Cerebellar Ataxia but Normal Neuroimaging: Now What?

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Cerebellar ataxia is characterised by loss of fine coordination of muscle groups during volitional movements and can affect cranial, trunk or limb musculature. CT/MRI brain imaging often represents a core investigative modality but can be normal or reveal minor changes that may not fully explain the degree of clinical ataxia evident at the bedside. The aim of this article is to provide the general physician and neurologist with information on how to practically approach the patient with cerebellar ataxia but with normal neuroimaging findings. Important differential diagnoses of such cases are also individually discussed.

Introduction

Cerebellar ataxia denotes incoordination that arises as a consequence of dysfunction of the cerebellum and can take on different manifestations depending on the anatomical regions involved. Ataxia of the upper limbs is characterised by dysmetria, intention tremor and dysdiadochokinesia, and of the lower limbs by a broad-based, clumsy, unsteady gait. Ataxia of speech manifests as a scanning dysarthria but with preserved linguistic abilities. Identifying ataxia is often straightforward and when new, is typically investigated with a CT or MRI brain scan. However, difficulty can arise when the brain scan is reportedly normal and there is no obvious radiological evidence of structural pathology. The aim of this article is to provide the general physician and neurologist with information on how to practically approach the patient with cerebellar ataxia but with normal neuroimaging findings. Important differential diagnoses of such cases are also individually discussed.

As is frequently indoctrinated throughout the physician’s training, the diagnosis is always in the history and to a lesser extent, the examination. If difficulties are encountered in formulating the differential diagnoses, it is important to revisit the clinical history and ask the right questions as this contributes the greatest yield of information when reaching the correct diagnosis.
Is this truly a cerebellar ataxia?
The first question to ask when confronted with a patient who supposedly has a cerebellar ataxia is: is this really a cerebellar ataxia or a mimic? Differentials to consider include a sensory ataxia, apraxia or a functional neurological disorder.

Sensory ataxia can be unmasked by removing visual cues that aid with co-ordination. This can be assessed by testing Romberg’s sign (stand with feet together and eyes closed – significant body sway suggests a positive sign), or by asking them to walk, or to touch their nose with a finger, with their eyes shut. Further assessments include directly examining proprioception of selected joints or vibration sensation with a 128Hz tuning fork, which can both probe the integrity of the dorsal column-medial lemniscus pathway. Sensory ataxia would suggest the presence of a large fibre sensory neuropathy, neuronopathy and/or dorsal column tract injury.

Apraxia of the limbs can similarly present as a clumsiness that can mimic an ataxia to the untrained eye. This can be identified by requesting a patient to perform certain skilled gestures, such as asking them to pretend to brush their teeth, comb their hair or use a pair of scissors, though it is imperative to ensure that any limitations are not directly due to weakness of the relevant muscle groups. The dyspraxic patient may struggle altogether with these tasks or they may typically perform a ‘body part as object’ error. A gait apraxia, classically seen in normal pressure hydrocephalus (NPH), resembles the appearance of a magnetic gait, and can sometimes be falsely misinterpreted as a gait ataxia. Inquiring about associated symptoms such as cognitive impairment or urinary incontinence may help clarify this diagnosis.

Functional neurological disorders represent the second commonest presentation to the neurologist in the outpatient setting. Be wary of labelling a patient with a functional syndrome just because their constellation of symptoms and signs ‘doesn’t make sense’ or ‘doesn’t fit into a single diagnosis’ (Hickam’s dictum – “patients can have as many diseases as they damn well please”). Search for positive findings that support non-organic pathology – clear inconsistencies in the history and examination (which may require more than 1 consultation to elicit), evidence of distractible clinical signs or in the case of associated weakness, using established examination strategies such as a Hoover’s test.

