HHS Public Access

Author manuscript

Semin Neurol. Author manuscript; available in PMC 2023 July 19.

Published in final edited form as:

Semin Neurol. 2023 February ; 43(1): 48–64. doi:10.1055/s-0043-1763511.

Ataxias: Hereditary, Acquired, and Reversible Etiologies

Chi-Ying R. Lin, MD, MPH[1,2], **Sheng-Han Kuo, MD**[3,4]

[1]Department of Neurology, Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine, Houston, Texas

[2]Department of Neurology, Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine, Houston, Texas

[3]Department of Neurology, College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, New York

[4]Initiative for Columbia Ataxia and Tremor, Columbia University Irving Medical Center, New York, New York

Abstract

A variety of etiologies can cause cerebellar dysfunction, leading to ataxia symptoms. Therefore, the accurate diagnosis of the cause for cerebellar ataxia can be challenging. A step-wise investigation will reveal underlying causes, including nutritional, toxin, immune-mediated, genetic, and degenerative disorders. Recent advances in genetics have identified new genes for both autosomal dominant and autosomal recessive ataxias, and new therapies are on the horizon for targeting specific biological pathways. New diagnostic criteria for degenerative ataxias have been proposed, specifically for multiple system atrophy, which will have a broad impact on the future clinical research in ataxia. In this article, we aim to provide a review focus on symptoms, laboratory testing, neuroimaging, and genetic testing for the diagnosis of cerebellar ataxia causes, with a special emphasis on recent advances. Strategies for the management of cerebellar ataxia is also discussed.

Keywords

ataxia; cerebellum; cerebellar ataxia

Ataxia refers to a specific constellation of symptoms and signs, characterized by a combination of the following features: lack of coordination in eye movements, speech fluency and voice volume, limb dexterity, and gait stability. These symptoms mainly arise from dysfunction of the cerebellum. Meanwhile, the cerebellum also depends on sensory input for its proper function; therefore, people with sensory dysfunction, especially

Address for correspondence Chi-Ying R. Lin, MD, MPH, 7200 Cambridge St, Suite 9A, Houston, TX 77030, (Chi-Ying.Lin@bcm.edu).

Author Contributions

C.R.L. and S.H.K.: original draft and critical revision of the manuscript.

Conflict of Interest

S.H.K. served as the Scientific Advisor for Praxis Precision Medicines and Sage Therapeutics. C.R.L. reports no conflict of interest.

proprioception loss seen in large fiber neuropathy, may also have ataxic symptoms (i.e., sensory ataxia). Given the diverse etiologies, the manifestation of ataxia symptoms varies in terms of disease chronicity or occurs in combination with nonataxia symptoms. Specifically, nonsensory and noncerebellar circuitry involved in these nonataxic symptoms, associated with dopaminergic and pyramidal dysfunction, adds to the diagnostic uncertainty and complexity. In this article, we provide the latest review and practical approaches to cerebellar ataxia for clinicians.

Ataxia Clinical Examination

The first step to approach patients with possible ataxia is to accurately identify the signs and symptoms of ataxia. As the cerebellum is important to the control of the *precision of movement*, the core clinical feature of ataxia is the *variability* of motor function.[1] For gait assessment, variability of step width, step length, and direction of the walking path are key features of gait ataxia. A wide-based gait, a common gait pattern described in ataxia patients, is compensatory to progressive gait instability and tends to emerge later in the disease course. Ataxic patients with a wide-based gait still retain the core feature of variability of gait as mentioned above. Of note, a wide-based gait is not specific to ataxia patients and can also be seen in patients with functional movement disorders, normal pressure hydrocephalus, and sensory neuropathy.[2–4] Variability of movement in other body regions is also observed in ataxia patients. Speech often manifests as variability of rhythm, volume, and tone control, and can further assist in the diagnosis of ataxia. There are interruptions of speech output due to overemphasized consonants and distorted, underemphasized vowels. Following the same principle, ataxic patients also have hand dexterity variability, manifesting as intention tremor with dysmetria on the finger–nose–finger test, dysdiadochokinesia in the fast alternating hand movement test, and overshooting or undershooting on the finger chase test. For leg movements, ataxia patients show variability in keeping the heel on track with the tibia shaft in the contralateral leg in the heel–knee–shin test. Finally, eye movements can present with a variety of abnormalities, such as square wave jerks (i.e., horizontal saccadic intrusions that interfere with the visual fixation on a target), hypermetric or hypometric saccades, and multidirectional, nonsuppressible nystagmus. These clinical features are commonly observed in patients with cerebellar ataxia. Of note, an individual with cerebellar ataxia is not expected to have all of the aforementioned signs. The majority of individuals with ataxia have gait difficulty as the initial presenting symptom. In a study investigating the initial symptoms of spinocerebellar ataxia (SCA), using the natural history of the Clinical Research Consortium for SCAs (CRCSCA) that studies SCA patients in North America, greater than 80% of SCA1, 2, 3, and 6 patients (SCA1: 92.3%, SCA2: 87.0%, SCA3: 87.5%, SCA6: 83.8%) had gait difficulty as their first symptom.[5] In addition, speech and eye movement abnormalities at onset are not uncommon, which may be easily missed in the early stages. As the disease progresses, other ataxic symptoms and signs can become obvious, affecting all aspects of activities of daily living.[6,7]

Experts have developed clinical rating scales to comprehensively capture ataxia symptoms, to quantify and compare the ataxia severity, and to longitudinally follow up patients with ataxia. The International Cooperative Ataxia Rating Scale (ICARS; total score = 100)

measures specific core ataxic symptoms, and is divided into three compartments to measure postural and gait disturbances, kinetic functions for limb and speech, and oculomotor abnormalities.[8] While ICARS is quite comprehensive, it may not be suitable for daily clinical practice due to the time needed for administration and its overlapping nature of certain items within the three compartmentalized measures.[9] The Scale for the Assessment and Rating of Ataxia (SARA; total score = 40) and Brief Ataxia Rating Scale (BARS; total score = 30) were later developed. With high reliability and validity, SARA is now the most widely used rating score for cerebellar ataxia, which constitutes gait, finger–nose–finger, heel–knee–shin, and speech disturbance, sitting, stance, finger chase, and rapid alternating movements. In contrast to BARS, SARA does not measure oculomotor abnormalities. In addition to motor dysfunction, individuals with ataxia are also known to have a variety of cognitive and behavioral symptoms, such as executive dysfunction and depression; therefore, the Cerebellar Cognitive Affective Scale was developed to characterize and track the level of cognitive impairment in cerebellar ataxia.[10] Impulsive and compulsive behaviors have been recently identified in patients with cerebellar ataxia and can also be highly disabling.[11–17] Most recently, the Patient-Reported Outcome Measure of Ataxia (PROMAtaxia) was developed, assessing physical capability, mental health, and activities of daily living from the patient's perspective. These measures will be critical for future clinical trials to demonstrate clinical meaningfulness.[18]

Reversible Causes of Ataxia

After identifying ataxia signs and symptoms in a patient, the next step is to look for reversible causes, which often fall into nutritional and immune-mediated causes (►Fig. 1; ►Table 1). One important consideration is that such a "reversible" cause may also be a contributor to the accompanying nonataxia deficits and symptoms. Depending on the timing of treatment initiation, neurological deficits may be permanent despite correcting the underlying etiology of cerebellar ataxia.[19]

