-dependent diabetes mellitus. Clinically, it is characterised by a slowly progressive cerebellar syndrome associated with cerebellar atrophy on MRI in about half of cases. Other diseases Celiac disease, autoimmune thyroiditis
- Ataxia due to acquired vitamin deficiency: Adult-onset acquired ataxia can occur as a result of a deficiency in vitamin B1, vitamin B12, or vitamin E.
- Superficial siderosis: Superficial siderosis is characterised by deposition of free iron and haemosiderin along the pial and subpial structures of the brain and spinal cord, resulting in damage to the cerebellar cortex, cochlear nerves, cerebral cortex, and spinal cord
- Ataxia in chronic CNS infection: Acute cerebellar ataxia can occur as a post-infectious complication of various viral infections. The most common infections related to progressive sporadic ataxia are neurosyphilis, Whipple’s disease, Lyme disease and HIV.

(Perlman 2007) Sensory ataxia has no vertigo or dizziness, also spares speech, worsens when the eyes are closed (positive Romberg sign), and is accompanied by decreased vibration and joint position sense. Cerebellar influence is ipsilateral (the right cerebellar hemisphere controls the right side of the body), and within the cerebellum are regions responsible for particular functions. The midline cerebellum controls gait, head and trunk stability, and eye movements. The cerebellar hemispheres control limb tone and coordination, eye movements, and speech. Cerebellar signs on the neurologic exam can help to determine whether a process is unilateral or involves the entire cerebellum, and

whether a particular region of the cerebellum has been targeted (vermis, outflow tracts,

Table 1. IDENTIFIABLE CAUSES OF NONGENETIC ATAXIA

Type		Cause
Congenital		Developmental
Mass lesion of a specific type		Tumor, cyst, aneurysm, hematoma, abscess, normal pressure or partial obstructive hydrocephalus
Vascular		Stroke, hemorrhage; subcortical vascular disease
Infectious/Post-infectious/ Post-vaccination		Anthrax; Epstein-Barr; enterovirus; HIV; HTLV; prion disease; Lyme disease; syphilis; measles, rubella, varicella; Whipple's disease; progressive multifocal leukoencephalopathy
Post-anoxic, post-hyperthermic, post-traumatic		
Chronic epilepsy		
Metabolic		Acute thiamine (B1) deficiency; chronic vitamin B12 and E deficiencies; autoimmune thyroiditis and low thyroid levels
Toxic	*Drug reactions*	Amiodarone, cytosine arabinoside, 5-fluorouracil, lithium, phenytoin, valproic acid, and others
	Environmental	Acrylamide, alcohol, organic solvents, organo-lead/mercury/tin, inorganic bismuth/mercury/thallium
Immune-mediated	*Vasculitis*	Behcet's, giant cell arteritis, lupus, and others
	Paraneoplastic [a]	Anti-Yo, Hu, Ri, MaTa, CV2, Zic 4; anti-calcium channel; anti-CRMP-5, ANNA-1,2,3, mGluR1, TR
	Other autoantibodies	Anti-GluR2, GAD[b], MPP1, GQ1b ganglioside; anti-gliadin (most common – reported also in the inherited syndromes as a possible secondary factor; treated with gluten-free diet)[c-e]
	Anti-immune therapies used in reported cases of immune-mediated cerebellar ataxia	Steroids, plasmapheresis, IVIG, rituximab, mycophenolate mofetil, methotrexate, and others

[a] Bataller, L., and J. Dalmau. Paraneoplastic neurologic syndromes: approaches to diagnosis and treatment. *Semin Neurol*, 2003. 23(2): p. 215-24.
[b] Mitoma, H., et al. Presynaptic impairment of cerebellar inhibitory synapses by an autoantibody to glutamate decarboxylase. *J Neurol Sci*, 2000. 175(1): p. 40-44.
[c] Bushara, K.O., et al. Gluten sensitivity in sporadic and hereditary cerebellar ataxia. *Ann Neurol*, 2001. 49(4): p. 540-43.
[d] Hadjivassiliou, M., et al. Dietary treatment of gluten ataxia. *J Neurol Neurosurg Psychiatry*, 2003. 74(9): p. 1221-24.
[e] Hadjivassiliou, M., et al. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain*, 2003. 126(Pt 3): p. 685-91.

flocculonodular lobe, etc.). Certain aetiologies may then become more likely. Look at the table of identifiable causes of nongenetic ataxia underneath.