Is the brain imaging really normal?
Once it is established that a patient has cerebellar ataxia and you are confronted with supposedly normal neuroimaging, it’s essential to question even that. Review the imaging yourself and if necessary discuss it with an experienced neuroradiologist. What imaging modality was employed? If a CT head, the sensitivity of identifying many cerebellar lesions is low, particularly in small ischaemic strokes and inflammatory demyelination. Although an MRI brain scan is more sensitive for most lesions than a CT head, even with modern data acquisition and processing techniques, subtle lesions can still be missed, especially if inappropriate imaging sequences were used. Was the scan performed with contrast? If neoplastic infiltration of the meninges or cranial nerves are suspected, for example, then a gadolinium contrast-enhanced scan may be required as these could be missed on a non-contrast scan.

Methods
A selection of relevant original research and review articles was obtained from the author’s personal archive and by searching PubMed, EMBASE and Medline using a combination of the terms cerebellar ataxia, cerebellar syndrome and normal neuroimaging or CT/MRI.

Results
Diverse ranges of aetiologies underpinning cerebellar syndromes, which may occur in the context of unremarkable neuroimaging, were identified and are discussed separately below.

Stroke
Stroke has always been, and remains, a clinical diagnosis. Sudden onset cerebellar ataxia with maximal deficit at the time of onset, and which slowly improves over time is strongly suggestive of a vascular event. An initial stuttering temporal profile may be more suggestive of a thrombotic aetiology rather than embolic. A CT brain scan is often normal in the hyperacute ischaemic stroke and whose primary purpose is to exclude a bleed during the thrombolysis time window. The sensitivity of a non-contrast CT head in identifying ischaemic posterior fossa strokes within 30 hours of onset may be as low as 41.8% [1].

Although MRI diffusion-weighted imaging (DWI) is the most sensitive sequence for radiologically confirming ischaemic strokes, this is not bulletproof. A recent meta-analysis of patients with acute ischaemic strokes (n=3236) yielded a pooled prevalence of DWI-negative strokes of 6.8% (95% CI 4.9-9.3). Furthermore, patients with posterior circulation strokes had 5 times the odds of having DWI-negative scans than those with anterior territory strokes [2].

It is often helpful to search for clinical features that may suggest the underlying stroke aetiology such as a combination of Horner’s syndrome, crossed spinothalamic sensory deficits, vertigo and bulbar deficit in cases of vertebral artery dissection – this may be flagged by fat suppressed T1 weighted axial sequences on MRI, which could subsequently be verified by CT or MR angiography.

Toxic causes
Drugs represent common causes of cerebellar ataxia and in a systematic review were reported in 93 individual drugs, though this number will undoubtedly rise with ongoing drug discovery [3]. Acute alcohol intoxication is perhaps the most frequent cause of cerebellar syndrome in humans and is swiftly revealed by testing a blood alcohol level. Epileptic patients taking regular anti-convulsants are also susceptible to cerebellar syndromes. Phenytoin and carbamazepine are common culprits amongst others - in the former case, phenytoin's non-linear kinetics can lead to unpredictable and dramatic rises in serum drug levels to toxic values even with minor dose adjustments. Both drugs are highly protein-bound, so if this binding is reduced, such as in cases of...
hypoalbuminaemia or uraemia, then serum-free drug levels can rise and risk symptoms and signs of toxicity. In circumstances of suspected toxicity, it may be necessary to check anti-epileptic drug levels and inquire if new medications or over-the-counter herbal remedies had recently been commenced owing to the risk of potential drug-drug interactions. Phenytoin also has a particular predilection to induce toxicity in Purkinje cells and can lead to irreversible cerebellar degeneration in patients on long-term maintenance therapy. Other drugs that can cause cerebellar ataxia include lithium, various antineoplastic agents such as cytarabine or fluorouracil, drugs of abuse (heroin, cocaine) and various environmental toxins such as manganese, mercury and lead. Thus, it is imperative to undertake a thorough drug and occupational history when consulting the cerebellar patient.