Alcohol-Induced Cerebellar Ataxia

Alcoholic cerebellar degeneration usually occurs with chronic heavy alcohol use. In this type of cerebellar ataxia, the pathology predominantly affects the anterior and superior vermis of the cerebellum, resulting in truncal ataxia and relatively mild appendicular ataxia. As opposed to acute alcohol intoxication that causes synaptic dysfunction in the cerebellum,[20] oxidative and endoplasmic reticulum stress on the cerebellar cortex has been proposed as the main mechanism of chronic ethanol toxicity,[21] resulting in Purkinje cell degeneration.[22] The amount and the duration of alcohol consumption needed to cause cerebellar degeneration remains inconclusive. It has been proposed that alcohol-induced cerebellar degeneration requires a large amount of daily alcohol drinking (>140 g or 50 ounces of wine per day, approximately 10 times of a standard drink) for more than 10 years.[23,24] A study found that this amount of alcohol is associated with cerebellar vermis atrophy identified by a computed tomography imaging study in 41 cases attributed to alcohol use.[23] On the other hand, a small amount of daily alcohol ingestion with 5 g for a similar length of time can also lead to ataxia.[25] The exact amount and the duration of alcohol use have not been consistently established; therefore, clinicians should always have

high suspicion for alcohol-induced cerebellar ataxia. Another important consideration is the individual susceptibility to alcohol. Of note, alcohol can also contribute and perhaps aggravate other forms of cerebellar ataxia, such as gluten ataxia.[26] Multifactorial causes should also be considered. Alcohol abstinence has been the major intervention; however, improvement of truncal ataxia after cessation of alcohol is not uniform.[22,27] Alcohol-induced cerebellar ataxia is associated with Wernicke encephalopathy, which we will discuss in the below section. Of note, excessive alcohol consumption can cause alcoholic polyneuropathy, involving sensory, motor, and autonomic systems. Large and small sensory fiber function abnormality, including paresthesia and loss of vibratory sensation, is seen in a symmetric and distally predominant distribution, further contributing to gait ataxia.[28,29]

Nutritional Deficiency Cerebellar Ataxia

Frequently associated with alcohol overuse, Wernicke encephalopathy due to thiamine deficiency can be found in people with alcohol abuse or other causes of malnutrition, such as cancer, pregnancy, or gastric bypass surgery.[30] While the classic triad for Wernicke encephalopathy is gait ataxia, ophthalmoplegia, and encephalopathy, the caveat for diagnosis is that with incomplete presentations of the triad, varying degrees of oculomotor dysfunction and atypical manifestations such as a stroke mimic have been frequently reported.[31–33] Similarly, while Wernicke encephalopathy typically affects midline structures such as thalamus, mammillary bodies, and periaqueductal gray matter, in addition to the cerebellar hemisphere and superior anterior vermis,[30,34] a wide range of radiographic findings have been reported, including stroke-like cortical T2 hyperintensity or the absence of an overt imaging abnormality.[33,35,36] Given that ataxia associated with thiamine deficiency is treatable, patients with ataxia and risk factors for nutritional deficiency should be treated empirically with high-dose intravenous thiamine to avoid devastating brain hemorrhage,[37] preferably after sending a test of whole blood thiamine level.[30] Analternative is to measure the activity of erythrocyte thiamine transketolase, as thiamine is the cofactor for the transketolase.[38,39] However, in clinical practice, sending an erythrocyte thiamine transketolase activity test can be nontimely as it is usually not immediately available and the precision is considered low, partly due to the instability of the transketolase.[40] A standardized protocol was also recently proposed to solve the issues of lack in consensus on the cut-off value.[38] Of note, even with treatment, about half of patients with Wernicke encephalopathy will have an incomplete recovery with residual ataxia, and 25% will evolve into Wernicke–Korsakoff syndrome, often requiring care in long-term facilities.[41]

Vitamin E deficiency-related cerebellar ataxia will be discussed in the hereditary ataxia section below, since it is caused by genetic defects in the vitamin E metabolism pathway. Sensory ataxia with high steppage gait, peripheral neuropathy, and hyperreflexia are classic signs of subacute combined degeneration resulting from vitamin B12 deficiency. Other causes, such as nitrous oxide toxicity as well as metformin use, should also be screened.[42] Serum vitamin B12 and E levels should be determined in patients with cerebellar ataxia.[43–45]

Immune-Mediated Ataxia

Cerebellar ataxia is a well-established common symptom in multiple sclerosis (MS).[46] Depending on the demyelinating lesion sites, cerebellar ataxia can be truncal and/or appendicular, and can manifest as acute or chronic. In progressive MS, the prevalence of cerebellar ataxia is as high as 80%.[46] Extensive cerebellar involvement, along with white matter hyperintensities in the middle and superior cerebellar peduncles, are commonly identified on brain magnetic resonance imaging (MRI),[47,48] Moreover, cerebellar gray matter cortical volume loss and demyelination extending from the white matter may be a distinctive pathological hallmark of MS.[49] Cerebellar involvement in MS is often associated with cognitive deficits, especially in the posterior–inferior lobes responsible for nonmotor functions.[50] A recent study showed that greater superior and middle cerebellar peduncle volume is associated with better motor and cognitive function, further highlighting the importance of the cerebellar status on overall functioning in MS.[51]

Ataxia associated with primary Sjogren syndrome (pSS) presents as a sensory ataxia due to a sensory neuronopathy affecting large sensory fibers.[52] Cerebellar ataxia in pSS, although rare, can occasionally occur—both acute and chronic cerebellar ataxia have been reported.[53–55] Therefore, we still recommend testing the antinuclear antibody with reflex testing, together with tests of other autoimmune disorders such as gluten ataxia and Hashimoto encephalopathy (details addressed below), as part of the initial workup for cerebellar ataxia. Of note, a greater incidence of multiple system atrophy (MSA) has been observed in a large cohort of pSS patients, and a higher prevalence of pSS in MSA has been reported, advancing the hypothesis that systemic autoimmune disorders can contribute to neurodegenerative diseases.[56]

Gluten ataxia refers to an immune-mediated cerebellar ataxia resulting from heightened gluten sensitivity,[57,58] which can present as acute, subacute, or chronic ataxia.[59] Anti-transglutaminase 6 antibody appears to be most specific to gluten ataxia; however, this test has not been commercially available. Therefore, the commercially available anti-gliadin antibody test should be considered to aid in the diagnosis of gluten ataxia.[60] A gluten-free diet is the first-line intervention for gluten ataxia, and immunotherapy with intravenous immunoglobulin (IVIG) has been proposed as well.[61]

Steroid-responsive encephalopathy associated with antithyroid antibodies (SREAT), or Hashimoto encephalopathy, is another type of immune-mediated ataxia with heterogeneous clinical manifestations, including dementia, epilepsy, myoclonus, and ataxia.[62] The cerebellar ataxia in SREAT can present at the onset or late in the disease course.[63,64] Of note, patients with SREAT do not need to have clinical or laboratory hyper- or hypothyroidism; a euthyroid status does not rule out SREAT. Serum anti-thyroperoxidase (anti-TPO) antibodies are the standard tests for SREAT; however, the cut-off values for confirmatory diagnosis and the need for testing these antibodies in cerebrospinal fluid (CSF) remain unclear.[65] Some studies have proposed testing for antibodies against the N-terminus of α-enolase, considered to be more specific for SREAT, but this has not been widely adopted in clinical practice.[66] Intravenous steroids are the standard treatment for SREAT,[67] and the success of IVIG has been reported as well.[68] Another rare form of immune-mediated

ataxia is caused by anti-GluRd2 antibody, which produces tremor along with cerebellar ataxia.[69,70] Testing the anti-GluRd2 is feasible, but not widely available. Resolution of anti-GluRd2 ataxia after steroid administration was reported.[69]