Studies in aircraft maintenance workers

(Knave et al. 1976)
Long-term exposure to jet fuel: An investigation on occupationally exposed workers with special reference to the nervous system. Scand. j. work environ. & health 3 (1976) 152 - 164. In the present study the results of a neurological and neurophysiological health examination of 29 aircraft factory workers chronically exposed to jet fuel vapours are presented. The exposed subjects were classified into a heavily exposed and a less heavily exposed group. The examination included a standardized clinical neurological examination, measurements of the conduction velocities in the peripheral nerves, and threshold determinations of vibratory sensations in the extremities. All 13 persons examined in the heavily exposed group and 7 of the 16 in the less heavily exposed group stated that they had repeatedly experienced acute effects (dizziness, respiratory tract symptoms, heart palpitations, a feeling of pressure on the chest, nausea, headache) of the jet fuel vapours in the inhaled air. A high rate of symptoms indicative of neurasthenia and psychasthenia and

symptoms and signs indicative of polyneuropathy was observed both in the heavily exposed group and in the two groups combined in comparison with reference groups. Considering the presented facts concerning (a) the acute effects on repeated occasions, (b) the high rates of symptoms indicative of neurasthenia and psychasthenia and symptoms and signs indicative of polyneuropathy, and (c) the differences in the observations made between the two groups with varying degrees of exposure to jet fuel, the authors interpreted the results as indicative of a possible effect of long-term exposure to jet fuel on the nervous system.

(Guest et al. 2011)
Objective: This study aimed to examine possible persisting peripheral neuropathy in a group who undertook fuel tank repairs on F-111 aircraft, relative to two contemporaneous comparison groups. Methods: Vibration perception threshold (VPT) was tested using biothesiometry in 614 exposed personnel, compared with two unexposed groups (513 technical trades and 403 nontrades). Regression modelling was used to examine associations, adjusting for possible confounders. Results: We observed that 26% of participants had chronic persistent increased VPT in the great toe. In contrast, statistically significant higher VPT of the great toe was observed in the comparison groups; however, the effect was small, about 1/4 the magnitude of diabetes. Age, height, and diabetes were all significant and strong predictors in most models. Conclusion: This study highlights chronic persisting peripheral neuropathy in a population of aircraft maintainers.

This large cohort study has described the level of peripheral neuropathy in a selected RAAF population within Australia. It is the first Australian study of a military population to be published, which has examined vibration perception in the hands and feet. The strength of this study is the sample size of 1538, being one of the largest studies investigating the relationship between solvent exposure and persistent peripheral neuropathy

Overview of toxic agents causing ataxia

(Manto 2012) Toxic agents causing cerebellar ataxias

Drugs	Toxic chemicals
Phenytoin	Mercury
Carbamazepine	Lead
Other anticonvulsants (phenobarbital, vigabatrin, gabapentin, lamotrigine)	Manganese
Antineoplastics (5FU, AraC, methotrexate, cisplatin, oxaplatin, paclitaxel, capecitabine, epothilone D)	Aluminium
Lithium salts	Thallium
Amiodarone	Germanium
Procainamide	Uranium
Ciclosporin and calcineurin inhibitors	Vanadium
Bismuth	Toluene/benzene derivatives
Bromides, bromvalerylurea	Episodes of hyperthermia
Mefloquine	Carbon monoxide
Isoniazid	chemical weapons (diphenylarsinic acid)
Lindane	Insecticides/herbicides (paraquat, chlordecone and organophosphates)
Perhexiline maleate	Eucalyptus oil
Cimetidine	Saxitoxin (Shellfish poisoning)
Metronidazole	Cyanide
Glycoprotein IIB/IIIA Inhibitors (Eptifibatide)	Scorpion envenomation
Zaleplon	Carbon sulphide
Nicotine	Phosphine
Cocaine	
Heroin	
Phencyclidine	
Ceremonial herbs, Kava	
Methadone	