**Nutritional and metabolic**

Thiamine (vitamin B1) deficiency can lead to the clinical syndrome of Wernicke’s encephalopathy, which is characterised by ataxia, ophthalmoplegia, nystagmus and confusion, and is typically seen in cases of chronic alcohol abuse, but also in primary nutritional deficiencies. Although signature MRI neuroimaging findings, independent of aetiology, include bilateral T2 hyperintensity in the mammillary bodies, anterior and medial thalamic nuclei, periventricular gray matter and the superior and inferior colliculi [4], MRI sensitivity for Wernicke’s is only 53% [5]. Thus, its diagnosis heavily relies on good quality clinical acumen. Treatment rests on urgent thiamine replacement, usually as part of high dose parenteral multi-vitamins (e.g. parabrinex) in order to prevent progression to Korsakoff’s psychosis, which is an irreversible syndrome of dense anterograde and retrograde amnesia (following a temporal gradient), confabulation and lack of insight.

Vitamin E deficiency, which may be due to cholestatic liver disease, fat malabsorption, abetalipoproteinaemia or the autosomal recessive condition Ataxia with Vitamin E Deficiency (AVED), can lead to a combination of spinocerebellar ataxia and peripheral neuropathy – the latter is sometimes mistaken for Friedreich ataxia due to the overlapping clinical features [6].

Coeliac disease, a gluten-sensitive enteropathy, can present with a slowly progressive ataxia with peripheral neuropathy and other neurology, which may not necessarily be explained by malabsorption alone. Thus, suspected patients should be tested for anti-endomysial antibodies and, if the index of suspicion is high, undergo a duodenal biopsy [7]. Cerebellar ataxia has also been reported in hypothyroidism, which may reverse with thyroid hormone replacement therapy and euthyroid autoimmune thyroiditis, which may not. Patients with otherwise unexplained ataxia should therefore have thyroid function tests (TFTs) and anti-thyroid antibody levels measured [8].

**Neurodegeneration**

The neurodegenerative diseases that can have ataxia as a prominent feature of their clinical presentation include multi-system atrophy (MSA) amongst others (see genetics section). MSA is an alpha-synucleinopathy, with a mean age of onset of 55 years and median interval to death of 9 years, which clinically manifests as progressive Parkinsonism, ataxia (prominent in the MSA-C variant) and autonomic failure [9]. The sensitivity of classic MRI findings in MSA, namely putaminal rim hyperintensity and the ‘hot cross bun’ sign is estimated to be 34.5% and 63.3% respectively, though this increases with disease progression [9]. Fragile X-associated tremor/ataxia syndrome (FXTAS) can sometimes mimic MSA-C clinically. It is a trinucleotide repeat expansion disorder in the pre-mutation range (55-200 CGG repeats) of the gene encoding the fragile X mental retardation protein. Men are largely affected in their 70s and can develop progressive ataxia, tremor, cognitive decline, mild parkinsonism, peripheral neuropathy and autonomic dysfunction. Although classic MRI findings include T2 hyperintense middle cerebellar peduncles (MCP sign), this occurs in 60% of cases [10]. FXTAS demonstrates anticipation so enquiring if any grandchildren have autistic features or developmental delay (suggesting undiagnosed fragile X syndrome) may help clinch the diagnosis.

In it’s classic form, Creutzfeldt-Jakob disease (CJD) presents with rapid, global cognitive decline, in association with cerebellar ataxia, myoclonus and pyramidal and extra-pyramidal features. This culminates in a state of akinetic-mutism and then death within 1 year in 90% of cases [11]. In approximately 10% of CJD cases, ataxia is the dominant clinical feature, without cognitive involvement or myoclonus [11]. The MRI features of CJD (hyperintense cortical ribbon and striatum in sporadic CJD, or hyperintense pulvinar thalamus in variant CJD) in DWI and FLAIR sequences, though helpful, are not always present. Supportive investigation findings include periodic sharp wave complexes on EEG in sporadic CJD (half of cases) and a non-inflammatory cerebrospinal fluid (CSF) with protein 14-3-3. Recently, real-time quaking-induced conversion (RT-QuIC) assays of CSF samples have revolutionised the diagnosis of sporadic CJD. This test relies on the tendency of the scrapie prion protein isoform (PrPSc) to induce conversion of the normal PrP into the misfolded form, leading to aggregation, which can be scrutinised in real-time using fluorescent dyes. The sensitivity and specificity of the RT-QuIC assay at the UK National CJD Research and Surveillance Unit is reported to be 92% and 100%, respectively [12].