Paraneoplastic cerebellar degeneration (PCD) should be considered in a patient with the subacute onset of ataxia with a rapidly progressive course. Purkinje cells attacked by onconeural antibodies from a heightened immune response to proteins expressed by tumor cells is the main mechanism.[71] Several paraneoplastic onconeural antibodies have been identified, including Purkinje cytoplasmic antibody type 1 (PCA-1), also known as anti-Yo, or anticerebellar degeneration-related antigen 2 (CDR2), strongly associated with ovarian and breast cancers and one of the most well-known causes of PCD.[72,73] Anti-Hu (ANNA-1) with small cell lung cancer and testicular cancer, Purkinje cytoplasmic antibody type 2 (PCA-2) with small cell lung cancer, and Purkinje cytoplasmic antibody type tr (PCA-Tr), also known as anti-Tr or anti-Delta/Notch-like epidermal growth factor-related (DNER) with Hodgkin lymphoma are also common forms of PCD.[71,74] Anti-DNER-associated PCD has been recently identified. The long-term outcomes of paraneoplastic syndrome with anti-DNER antibodies were further characterized in a cohort of 28 patients: 96.4% had cerebellar ataxia and became moderately to severely disabled, of whom 50% improved and 32.1% only had slight or absent disability after 26-month follow-up.[75] Younger age, less reduced cerebellar gray matter volume, and milder clinical symptoms are all associated with favorable outcomes (i.e., modified Rankin Scale score 2).[75] The full list of PCD onconeural antibodies and the respective underlying malignancies are listed in ►Table 2.

The glutamic acid decarboxylase (GAD) autoantibody is known to be associated with type 1 diabetes and movement disorders, especially cerebellar ataxia and stiff-person syndrome.[76] Other neurological manifestations, including seizures, cognitive decline, and behavioral disturbance, seen in limbic encephalitis can also occur.[77,78] The prevalence of anti-GAD in the general population remains unclear, which raises several questions, including the possibility of overdiagnosis of stiff-person syndrome in the context of mildly elevated GAD seropositivity. The association between anti-GAD antibodies and cerebellar ataxia was first reported in 2000,[79] and a titer higher than 2,000 IU/mL (normal reference range: <5.0 IU/mL) is considered convincing for the diagnosis of anti-GAD ataxia.[80–82] Broadly speaking, GAD autoimmunity can be considered a paraneoplastic syndrome. The reports of cancer prevalence in GAD seropositivity cases vary from 4 to 26%, yet seem to be higher in cases of cerebellar ataxia and limbic encephalitis than stiff-person syndrome. In ataxia, nonsmall cell lung cancer and pancreatic neuroendocrine tumor are the most commonly associated malignancies, while in stiff-person syndrome, thymoma, kidney, and colorectal cancer predominates.[83–88] Assessing for malignancy in GAD-positive cases is thus recommended, and IVIG and intravenous methylprednisolone are treatments of choice.[89–91]

A recent history of infection prior to the ataxia onset can be informative. Several viruses, including varicella-zoster, herpes simplex type 1, mumps, measles, rubella, Epstein–Barr, coxsackie, and rotavirus are known to cause acute cerebellitis.[92] Postinfectious acute cerebellar ataxia is the most common neurological complication of varicella infection in the pediatric population,[93] accounting for approximately 10% of cases of varicella

infection requiring hospitalization in one retrospective study.[94] Since the coronavirus disease (COVID) pandemic began, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been identified as the newly emerging virus for postinfectious cerebellar ataxia in adults and children.[95–99] Of note, although white matter signal changes in the corpus callosum, middle cerebellar peduncle, and cerebellar hemispheric were reported,[95,99,100] some cases had a normal appearing cerebellum on brain MRI.[96–98] Acute COVID infection can worsen any already existing ataxia symptoms, and some patients may be left with increased dizziness and ataxia symptoms long after the infection. Subacute cerebellar ataxia after SARS-CoV-2 infection has also been reported, with ataxia symptoms emerging after the resolution of COVID respiratory symptoms.[99]

Drug-Induced Ataxia

A wide range of drugs can cause cerebellar ataxia. Drug-induced cerebellar ataxia typically presents with an acute to subacute onset, from days to weeks from drug initiation. While complete recovery is expected after discontinuation of such drugs, some, especially lithium, are associated with chronic cerebellar ataxia, suggesting irreversible damage.[101] The common offending agents associated with cerebellar ataxia are: (1) amiodarone, commonly used for atrial fibrillation, cerebellar ataxia, and bilateral vestibulopathy are typical symptoms for amiodarone-induced ataxia[102,103]; (2) cyclosporine and tacrolimus, used in the kidney and liver transplant population; in addition to cerebellar ataxia, these drugs can also cause tremor, paresthesias, or even seizures, encephalopathy, and cognitive dysfunction[104–107]; (3) metronidazole, an antibiotic for anaerobic coverage, can cause bilateral dentate hyperintensity on T2 FLAIR as the classic imaging finding, which can be reversible after drug discontinuation[108,109]; (4) irinotecan and cytarabine, chemotherapy agents used to treat colorectal cancer[110,111] and acutemyeloid leukemia, respectively; high doses of either medication can result in irreversible cerebellar atrophy and persistent ataxia followed by an acute phase[101]; postmortem examination reveals cerebellar Purkinje cell loss despite normal imaging, suggesting toxicity to Purkinje cells[112]; (5) lithium, a mood stabilizer; lithium-induced cerebellar ataxia should be particularly considered in the setting of impaired renal function, active infection, and dehydration. Lithium may still induce cerebellar ataxia, despite being in a “therapeutic range.”[113] Thus, the diagnosis of lithium-induced ataxia should be based on clinical symptoms, such as nausea, vomiting, tremor, and myoclonus associated with ataxia, as well as the temporal relationship between the drug initiation and symptom development. Hemodialysis should be considered in acute lithium intoxication,[114] and long-term cerebellar ataxia, despite drug discontinuation, occurs in 1% of the lithium users[101]; and (6) antiseizure medications, especially lamotrigine and oxcarbazepine, which have the highest likelihood of causing cerebellar ataxia.[101] Phenytoin and valproate can both cause acute and chronic cerebellar ataxia, despite serum levels being within the therapeutic range. Coexistence of sensory ataxia due to folate deficiency can occur in long-term phenytoin users, given that phenytoin inhibits folate conjugase activity in human jejunum and also inhibits folate polyglutamate.[115] In patients with cerebellar ataxia, these medications should be discontinued or at least adjusted for dose reduction. Even in patients with a clear diagnosis of degenerative or genetic causes of ataxia, these medications are likely to contribute to the symptoms.

Degenerative Causes of Ataxia

Multiple System Atrophy

MSA is one of the diseases commonly referred to as an atypical parkinsonism, or Parkinson-plus syndrome, and parkinsonian symptoms are among the core features of MSA. However, some MSA patients may have predominant cerebellar ataxia with relatively subtle parkinsonian signs. As reflective of its nomenclature, MSA affects several brain regions, constituting four major systems: autonomic, dopaminergic, cerebellar, and pyramidal systems. Based on the motor symptoms, MSA can be further categorized into MSA-parkinsonian (MSA-P) or MSA-cerebellar (MSA-C) subtypes. Pyramidal symptoms and signs, such as hyperreflexia, are an often neglected but useful clinical pearls to assist diagnosis. Pyramidal signs are more common in MSA-P patients[116] and can be associated with pathology in the motor cortex.[117] As opposed to Lewy bodies consisting of aggregates of neuronal α-synuclein in Parkinson disease (PD), in MSA, α-synuclein deposits are primarily found in the glial cells, called glial cytoplasmic inclusions, as the hallmark of MSA pathology. MSA patients also have common signs associated with synucleinopathy: (1) rapid eye movement behavioral disorder (RBD), (2) hyposmia, and (3) constipation. Anterocollis is frequently seen in MSA cases and remains very difficult to treat despite botulinum toxin injection.[118] With high diagnostic predictive value, laryngeal stridor is an important feature of MSA and can be an adverse prognostic factor for survival.[119] Patients may need continuous positive airway pressure and eventually tracheostomy in the later stages of the disease.[119] Classic yet not pathognomonic brain MRI findings for MSA are (1) “hot crossed bun” sign (►Fig. 1A) along with reduced pontocerebellar volume in MSA-C and (2) external striatal linear T2 hyperintensity in MSA-P (►Fig. 1B).