(Ehler et al. 2011) Dichloromethane (methylene chloride) and iodomethane are colourless relatively volatile liquids, which are used as solvents in chemical manufacturing processes. The major route of exposure is via inhalation and to a lesser extent through the skin and digestive tract. Both substances are characterized by significant neurotoxic effects. A 37-

year-old chemist subjected to long-term inhalation exposure to both substances had been experiencing headaches, dizziness and fatigue for about 5 years. After an exceptional acute exposure, the man developed ataxia, increasing inhibition and a confusional and delirious state. Magnetic resonance imaging (MRI) of his brain in the acute state demonstrated the presence of a T2-hyperintense lesion in the splenium of the corpus callosum, suggestive as myelinolysis. On MRI 16 days later, the MRI changes had completely resolved and the clinical picture had improved significantly. To the best of our knowledge, this is the first published report of a case of ‘‘reversible focal splenial lesion syndrome of the corpus callosum’’, which was likely caused by industrial toxic substances

(Pennisi et al. 2013) Acrylamide (ACR) is a water-soluble chemical used in different industrial and laboratory processes. ACR monomer is neurotoxic in humans and laboratory animals. Subchronic exposure to this chemical causes neuropathies, hands and feet numbness, gait abnormalities, muscle weakness, ataxia, skin and in some cases, cerebellar alterations. ACR neurotoxicity involves mostly the peripheral but also the central nervous system, because of damage to the nerve terminal through membrane fusion mechanisms and tubulovescicular alterations. Nevertheless, the exact action mechanism is not completely elucidated. In this paper we have reviewed the current literature on its neurotoxicity connected to work-related ACR exposure. We have analysed not only the different pathogenetic hypotheses focusing on possible neuropathological targets, but also the critical behaviour of ACR poisoning. In addition we have evaluated the ACR-exposed workers case studies. Despite all the amount of work which have being carried out on this topic more studies are necessary to fully understand the pathogenetic mechanisms, in order to propose suitable therapies.

Differential diagnosis

(Chhetri et al. 2014) Ataxia is a common neurological syndrome resulting from cerebellar, vestibular or sensory disorders. The recognition and characterisation of sensory ataxia remains a challenge. Cerebellar ataxia is the more common and easier to identify; sensory ataxia is often mistaken for cerebellar ataxia, leading to diagnostic errors and delays.

The first step is to distinguish cerebellar, sensory and vestibular ataxia.

Neurophysiology is important in diagnosing sensory ataxias by helping to localise the lesion and to suggest the pathological process, that is, axonal versus demyelination.