**Paraneoplastic**

Paraneoplastic syndromes are immune-mediated phenomena that arise as a consequence of antibody generation against neural antigens ectopically expressed by a tumour. Importantly, the neurological deficits are not due to local or metastatic infiltration of the neuraxis but are a consequence of autoimmune insult. The antibodies, an ever-expanding list, may primarily be targeted against intracellular epitopes (as in the classical onconeural antibodies such as anti-Yo, Hu, Ma2, CRMP-5, Ri and anti-amphiphysin) or against cell-surface antigens (e.g. anti-NMDA or anti-VGKC antibodies) - the former panel of onconeuronal antibodies have a strong association with underlying malignancy and their presence, in the context of a new neurological syndrome, demands a comprehensive oncological workup [13].
Cerebellar dysfunction may occur in isolation as in the case of paraneoplastic cerebellar degeneration (PCD), which is represented by a rapidly progressive ataxia of the limbs, followed by the trunk and bulbar decline, over the course of several weeks – this is followed by a plateau in symptomatology and is usually refractory to immunomodulatory treatments. Although the prognosis is often poor, efforts should be made to hunt and treat the causative malignancy. The presence of a new rapidly progressive, severe cerebellar ataxia alongside initial normal neuroimaging findings should raise the index of suspicion for a paraneoplastic syndrome [14]. PCD is most strongly associated with anti-Yo antibodies and frequently due to ovarian, breast or endometrial carcinoma [13]. Alternatively, paraneoplastic cerebellar dysfunction may occur as part of a multifocal process as seen in brainstem encephalitis, where one would also expect cranial nerve palsies and long tract signs, or opscoclonus-myoclonus, which is associated with chaotic multidirectional high amplitude saccades and myoclonus [14].

Autoimmune conditions

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease with dissemination in neural space and time. Although arguably one of the commonest causes of new-onset cerebellar ataxia in young adults, diagnosis heavily relies on MR imaging of the neuraxis. Lesions are most readily identified on T2 weighted and FLAIR sequences and have a predilection for optic nerves, periventricular, juxtacortical, spinal cord, brainstem and cerebellar white matter [15]. However, due to the oft-relapsing nature of the disease process, it is possible for radiological resolution to occur if imaging is performed late after recovery of the index clinical event. Be aware of other autoimmune disorders such as systemic lupus erythematosus (SLE), neurosarcoïdosis, primary CNS vasculitis and Behcet’s, which can occasionally mimic MS.

Miller-Fisher syndrome (MFS) is a variant that belongs to the spectrum of Guillain-Barré syndrome (GBS) disorders, a continuum of acute, inflammatory, demyelinating polyneuropathies [16,17]. The clinical triad of MFS encompasses ataxia, opthalmoplegia and areflexia (with an absence of limb weakness in at least 95% of cases). It has a monophasic disease course and its diagnosis is supported by CSF albuminocytological dissociation and the presence of serum anti-GQ1b antibodies. Treatments of choice are intravenous immunoglobulins (IVIG) and/or plasma exchange. Clinical features of MFS in conjunction with encephalopathy and hypersomnolence would point towards a diagnosis of Bickerstaff Brainstem Encephalitis (BBE). MRI brain imaging with gadolinium contrast is imperative in suspected MFS and BBE in order to exclude mimics such as a brainstem tumour or leptomeningeal carcinomatosis near the skull base.