Currently, the diagnosis of MSA is based on clinical features and neuroimaging findings. To optimize the diagnostic accuracy, especially in the early phase,[120] the International Parkinson and Movement Disorders Society (MDS) released recommended criteria in 2022.[121] Compared with the second consensus established in 2008,[122] the overarching revision of the present criteria proposed a category to define “possible prodromal MSA,” including people with at least one of the following core clinical features: RBD diagnosed via polysomnography, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and urogenital failure. Either subtle parkinsonism or subtle cerebellar ataxia signs need to be identified in addition to the core features to fulfill this category. Another improvement in the new criteria is the delineation of objective measures for autonomic dysfunction with clearly defined cut-off values: the neurogenic orthostatic hypotension is re-defined as the drop of systolic blood pressure of 20 mm Hg and diastolic blood pressure of 10 mm Hg, with “within 3 minutes” for the “clinically established” MSA and “within 10 minutes” for the “clinically probable” MSA. Of note, “possible prodromal” MSA is a newly created category to further the research for current unmet needs in MSA, not meant for clinical practice, and a neurogenic orthostatic hypotension that happens within 10 minutes is listed as one of the four core clinical features in possible prodromal MSA. The agedefined cut-off of 60 years has been proposed for the definition of early erectile dysfunction, and the incomplete urinary voiding volume is defined as postvoiding residual volume >100 mL, further highlighting the use of bladder ultrasound to assist the diagnosis. Of note,

to increase diagnostic specificity, while cognitive impairment and behavioral disturbance can be expected in MSA, the criteria proposed exclude early emergence of dementia and visual hallucinations, defined as within 3 years of disease onset.[121] This revision intends to minimize the possibility of diagnosing cognitive disorders with parkinsonism, especially dementia with Lewy bodies as MSA.[123] Last but not least, an unexplained Babinski sign is listed as a supportive motor feature based on the involvement of the pyramidal system.[116]

Challenges remain in differentiating MSA versus PD in the context of parkinsonism with neurogenic orthostatic hypotension. Laboratory tests such as scintigraphy with 123I-metaiodobenzylguanidine enable the quantification of post-ganglionic sympathetic cardiac innervation to differentiate MSA versus PD,[124] but clinical application has so far been limited because it is not widely performed in clinical settings. Recently, using skin biopsies to quantify phosphorylated α-synuclein in intraepidermal nerve fibers has shown potential utility for differentiating MSA versus PD, despite biopsy sites varying across studies.[125,126] The phosphorylated α-synuclein deposits in MSA were primarily found in epidermal somatic fibers, while in PD with orthostatic hypotension, the deposits were found in the autonomic fibers innervating the sweat glands, pilomotor, and vasomotor structures.[125] A recent novel CSF assay demonstrated the ability to differentiate conformational strains of α-synuclein in MSA versus PD, which holds promise for future diagnostic precision.[127] Treatment of MSA should focus on specific symptoms and is outside of the scope of this review. Orthostatic hypotension can be treated with fludrocortisone, midodrine, droxidopa, and atomoxetine.[128–131] Although associated with an overall poorer response than in PD, levodopa remains first-line treatment, and a total daily dose of up to 900 to 1,000 mg is recommended before considering levodopa ineffectiveness.[132]

While assessing people with suspected MSA-C, it is of importance to keep two genetic disorders which are MSA-C mimickers, the *replication factor C subunit 1 (RFC1*)-related spectrum disorders and Fragile X-associated tremor ataxia syndrome (FXTAS), in mind. Given its diverse presentation and frequent autonomic system involvement, testing *RFC1* in suspected MSA-C cases with relatively atypical presentation can further reveal the etiology. These atypical features include slow progression and life expectancy longer than 9 years, coexisting pronounced sensory and vestibular dysfunction, and mild autonomic dysfunction.[133] Sullivan et al studied 207 patients with possible and probable MSA and found 3 cases with *RFC1* expansion.[134] Similarly, autonomic dysfunction is frequently seen in FXTAS.[135] The European MSA Study Group found 4 out of 426 MSA-C cases carrying *FMR1* premutation and recommended that for cases with slow disease progression and tremor predominant feature, the FXTAS needs to be considered.[136] The details of *RFC1* ataxia and FXTAS will be further discussed in the “Genetic Causes for Ataxia” section.

Progressive Supranuclear Palsy—Cerebellar Ataxia Subtype

Although cerebellar ataxia was intentionally placed in the exclusion condition in both NINDC-SPSP[137] and MDS progressive supranuclear palsy (PSP) criteria to increase the diagnostic specificity for PSP, the MDS-PSP Study Group acknowledged the presence of cerebellar ataxia in rare PSP cases (i.e., PSP-C).[138] Dentate nucleus degeneration was found in PSP via neuroimaging and neuropathological studies with or without

cerebellar ataxia.[139,140] The compromise of cerebellar function was supported by an electrophysiological study using transcranial magnetic stimulation to assess the dentato-thalamo-cortical pathway.[141] Varying genetic and environmental influences have been hypothesized given the higher prevalence of PSP-C higher in Asia, especially in Japan, than in Western countries.[142–144] Ando et al proposed the diagnostic criteria for PSP-C based on increasing recognition of cerebellar ataxia in PSP cases.[145] The criteria highlight the importance of early truncal ataxia, limb ataxia, and falls (i.e., all within 2 years of symptoms onset). The key feature, supranuclear gaze palsy, is also listed in the criteria. The criteria will help researchers to further investigate and delineate the features of PSP-C.

Creutzfeldt–Jakob Disease

Cerebellar ataxia is one of the four core clinical features for Creutzfeldt–Jakob disease (CJD).[146] CJD is a prion disease, and patients with prion disease most commonly have limb ataxia as well as gait disturbance (either ataxic or apraxic gait) in the earliest stage of the disease.[147] Ataxia can present as an isolated, early feature before the cognitive symptoms manifest in CJD.[148–150] Rapidly progressive aphasia to akinetic mutism and cortical blindness are common cognitive deficits,[146] and other higher cortical dysfunction, such as apraxia or auditory agnosia, can also occur.[149,151] The diagnosis of CJD has dramatically improved because of the recent development of CSF RT-QuIC analysis (sensitivity 92%, specificity 100% at UK National CJD Research and Surveillance Unit).[146,152,153] It is important to consider CJD in the differential diagnosis when encountering patients with cerebellar ataxia, especially for those with a rapidly progressive disease course in combination with myoclonus and dementia.