Table 2 Acquired causes of sensory ataxia

Site	Onset	Aetiology	Ancillary investigations
Peripheral nerve/nerve root	Acute	Miller Fisher syndrome[7]	Anti-GQ1b antibodies, CSF, NCS
		Sensory variant of GBS[8]	Anti-ganglioside antibodies, CSF, NCS
		Semisynthetic penicillins[9]	History of exposure
	Subacute	Lyme disease [10]	Lyme serology
		Neurosarcoidosis [11]	CSF, NCS, ACE, chest X ray, HPE
	Chronic	CIDP[12]	NCS, CSF
		Paraproteinaemia[13 14]	Electrophoresis, anti-MAG
		Diabetes mellitus[15]	Plasma glucose.
		Coeliac disease[16]	Anti-tTG antibodies
		Vitamin E deficiency[17]	Serum vitamin E level
Dorsal root ganglion	Subacute	HIV[18] HTLV-1,[19] HCV[20]	Serology
		Small cell lung cancer[21]	Anti-Hu, CRMP-5, relevant imaging
		Pyridoxine intoxication [22]	History of exposure; pyridoxine levels
		Chemotherapeutic agents[23]	History of exposure
		Thalidomide[24]	History of exposure
		Organophosphate exposure[25]	History of exposure
		Colonic carcinoma[26]	Relevant imaging
		Neuroendocrine tumour[27]	Relevant imaging
		Breast and ovarian cancer[28]	Relevant imaging
	Chronic	Sjögren's syndrome[29]	ENA (Anti-SSA/SSB) abs, lip biopsy
		Chronic active hepatitis[30]	RF, ANA, ASMA, hepatitis serology
Spinal root	Chronic	CISP[31]	NCS, SSEP, CSF, MRI
Dorsal column	Chronic	Vitamin B12 deficiency[32]	Serum B12, Schilling's test*
		Copper deficiency[33]	Serum copper and caeruloplasmin level.
		Tabes dorsalis[34]	Syphilis serology
		HIV,[18] HCV[35]	Serology
		Cervical myelopathy[36]	Neuroimaging

Abs, antibodies; ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; ASMA, antismooth muscle antibodies; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CISP, chronic immune sensory polyradiculopathy; CRMP-5, collapsin response mediator protein 5; CSF, cerebrospinal fluid analysis; ENA, extractable nuclear antigen; GBS, Guillain–Barré syndrome; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPE, histopathology; HTLV-1, human T cell lymphotrophic virus type 1; MAG, myelin-associated glycoprotein; NCS, nerve conduction studies; RF, rheumatoid factor; *Schilling's test, useful but obsolete in UK; SSA, Sjögren's syndrome A; SSB, Sjögren's syndrome B; SSEP, somatosensory evoked potentials; tTG, tissue transglutaminase.

Sensory ataxia secondary to peripheral neuropathies

Peripheral neuropathies may present with either chronic or, less commonly, acute sensory ataxia.

Acute/subacute

- Miller Fisher syndrome is an acute form of sensory ataxia. There may be either antecedent infection (mainly Campylobacter jejuni and Haemophilus influenzae) and/or underlying autoimmune or neoplastic disorder.7 The syndrome is characterised by ophthalmoplegia, ataxia and areflexia. Although limb weakness and superficial sensory loss are not part of the classical triad, about one-third have these features.7 The serum anti-GQ1b IgG antibody titre is elevated in over 80% of cases.7
- The sensory variant of Guillain–Barré syndrome, which solely involves the large sensory fibres, is rare but can also present as acute sensory ataxia.8 The clinical findings include sensory ataxia, impaired joint position and vibration sense and areflexia, but usually normal strength. Serum antibodies to GD1b and GQ1b gangliosides may be positive.8 Nerve conduction in both conditions may show demyelinating polyradiculoneuropathy, although in Miller Fisher syndrome they are often either normal or show small SNAPs.7 8 Cerebrospinal fluid commonly has a normal cell count but raised protein.
- Semisynthetic penicillin's may cause acute sensory ataxia.9
- Lyme disease10 and neurosarcoidosis11 may uncommonly present with subacute sensory ataxia.

Chronic

Chronic sensory ataxia can result from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP),12 paraproteinaemia,13 14 diabetic neuropathy,15 coeliac disease,16 vitamin E deficiency17 and mitochondrial dysfunction.40 Chronic sensory ataxia can uncommonly be associated with anti-GD1b IgM antibody; it is worthwhile measuring antiganglioside antibodies in all patients with otherwise idiopathic sensory ataxic neuropathies, as intravenous immunoglobulin treatment is often effective.41