Anti-glutamic acid decarboxylase antibody (Anti-GAD Ab)-associated cerebellar ataxia has been reported and occurs in association with other autoimmune conditions including type 1 diabetes and stiff-person syndrome [18,19]. Patients may respond to immunotherapies such as corticosteroids, IVIG and immunosuppressants [20].

Genetic

The genetic ataxic syndromes are often accompanied by cerebellar atrophy on MRI brain imaging, but can be normal early during the disease course.

The spinocerebellar ataxias (SCAs) form a large group (>40) of heterogeneous autosomal dominant, neurodegenerative disorders. As well as a slowly progressive cerebellar ataxia, depending on the subtype, there may be other associated signs of neurological disease. These include ophthalmoplegia, abnormal saccades, cognitive deterioration, pyramidal/extrapyramidal signs, peripheral neuropathy and retinal degeneration [21].

Other genetic ataxias include Friedreich ataxia, ataxia telangiectasia (AT) and the episodic ataxias. Friedreich ataxia is autosomal recessive, begins between 5-15 years of age and is associated with peripheral neuropathy, scoliosis, diabetes mellitus and cardiomyopathy. AT is autosomal recessive, associated with conjunctival telangiectasia, immunodeficiency and a strong predisposition to various malignancies (leukaemia and lymphoma) owing to defective DNA repair mechanisms [22]. The episodic ataxias (EA) are a rare group of channelopathies in which patients develop paroxysmal attacks of ataxia, which may be associated with myokymia and last for a few minutes (EA1) or may last for several hours to a day with interictal nystagmus (EA2). Although rare, their diagnosis is important as patients may show treatment responses to acetazolamide [23].

The presence of dystonia and Parkinsonism alongside ataxia, particularly in the younger cohort, should raise suspicion for Wilson’s disease and neuroacanthocytosis, whereas chorea and motor impersistence would point towards Huntington’s disease. The identification of oculomotor apraxia, with an impaired ability to initiate horizontal saccades, in an ataxic child or young adult may suggest the rare hereditary disorder ataxia with oculomotor apraxia, of which multiple subtypes exist – patients invariably develop cerebellar atrophy but MRI brain imaging may be normal early in the disease course [24,25].

Dentatorubral-pallidoluysian atrophy (DRPLA) is an autosomal dominant trinucleotide repeat expansion disorder affecting the gene encoding atrophin-1, with greatest prevalence in Japan. Below the age of 20, it presents as progressive myoclonic epilepsy but patients with late onset (>40 years) develop a slowly progressive cerebellar ataxia with dementia [26] – cerebellar atrophy is common especially in advanced disease.

Other

Post-traumatic cerebellar syndromes in the context of normal neuroimaging have been described and can occur even after minor head injury [27,28]. Axonal shearing of the superior cerebellar peduncles, which constitute the major outflow tracts of the cerebellum, as a result of sudden acceleration/deceleration forces, has been proposed as a plausible mechanism underpinning post-traumatic cerebellar syndromes [27,28].
Acute cerebellitis is a rare disorder of isolated inflammation of the cerebellum, which may be infectious, post-infectious or post-vaccination. It is commoner in children and recovery usually occurs over the course of several weeks - unless severe, neuroimaging is typically normal [29].

Conclusions
Cerebellar ataxia is a commonly encountered neurological problem and despite technological advancements, with rising sensitivities of neuroimaging modalities, negative scans still do not exclude all of the important causes of ataxia. This is particularly relevant when attempting to make a diagnosis early as radiological evidence of cerebellar changes or damage may only become apparent with advanced disease in many instances. Furthermore, a normal MRI scan in a patient with new ataxia should not lead to false reassurances that 'there is nothing wrong with the patient,' which may lead to inappropriate management and consequent patient morbidity. Difficulties in reaching a final diagnosis may be overcome by revisiting the clinical history in depth as exploring the spatiotemporal profile of events and associated symptoms can greatly facilitate the diagnostic process.

References