Idiopathic Late-Onset Cerebellar Ataxia

After extensive investigation (►Fig. 2), if a specific etiology is still unable to be identified, most such cases will be classified as idiopathic late-onset cerebellar ataxia (ILOCA).[154,155] ILOCA should be taken as a form of degenerative ataxia with slow progression instead of a diagnostic waste bin, since the prognosis is distinct from MSA.[156] Some experts also call ILOCA a sporadic adult-onset ataxia of unknown etiology.[157] ILOCA is late-onset cerebellar ataxia without parkinsonism or autonomic features, and ILOCA patients have a longer life expectancy and slower progression than MSA patients.[158,159] Cerebellar atrophy without involvement of other intracranial structures is the standard neuroimaging finding in ILOCA.[158,159]

The gene *FGF14* that encodes fibroblast growth factor 14 first gained its attention in a Dutch family with 14 affected relatives who presented with cerebellar ataxia due to alteration of the coding sequence,[160] which was later named SCA type 27 (SCA27).[161] Recently, the intronic GAA repeat expansion in *FGF14*, a different type of mutation, was also identified as the cause of cerebellar ataxia revealed from an Australian cohort, named SCA50.[162] Interestingly, the intronic *FGF14* GAA repeat expansion was found in patients who were previously diagnosed with ILOCA, including 61% in French Canadian, 18% in German, 15% in Australian, and 10% in Indian cohorts from a multicentered study.[163] These findings overall highlight that novel genetic mutations can account for a significant portion of sporadic late-onset ataxia cases.

Miscellaneous

Here we aim to highlight several conditions to be considered when assessing acquired causes of cerebellar ataxia. Essential tremor (ET) patients can have subtle ataxia signs, such as difficulty in tandem gait, recently proposed as having "ET-plus." These ataxic signs are rather mild (e.g., difficulty with tandem gait, but with no truncal sway on normal ambulation) or subclinical (i.e., detected only in laboratory gait analysis).[164,165] Whether ET-plus represents separate disease entities or different stages of disease progression remains controversial.[166,167] In pathological analysis, ETs with and without difficulty in tandem gait are not different in terms of cerebellar pathology.[168] While the majority of the gait impairment in ET is rather subtle, a small subset of ET cases can eventually develop pronounced gait ataxia.[169] In this population, investigating other ataxia causes will be necessary.[170] Overall, how tremor and ataxia derive from a dysfunctional cerebellum and how these two symptoms interact in the context of cerebellar degeneration remain of high interest in the field.[171,172]

When sensorineural hearing loss is seen in cerebellar ataxia, superficial siderosis (SS) should be on the differential diagnoses. As a rare neurological disorder, SS can be idiopathic, iatrogenic, or from a variety of vascular factors such as subarachnoid hemorrhage or arteriovenous malformation. It is usually slowly progressive and can result in dementia. MRI is a necessary diagnostic tool to display rim hemosiderin deposition in the subpial space of the brain and spinal cord on gradient recalled echo or susceptibility-weighted images. Deferiprone is the chelation therapy in addition to surgical repair of bleeding sources.[173–175] An ATP1A3-related disorder, the cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndrome should be a top consideration in pediatric patients with a dominant family history of relapsing ataxia and hearing loss.[176–178] Cerebellar ataxia can also be a postradiotherapy complication. This was described in lung cancer patients who received whole brain radiation therapy[179,180] whose FDG-PET (fluorodeoxyglucose-positron emission tomography) showed profound hypometabolism of the cerebellum while structural MRI did not reveal any remarkable abnormality.[180]

Ataxia is also associated with developmental structural abnormalities. The most common disorder in this category is Chiari malformation. Chiari malformation type 1 is a condition associated with cerebellar atrophy and adult-onset ataxia.[181] The compressive effect of the downward shifted brain tissues on the vasculature or inferior olivary nucleus has been proposed as the cause of cerebellar degeneration Surgical decompression of the posterior fossa is the standard treatment. Chiari malformation type 2 is accompanied by spinal bifida and myelomeningocele. The ataxia seen in Chari type 2 typically starts from infancy, together with other symptoms such as headache from hydrocephalus. Chiari malformation type 3 is extremely rare and usually life-threatening in infancy.

Genetic Causes for Ataxia

Genetic Approaches for Cerebellar Ataxias

Genetic mutations are common causes of ataxia, and should be considered in patients with young onset of ataxia symptoms and when there is one or more affected family members

with ataxia, peripheral neuropathy, or parkinsonism. One should also keep in mind that a lack of family history of ataxia does not preclude the possibility of genetic ataxias. Specifically, autosomal recessive cerebellar ataxias (ARCAs) or autosomal dominant cerebellar ataxias (ADCAs) of de novo mutations or expanded repeats are inherited from parents who are carriers or intermediate repeat expansions.[182]

The first step to the approach for genetic ataxias is to test for genetic mutations associated with repeat expansions. Interestingly, the most common causes of ADCA, ARCA, and X-linked cerebellar ataxias are all due to pathological expansions of naturally occurring repeats in the respective genes.[1,7] These repeat expansions either exist in the coding region that leads to toxic gain of function of the abnormal protein being produced or in the noncoding region that causes epigenetic changes resulting in abnormal RNA expression. These expanded repeats are not readily detectable by whole exome or whole genome sequencing technologies. Therefore, unless the patient's clinical presentation points to a specific genetic form of cerebellar ataxia, a panel of repeat expansion mutations should be considered first. If the repeat expansion-related causes of cerebellar ataxias are excluded, whole exome sequencing or whole genome sequencing should be the next step, which is effective in detecting sequence alterations. Other considerations include structural genomic mutations such as large deletions, inversions, duplications, and translocations, which may not be readily captured by whole exome sequencing. In these cases, chromosomal microarray analysis thus can be implemented. Finally, mitochondrial DNA mutations may not be captured in blood, and muscle biopsy thus is warranted.

Autosomal Dominant Cerebellar Ataxias

Most ADCAs are designated as SCAs, except for dentatorubral-pallidoluysian atrophy (DRPLA). SCAs are often adult-onset, progressive neurodegenerative disorders affecting the cerebellum and its afferent and efferent pathways. SCAs are numbered in the order of discovery, and the number of described SCAs has recently reached 49.[183] SCAs are rare disorders, and the estimated prevalence of SCAs is 1.0 to 5.6 in 100,000.[184–186] Among all subtypes of SCAs, SCA1, SCA2, SCA3, SCA6, SCA7, and SCA8 are most common in the United States and Europe, while the prevalence of SCA subtypes can vary widely in different geographic regions throughout the world,[187] reflecting founder effects.

CAG repeat expansions, which encode poly-glutamine peptide (PolyQ), are the most common genetic mutations for SCAs. This group includes SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, and DRPLA.[188–190] In these CAG repeat expansion disorders, the age of onset is inversely correlated with the size of repeat expansions.[186] SCA8 is caused by the CTG repeat expansion in the 3′-untranslated region of the *ATXN8OS* gene and is one of the few SCAs with incomplete penetrance. SCA10, SCA12, SCA31, SCA36, and SCA37 are also caused by repeat expansions. Other types of genetic mutations of SCAs are point mutations (SCA13), deletions (SCA15/16), translocations (SCA27), and duplications (SCA20).[191,192]

The term "anticipation" means progressively earlier onset of the disease in successive generations with increasing severity of the disease within a family, which correlates with intergenerational increase of the number of CAG repeats in PolyQ SCAs.[193] Anticipation is

especially prominent in SCA7 patients, leading to infantile or pediatric onset with complex neurological symptoms, including impaired vision.[194]

The most common initial clinical presentation for SCAs is gait difficulty, while some patients can have speech or hand dexterity problems as the first symptoms.[195] Cerebellar ataxia is the key clinical symptom in all SCAs, but each SCA can have its unique, additional features (►Table 3). SCA1 patients have early dysarthria and dysphagia.[196] SCA2 patients usually have slow saccades, hyporeflexia, truncal titubation, and postural and rest tremor.[171,172] SCA3 patients often have dystonia, depression, restless leg syndrome, and levodopa-responsive parkinsonism.[197,198] SCA6 patients are classically considered "pure ataxia" without extra-cerebellar symptoms, and SCA7 patients invariably have vision loss due to macular degeneration. SCA17 patients have complex symptoms, including dementia, chorea, and dystonia. Sometimes SCA patients can initially present with extra-cerebellar symptoms, such as parkinsonism, before developing cerebellar ataxia[199–201]; therefore, a detailed family history of ataxia is helpful to raise clinical suspicion of an SCA.