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
  CIDP typically presents with monophasic, relapsing or progressive symmetrical sensory and motor neuropathy, evolving over 8 weeks.39 The classical manifestations include paraesthesia, proximal weakness without wasting, areflexia and loss of vibration and/or joint position sense. Nerve conduction studies may show either conduction slowed to the demyelinating range or partial conduction block.39 The uncommon sensory ataxic form manifests as prominent numbness in the extremities, ataxia, areflexia and impaired vibration and/or joint position sense.12 Weakness may be mild or absent, by contrast with classical CIDP. Nerve conduction shows motor abnormalities typical of CIDP, and nerve biopsy shows demyelination and remyelination.12 It often responds to corticosteroids and/or intravenous immunoglobulins, and its management is along lines similar to typical CIDP.
- Paraproteinaemic neuropathy
  A range of paraproteinaemic neuropathies can cause sensory ataxia.13 42 Antimyelin-associated glycoprotein neuropathy is a distinct syndrome of late onset, a slowly progressive, demyelinating neuropathy characterised by distal and symmetrical, mainly sensory neuropathy. It results from monoclonal IgM antibodies against myelin-associated glycoprotein.13 42 There is predominant impairment of joint position and vibration sense. Patients may have tremor but little weakness. Clinicians should consider testing for antimyelin-associated glycoprotein antibody in all patients with IgM paraproteinaemic neuropathies, as nearly half of them have high titres.42 43 Nerve conduction studies usually show symmetrical and predominantly distal demyelination with disproportionately prolonged distal motor latencies.42 Waldenström's macroglobulinaemia, a lymphoplasmacytoid malignancy producing IgM paraprotein, can present with sensory ataxia if the IgM paraprotein shows antimyelin-associated glycoprotein activity.44 Note that IgM paraproteinaemic neuropathies may cause sensory ataxia in the absence of antimyelinassociated glycoprotein antibodies.13 42 CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, monoclonal IgM protein, cold agglutinins and disialosyl antibodies) is another antibody-mediated paraproteinaemic neuropathy.14 It is associated with anti-GQ1b and antidisialosyl antibodies. Note that a history of diabetes mellitus and alcohol excess (both common causes of neuropathy) do not preclude the possibility of coexisting pathology (Case 1, box 2). Serum immunoelectrophoresis and immunofixation are, therefore, important investigations in the diagnostic workup of ataxic neuropathy
- Diabetic neuropathy
  Diabetic neuropathy commonly presents with distal symmetrical polyneuropathy.15 The impairment may be sensory or motor and is length-dependent. Small fibres are usually affected first, giving pain, burning, impaired spinothalamic sensations and autonomic dysfunction. Large fibre sensation is affected later, when patients may develop paraesthesia and gait imbalance. On examination, there is often impaired

vibration, joint position and pressure sensations and loss of ankle reflex. In advanced stage, there may be sensory ataxia.15

- Coeliac ataxia
  Coeliac disease is a chronic inflammatory enteropathy associated with sensitivity to ingested gluten. Neurological complications occur in 6–10%; ataxia and peripheral neuropathy are the common presentations.16 The ataxia may be cerebellar or sensory. Patients may report problems with stance and gait secondary to proprioceptive deficits. Clinicians should therefore request serum antigliadin antibodies in patients presenting with sporadic idiopathic ataxia.16 38

Mitochondrial neuropathy

Sensory ataxic neuropathy, dysarthria and ophthalmoparesis (SANDO) is a rare heterogeneous systemic entity resulting from mitochondrial dysfunction, characterised by the triad of sensory ataxic neuropathy, dysarthria and ophthalmoparesis.40 As the clinical features include dysarthria, this leads to confusion with cerebellar pathology (case 2, box 3). Molecular analysis shows mutations in polymerase gamma (POLG) or TWINKLE genes.40

Sensory ataxia due to dorsal root ganglionopathies

Pathology of sensory neurones in dorsal root ganglia leading to degeneration of peripheral axons and central sensory projections in the dorsal columns cause a distinct entity called dorsal root ganglionopathy.28 38 There is a unique pattern of non-lengthdependent sensory nerve degeneration leading to asymmetric, patchy neuropathic symptoms of pain, burning, paraesthesia and sensory loss, with predilection for upper limbs. Clinical findings include early sensory ataxia, areflexia, markedly impaired proprioception, pseudoathetosis, but relatively preserved muscle strength.28 38 Electrophysiologically, there is often marked involvement of the sensory fibres, with reduced or absent SNAPs in a non-length-dependent fashion.28 38 This is frequently associated with paraneoplastic disorders, dysimmune conditions like Sjögren's syndrome or toxic exposure to drugs, such as chemotherapeutic agents and pyridoxine.