The natural history of SCAs has been well studied, both in Europe and in the United States, with defined rates of progression. Among the four most common types of SCAs, SCA1 progresses the fastest, followed by SCA2 and SCA3. SCA6 progresses the slowest.[202–204] Not only can pathological CAG repeat length determine the rate of disease progression, but ethnic background and educational levels appear to play important roles.[205,206]

Besides SCAs, primary episodic ataxias are another group of ADCAs, leading to recurring ataxic episodes with some patients developing progressive ataxia. The core symptoms are recurrent, brief episode of dizziness and gait unsteadiness, accompanied by other associated features (listed below). Episodic ataxias are mostly caused by mutations in genes that encode ion channels, including *KCNA1*, *CACNA1A*, *CACNB4*, *SLC1A3*, and *UBR4*,[207] resulting in neuronal firing abnormalities in the cerebellum.[208] Missense mutations in *KCNA1* have been identified in episodic ataxia type 1 (EA1) which causes the dysfunction of potassium channels. Symptoms onset is usually in early childhood or adolescence (<20 years old). The attacks of gait unsteadiness and dizziness can be precipitated by sudden movements or emotional stress and can be up to multiple times a day. The interictal myokymia is another core feature of EA1, which can be confirmed by electromyography.[209] EA2 is the most common type of primary episodic ataxia and the responsible gene is *CACNA1A*, affecting the P/Q-type calcium channel function.[210] Affected individuals, in addition to recurrent ataxia, can have the following characteristic feature: familial hemiplegic migraine and interictal gaze-evoked or/and down-beating nystagmus.[211] Similar to EA1, the onset of EA2 usually started from childhood or adolescence, but cases with late adulthood onset (>60 years old) were reported.[212] Of note, lack of a family history did not exclude the possibility of EA diagnosis,[213] and the associated migraine does not need to be hemiplegic.[214] Clinicians can consider carbamazepine, valproic acid, and acetazolamide in EA1, as well as 4-aminopyridine and acetazolamide in EA2 to decrease the frequency and severity of the spells.[215,216]

Autosomal Recessive Cerebellar Ataxias

ARCAs are often early onset, with symptoms starting at childhood, adolescence, or early adulthood and frequently accompanied by other neurological and systemic manifestations.[217–219] Peripheral neuropathy is the most common comorbid neurological sign in ARCAs. An algorithm has been recently developed when considering the diagnosis of ARCAs.[220] Different from SCAs, the nomenclature of ARCAs is not assigned with numbers. Instead, each ARCA has its own unique name. Because of the complex nomenclature of ARCAs, a new set of nomenclature was recently proposed.[221]

The most common of the ARCAs is Friedreich's ataxia (FA), which is characterized by vibratory sensation loss, hyporeflexia, scoliosis, pes cavus, diabetes, and cardiomyopathy.[222,223] The majority of FA patients have two alleles of large GAA repeat expansions in intron 1 of the *FXN* gene, whereas some patients have a compound heterozygous mutation, with a GAA expansion in one allele of the *FXN* gene and a point mutation in the other. The age of symptom onset is inversely correlated with the shorter expanded allele of *FXN* gene.[224] These genetic mutations cause insufficient production of frataxin, a key protein for mitochondrial iron homeostasis.[225,226] The consequences of mitochondrial dysfunction eventually lead to neurodegeneration in the dorsal root ganglia and cerebellar dentate nuclei, along with cardiomyopathy.[227–229] The age of onset of FA often falls between 10 and 16 years of age, but FA can also present in adulthood.[230] The natural history of FA has been well studied, with biomarker identification and vibrant therapeutic programs being developed.[223,231]

Another unique ARCA with a distinctive clinical presentation is cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS). Recently, the genetic mutation of CANVAS has been identified, which is the homozygous biallelic intronic AAGGG repeat expansion in the *RFC1* gene.[232] Not only is this genetic mutation associated with CANVAS, it is also associated with chronic cough and sensory neuropathy with or without cerebellar ataxia, which are considered part of the broader spectrum of RFC1-related disorders.[233,234] Since cerebellar ataxia in CANVAS often develops in older age, the symptoms can mimic MSA-C.[134,234]

POLG ataxia is ARCA caused by the mutation in the DNA polymerase subunit g-1 (*POLG*) gene, causing cerebellar ataxia and neuropathy. The most common presentation of *POLG* ataxia is SANDO syndrome, characterized by sensory ataxia neuropathy, dysarthria, and ophthalmoplegia. Patients with *POLG* ataxia often develop myoclonus and seizures. Since *POLG* mutations cause mitochondrial dysfunction, muscle biopsy in these patients shows mitochondrial proliferation.[235,236]

Three ARCAs are commonly associated with oculomotor apraxia: ataxia telangiectasia (A-T), ataxia with oculomotor apraxia type 1, 2, and 4 (AOA1, AOA2, and AOA4). A-T is caused by mutation in *ATM* gene, which encodes a protein important for DNA repair. A-T patients have early onset ataxia, choreoathetosis, telangiectasia, myoclonus, and dystonia. In addition, sensitivity to ionizing radiation, immune compromise with recurrent infection, and an increase in the incidence of hematological malignancies are hallmarks of A-T.[237] We discussed that cerebellar ataxia can be a complication of postradiation therapy in the

above section. Of note, A-T patients are prone to have heightened radiosensitivity to ionized radiation, including gamma- and X-rays.[238] Byrd et al reported a newly identified milder form of A-T case who developed a serious, unexpected adverse tissue reaction to radiation despite absence of preceding neurological symptoms.[239] For A-T patients who are in need of radiation therapy, alternative therapies or radiation dose reduction should be considered to minimize injury.[240] AOA1 and AOA2 share many clinical presentations with A-T, but there is a lack of telangiectasia and systemic features. AOA1, AOA2, and AOA4 are caused by the mutations in the *APTX* gene, the *SETX* gene, and the *PNKP* gene, respectively.[241,242] In addition to cerebellar ataxia, AOA1 patients exhibit dysarthria and mild intention tremor,[243] AOA2 patients have axonal sensorimotor neuropathy,[244] and AOA4 patients have combined dystonia, chorea, and seizures.[241,242] Nie-mann–Pick type C (NPC) is another ARCA with ataxia that gradually develops after late infantile stage.[245] Vertical saccade paresis is a very characteristic feature of NPC, which can serve as an important diagnostic clue in the context of cerebellar ataxia.[245,246]

Another group of ARCAs less often recognized is those associated with myoclonus and epilepsy,[247] which are categorized as myoclonic epilepsy syndromes. These patients often have childhood-onset neurological symptoms and have predominant symptoms of ataxia, myoclonus, epilepsy, dementia, or a combination of these symptoms.

X-Linked Cerebellar Ataxia

FXTAS is the most common X-linked ataxia.[248] FXTAS is caused by CGG triplets in the premutation range (55–200 CGG repeats) in the *FMR1* gene. Note that a “full” mutation with CGG repeats above 200 is associated with Fragile X syndrome, one of the most common causes of inherited intellectual disability and autistic spectrum disorders. FXTAS, a late-onset ataxic disorder, often has additional features of tremor, including postural, action, rest, and intention tremor in the hands. Parkinsonism and cognitive impairments are common in FXTAS.[249] Women with pre-mutations of *FMR1* can also develop FXTAS but may show Fragile X-associated primary ovarian insufficiency.[249] MRI brain of FXTAS patients often shows characteristically T2 hyperintensities in the middle cerebellar peduncles or corpus callosum.[250,251]

Mitochondrial Cerebellar Ataxias

Cerebellar ataxia can be the result of mitochondrial DNA mutations, which will have characteristic maternal inheritance. Common disorders in this category are Kearns–Sayre syndrome, myoclonus epilepsy with ragged-red fibers, and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). Epilepsy is very common, and myopathy, dementia, and myoclonus often occur in these disorders. Muscle biopsy is needed to assess mitochondrial cerebellar ataxia because mitochondrial defects are more likely to be detected in the nondividing cells such as in muscle.

Conclusion

This review covers the common diagnostic approach and considerations for cerebellar ataxias. The current and emerging therapies for cerebellar ataxia are another important topic

and were recently reviewed.[7] With a step-by-step approach, clinicians should be able to first recognize ataxia phenomenology, followed by identification of reversible and genetic investigations to pin down potential etiologies. As more genetic causes of ataxia have been identified, future precision medicine therapies may be on the horizon for certain cerebellar ataxias.

Funding

Dr. Kuo has received funding from the National Institutes of Health: NINDS #R01 NS118179 (principal investigator), NINDS #R01 NS104423 (principal investigator), NINDS #R03 NS114871 (principal investigator), Parkinson's Foundation, National Ataxia Foundation, and International Essential Tremor Foundation.

References

1. Kuo SH. Ataxia. Continuum (Minneap Minn) 2019;25(04): 1036–1054 [PubMed: 31356292]
2. Morel E, Armand S, Assal F, Allali G. Is frontal gait a myth in normal pressure hydrocephalus? J Neurol Sci 2019; 402:175–179 [PubMed: 31158556]
3. Nonnekes J, Růžička E, Serranová T, Reich SG, Bloem BR, Hallett M. Functional gait disorders: a sign-based approach. Neurology 2020;94(24):1093–1099 [PubMed: 32482839]
4. Stolze H, Kuhtz-Buschbeck JP, Drücke H, et al. Gait analysis in idiopathic normal pressure hydrocephalus–which parameters respond to the CSF tap test? Clin Neurophysiol 2000;111(09): 1678–1686 [PubMed: 10964082]
5. Luo L, Wang J, Lo RY, et al. The initial symptom and motorprogression in spinocerebellar ataxias. Cerebellum 2017;16(03): 615–622 [PubMed: 27848087]
6. Chen ML, Lin CC, Rosenthal LS, Opal P, Kuo SH. Rating scales and biomarkers for CAG-repeat spinocerebellar ataxias: implications for therapy development. J Neurol Sci 2021;424:117417 [PubMed: 33836316]
7. Kwei KT, Kuo SH. An overview of the current state and the future of ataxia treatments. Neurol Clin 2020;38(02):449–467 [PubMed: 32279720]
8. Trouillas P, Takayanagi T, Hallett M, et al. ; The Ataxia Neuropharmacology Committee of the World Federation of Neurology. International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. J Neurol Sci 1997;145 (02):205–211 [PubMed: 9094050]
9. Schmitz-Hübsch T, Tezenas du Montcel S, Baliko L, et al. Reliability and validity of the International Cooperative Ataxia Rating Scale: a study in 156 spinocerebellar ataxia patients. Mov Disord 2006;21(05):699–704 [PubMed: 16450347]
10. Hoche F, Guell X, Vangel MG, Sherman JC, Schmahmann JD. The cerebellar cognitive affective/ Schmahmann syndrome scale. Brain 2018;141(01):248–270 [PubMed: 29206893]
11. Amokrane N, Lin CR, Desai NA, Kuo SH. The impact of compulsivity and impulsivity in cerebellar ataxia: a case series. Tremor Other Hyperkinet Mov (N Y) 2020;10:43 [PubMed: 33133767]
12. Amokrane N, Viswanathan A, Freedman S, et al. Impulsivity in cerebellar ataxias: testing the cerebellar reward hypothesis in humans. Mov Disord 2020;35(08):1491–1493 [PubMed: 32497310]
13. Carta I, Chen CH, Schott AL, Dorizan S, Khodakhah K. Cerebellar modulation of the reward circuitry and social behavior. Science 2019;363(6424):eaav0581 [PubMed: 30655412]
14. Chen TX, Lin CR, Aumann MA, et al. Impulsivity trait profiles in patients with cerebellar ataxia and parkinson disease. Neurology 2022;99(02):e176–e186 [PubMed: 35428731]
15. Heffley W, Song EY, Xu Z, et al. Coordinated cerebellar climbing fiber activity signals learned sensorimotor predictions. Nat Neurosci 2018;21(10):1431–1441 [PubMed: 30224805]
16. Sendhilnathan N, Semework M, Goldberg ME, Ipata AE. Neural correlates of reinforcement learning in mid-lateral cerebellum. Neuron 2020;106(06):1055 [PubMed: 32553199]
17. Wagner MJ, Kim TH, Savall J, Schnitzer MJ, Luo L. Cerebellar granule cells encode the expectation of reward. Nature 2017;544 (7648):96–100 [PubMed: 28321129]