- Paraneoplastic dorsal root ganglionopathy
  This is most commonly associated with small cell lung cancer,21 although sometimes with other malignancies including colonic carcinoma,26 Hodgkin's lymphoma, neuroendocrine tumours, breast and ovarian carcinoma.27 28 Patients usually present with subacute and rapidly progressive sensory ataxia, pain and paraesthesia. Most patients with paraneoplastic dorsal root ganglionopathy have one of the antionconeural antibodies; anti-Hu (antineuronal nuclear autoantibodies type 1), antiamphyphysin, and anticollapsin responsemediator protein-5 (CRMP-5).45 Anti-Hu—the most commonly associated antibody—has a sensitivity of 82% and specificity of 99%, implying that their absence does not exclude an underlying malignancy.46 The syndrome may develop before the cancer becomes clinically overt (case 3, box 4) and can antedate the cancer diagnosis by 0.5–62 months.28
- Immune mediated dorsal root ganglionopathy
  Sjögren's syndrome, an autoimmune disease, causes dorsal root ganglionopathy through lymphocytic infiltration in the dorsal root ganglion.29 Patients may present with dry eyes and dry mouth resulting from mononuclear infiltration of the glands; lip biopsy can show destruction of small salivary glands and inflammatory infiltrates.47 The ganglionopathy almost always predates the diagnosis of Sjögren's syndrome.38 The sensory symptoms of numbness, tingling, burning pain and dysaesthesia are

often asymmetric at onset, and predominantly involve the upper limbs; with progression, the symptoms and signs become symmetrical and generalised.28 38 A negative ANA/ENA (antinuclear antibody/extractable nuclear antigen) (Anti-SSA (anti Sjögren's syndrome A) (Ro))/SSB (Sjögren's syndrome B) (La) antibodies) does not exclude the diagnosis.47 Lip biopsy established the diagnosis after prolonged delays in case 4 (box 5). Although ENA was negative, a positive lip biopsy gave the diagnosis.47 The initial explanation of sensory ataxia had been pyridoxine toxicity, and it was only after longterm follow up and continued disability that we suspected Sjögren's syndrome.

- Medication-induced dorsal root ganglionopathy
  Pyridoxine overuse can rarely cause sensory dorsal root ganglionopathy.22 Patients usually present with a pure sensory neuropathy with features of large fibre involvement. Doses as little as 200 mgs per day may be the cause.48 Anticancer drugs, particularly platinum compounds like cisplatin, can also cause sensory ataxic neuropathy; the severity of neuropathy usually correlates with the cumulative drug dose.23 With platinumcontaining compounds, the sensory deficits may progress for several months after stopping treatment, a phenomenon called 'coasting'. 23
- Infection-associated dorsal root ganglionopathy HIV is the most common infection associated with sensory ataxia, and typically presents acutely or subacutely. Peripheral neuropathy commonly complicates HIV infection, but a few patients may develop a subacute dorsal root ganglionopathy.18 Other infections causing sensory ataxia include hepatitis C, measles, Epstein–Barr, varicella zoster, and human T-cell lymphotropic virus type I infections.19 20 28
- Chronic idiopathic ataxic neuropathy
  A few patients with chronic sensory ataxia have no identifiable cause; they are usually diagnosed as chronic idiopathic ataxic neuropathy.49 Typically, they have normal strength with areflexia; cerebrospinal fluid analysis (CSF) electromyography and motor nerve conduction are often normal, but sensory potentials are absent. Presumably, it is an indolent, slowly progressive, dorsal root ganglionopathy, and is often refractory to treatment.49

Sensory ataxia due to sensory nerve root involvement

Chronic immune sensory polyradiculopathy results from preferential involvement of the large myelinated sensory nerve roots proximal to the dorsal root ganglion.31 It presents with ataxia and limb paraesthesia. On examination, there is usually sensory ataxia, areflexia, impaired joint position and vibration sense but normal strength. Nerve conduction studies are normal, but somatosensory-evoked potentials are abnormal, suggesting sensory root involvement.31 MR scan of the lumbar spine may show enlarged and enhancing nerve roots. CSF may show raised protein. Sensory rootlet biopsies may show demyelination similar to CIDP. The condition may respond to immunomodulation.31

Sensory ataxia due to posterior spinal column involvement

- Vitamin B12 deficiency
  Classical subacute combined degeneration from B12 deficiency is uncommon nowadays. It more likely occurs with nitrous oxide exposure—anaesthesia and dental staff or recreational abusers.32 However, gastric or ileal resections with bacterial overgrowth in blind loops, anastomoses or diverticula may continue to underlie this classical neurological syndrome. Patients present with limb paraesthesia, subacute

gait disorder with sensory ataxia and/or spasticity. Examination often shows signs of dorsal column impairment, including loss of proprioception and vibration as well as the combination of sensory ataxia and spastic paraparesis. Length-dependent peripheral neuropathy often coexists, and may manifest as depressed lower limb reflexes with stocking sensory loss.32 MR scan of spine may show increased T2 signal, most commonly in the dorsal cervical and thoracic cord. Note that some patients with subacute combined degeneration of the cord may have normal or borderline B12 level, and helpful tests to confirm the diagnosis include increased serum levels of homocysteine and methylmalonic acid.32

- Copper deficiency

  Copper deficiency is an under-recognised cause of neurological and haematological abnormalities.33 This essential trace element is absorbed in the stomach and proximal duodenum. Risk factors for copper deficiency include previous upper gastrointestinal surgery (eg, gastrectomy, bariatric surgery, small bowel resections) and malabsorption. Zinc overload—from zinc supplementation or ingestion of denture cream—competes with copper for absorption, causing copper deficiency. The clinical picture is often clinically and radiologically indistinguishable from vitamin B12 deficiency.33 There may be anaemia (microcytic, macrocytic, or normocytic), leucopenia and, rarely, thrombocytopenia. Plasma copper, caeruloplasmin levels and urinary copper levels are all reduced. Although copper deficiency is rare, the neurological syndrome is incapacitating and frequently irreversible, especially if treatment is delayed. Early diagnosis and treatment with copper supplementation is therefore essential.33

- Infections

  HIV infection can cause vacuolar myelopathy.18 This causes symptoms in about 10% of patients with AIDS, although half show pathological evidence at autopsy. The condition manifests with a slowly progressive painless spastic paraparesis, sensory ataxia and sphincter dysfunction.18 MR scan of the spine is usually normal although there may be non-specific tract hyperintensities. HIV-associated vacuolar myelopathy often occurs in the late stages of HIV infection, and commonly parallels the development of AIDS dementia complex.18 Tabes dorsalis results from degeneration of the dorsal columns of the spinal cord and sensory nerve roots in late-stage or tertiary neurosyphilis.34 38 The presentation is classically with lancinating or lightning-like pains, progressive sensory ataxia, proprioceptive loss and positive Romberg’s sign. Hepatitis C infection may cause transverse myelopathy; sensory ataxia may be its only manifestation.35

Compressive and demyelinating disorders

Cervical myelopathy commonly presents with painful stiff neck, upper limb paraesthesia and gait and balance disturbance.36 Other compressive pathologies (e.g., meningioma) can also cause sensory ataxia if there is predominant involvement of the posterior columns. In addition to spastic weakness in limbs, patients may have impaired joint position and vibration sense as well as a positive Romberg sign.36 Multiple sclerosis can cause sensory ataxia if demyelination involves the central sensory pathways

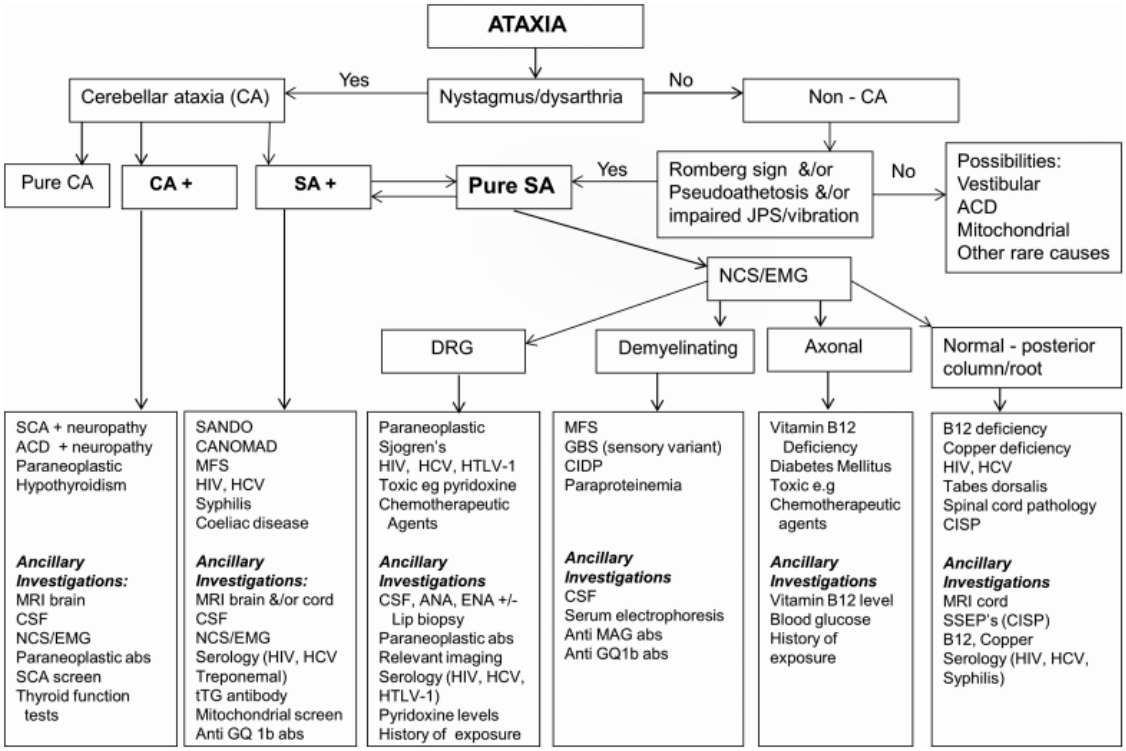

Figure 2 Integrated diagnostic algorithm to evaluate sensory ataxia. abs, antibodies; ACD, alcoholic cerebellar degeneration; ANA, antinuclear antibody; CA, cerebellar ataxia; CA +, cerebellar ataxia plus; CANOMAD, chronic ataxic neuropathy, ophthalmoplegia, monoclonal IgM protein, cold agglutinins and disialosyl antibodies; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CISP, chronic immune sensory polyradiculopathy; CSF, cerebrospinal fluid; DRG, dorsal root ganglionopathy; ENA, extractable nuclear antigen; GBS, Guillain–Barré syndrome; HCV, hepatitis C virus; HTLV1, human T cell lymphotrophic virus type 1; JPS, joint position sense; MAG, myelin-associated glycoprotein; MFS, Miller Fisher syndrome; NCS, nerve conduction studies; SA, sensory ataxia; SA +, sensory ataxia-plus; SANDO, sensory ataxic neuropathy, dysarthria and ophthalmoparesis; SCA, spinocerebellar ataxia; SSEP, somatosensory evoked potentials; tTG, tissue transglutaminase.

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