18. Schmahmann JD, Pierce S, MacMore J, L'Italien GJ. Development and validation of a patient-reported outcome measure of ataxia. Mov Disord 2021;36(10):2367–2377 [PubMed: 34115419]
19. Mitoma H, Manto M, Hampe CS. Time is cerebellum. Cerebellum 2018;17(04):387–391 [PubMed: 29460203]
20. Dar MS. Ethanol-induced cerebellar ataxia: cellular and molecular mechanisms. Cerebellum 2015;14(04):447–465 [PubMed: 25578036]
21. Luo J Effects of ethanol on the cerebellum: advances and prospects. Cerebellum 2015;14(04):383–385 [PubMed: 25933648]
22. Victor M, Adams RD, Mancall EL. A restricted form of cerebellar cortical degeneration occurring in alcoholic patients. AMA Arch Neurol 1959;1(06):579–688
23. Haubek A, Lee K. Computed tomography in alcoholic cerebellar atrophy. Neuroradiology 1979;18(02):77–79 [PubMed: 471226]
24. Mitoma H, Manto M, Shaikh AG. Mechanisms of ethanol-induced cerebellar ataxia: underpinnings of neuronal death in the cerebellum. Int J Environ Res Public Health 2021;18(16):8678 [PubMed: 34444449]
25. Setta F, Jacquy J, Hildebrand J, Manto MU. Ataxia induced by small amounts of alcohol. J Neurol Neurosurg Psychiatry 1998; 65(03):370–373 [PubMed: 9728953]
26. Shanmugarajah PD, Hoggard N, Currie S, et al. Alcohol-related cerebellar degeneration: not all down to toxicity? Cerebellum Ataxias 2016;3(01):17 [PubMed: 27729985]
27. Diener HC, Dichgans J, Bacher M, Guschlbauer B. Improvement of ataxia in alcoholic cerebellar atrophy through alcohol abstinence. J Neurol 1984;231(05):258–262 [PubMed: 6520618]
28. Fein G, Greenstein D. Gait and balance deficits in chronic alcoholics: no improvement from 10 weeks through 1 year abstinence. Alcohol Clin Exp Res 2013;37(01):86–95 [PubMed: 22691134]
29. Sosenko JM, Soto R, Aronson J, Kato M, Caralis PV, Ayyar DR. The prevalence and extent of vibration sensitivity impairment in men with chronic ethanol abuse. J Stud Alcohol 1991;52(04): 374–376 [PubMed: 1652043]
30. Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol 2007;6(05):442–455 [PubMed: 17434099]
31. Desai SD, Shah DS. Atypical Wernicke's syndrome sans encephalopathy with acute bilateral vision loss due to post-chiasmatic optic tract edema. Ann Indian Acad Neurol 2014;17(01): 103–105 [PubMed: 24753673]
32. Divya MB, Kubera NS, Jha N, Jha AK, Thabah MM. Atypical neurological manifestations in Wernicke's encephalopathy due to hyperemesis gravidarum. Nutr Neurosci 2022;25(10): 2051–2056 [PubMed: 34042559]
33. Lin CY, Yoo JY, Doshi A, Colman R. Clinical reasoning: a 61-year-old man with conjugate gaze deviation, hemiparesis, and asymmetric reflexes. Neurology 2017;89(09):e105–e108 [PubMed: 28847838]
34. Jung YC, Chanraud S, Sullivan EV. Neuroimaging of Wernicke's encephalopathy and Korsakoff's syndrome. Neuropsychol Rev 2012;22(02):170–180 [PubMed: 22577003]
35. Ramineni KK, Marupaka SK, Jakkani R, Ingle A. Wernicke encephalopathy with atypical findings on magnetic resonance imaging. Ann Indian Acad Neurol 2018;21(04):328–330 [PubMed: 30532369]
36. Zuccoli G, Santa Cruz D, Bertolini M, et al. MR imaging findings in 56 patients with Wernicke encephalopathy: nonalcoholics may differ from alcoholics. AJNR Am J Neuroradiol 2009;30(01): 171–176 [PubMed: 18945789]
37. Kuo SH, Debnam JM, Fuller GN, de Groot J. Wernicke's encephalopathy: an underrecognized and reversible cause of confusional state in cancer patients. Oncology 2009;76(01):10–18 [PubMed: 19018150]
38. Jones KS, Parkington DA, Cox LJ, Koulman A. Erythrocyte transketolase activity coefficient (ETKAC) assay protocol for the assessment of thiamine status. Ann N Y Acad Sci 2021;1498 (01):77–84 [PubMed: 33354793]
39. Leigh D, McBurney A, McIlwain H. Erythrocyte transketolase activity in the Wernicke-Korsakoff syndrome. Br J Psychiatry 1981;139:153–156 [PubMed: 7306754]

40. Pekovich SR, Martin PR, Singleton CK. Thiamine deficiency decreases steady-state transketolase and pyruvate dehydrogenase but not alpha-ketoglutarate dehydrogenase mRNA levels in three human cell types. J Nutr 1998;128(04): 683–687 [PubMed: 9521628]
41. Akhouri S, Kuhn J, Newton EJ. Wernicke-Korsakoff syndrome. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022
42. Qudsiya Z, De Jesus O. Subacute combined degeneration of the spinal cord. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022
43. Losa R, Sierra MI, Fernández A, Blanco D, Buesa JM. Determination of thiamine and its phosphorylated forms in human plasma, erythrocytes and urine by HPLC and fluorescence detection: a preliminary study on cancer patients. J Pharm Biomed Anal 2005;37(05):1025–1029 [PubMed: 15862682]
44. Lu J, Frank EL. Rapid HPLC measurement of thiamine and its phosphate esters in whole blood. Clin Chem 2008;54(05): 901–906 [PubMed: 18356241]
45. Talwar D, Davidson H, Cooney J, St JO'Reilly D. Vitamin B(1) status assessed by direct measurement of thiamin pyrophosphate in erythrocytes or whole blood by HPLC: comparison with erythrocyte transketolase activation assay. Clin Chem 2000;46 (05):704–710 [PubMed: 10794754]
46. Wilkins A Cerebellar dysfunction in multiple sclerosis. Front Neurol 2017;8:312 [PubMed: 28701995]
47. Anderson VM, Fisniku LK, Altmann DR, Thompson AJ, Miller DH. MRI measures show significant cerebellar gray matter volume loss in multiple sclerosis and are associated with cerebellar dysfunction. Mult Scler 2009;15(07):811–817 [PubMed: 19465449]
48. Calabrese M, Mattisi I, Rinaldi F, et al. Magnetic resonance evidence of cerebellar cortical pathology in multiple sclerosis. J Neurol Neurosurg Psychiatry 2010;81(04):401–404 [PubMed: 19965849]
49. Kutzelnigg A, Faber-Rod JC, Bauer J, et al. Widespread demyelination in the cerebellar cortex in multiple sclerosis. Brain Pathol 2007;17(01):38–44 [PubMed: 17493036]
50. D'Ambrosio A, Pagani E, Riccitelli GC, et al. Cerebellar contribution to motor and cognitive performance in multiple sclerosis: An MRI sub-regional volumetric analysis. Mult Scler 2017;23 (09):1194–1203 [PubMed: 27760859]
51. Fritz NE, Edwards EM, Ye C, et al. Cerebellar contributions to motor and cognitive control in multiple sclerosis***. Arch Phys Med Rehabil 2022;103(08):1592–1599 [PubMed: 34998712]
52. Jaques CS, de Moraes MPM, Silva EAR, et al. Characterisation of ataxia in Sjogren's syndrome. J Neurol Neurosurg Psychiatry 2020;91(04):446–448 [PubMed: 32015088]
53. Chen YW, Lee KC, Chang IW, Chang CS, Hsu SP, Kuo HC. Sjogren's syndrome with acute cerebellar ataxia and massive lymphadenopathy : a case report. Acta Neurol Taiwan 2013;22(02):81–86 [PubMed: 24030041]
54. Chuah SL, Jobli AT, Wan SA, Teh CL. Cerebellar degeneration in primary Sjögren syndrome: a case report. J Med Case Reports 2021;15(01):526
55. Farhat E, Zouari M, Abdelaziz IB, et al. Progressive cerebellar degeneration revealing Primary Sjögren Syndrome: a case report. Cerebellum Ataxias 2016;3(01):18 [PubMed: 27777786]
56. Conway KS, Camelo-Piragua S, Fisher-Hubbard A, Perry WR, Shakkottai VG, Venneti S. Multiple system atrophy pathology is associated with primary Sjögren's syndrome. JCI Insight 2020; 5(15):e138619 [PubMed: 32644976]
57. Bushara KO, Goebel SU, Shill H, Goldfarb LG, Hallett M. Gluten sensitivity in sporadic and hereditary cerebellar ataxia. Ann Neurol 2001;49(04):540–543 [PubMed: 11310636]
58. Lin CY, Wang MJ, Tse W, et al. Serum antigliadin antibodies in cerebellar ataxias: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2018;89(11):1174–1180 [PubMed: 29866704]
59. Newrick L, Hoggard N, Hadjivassiliou M. Recognition and management of rapid-onset gluten ataxias: case series. Cerebellum Ataxias 2021;8(01):16 [PubMed: 34120658]
60. Benson BC, Mulder CJ, Laczek JT. Anti-gliadin antibodies identify celiac patients overlooked by tissue transglutaminase antibodies. Hawaii J Med Public Health 2013;72(9, Suppl 4):14–17 [PubMed: 24052912]

61. Mitoma H, Hadjivassiliou M, Honnorat J. Guidelines for treatment of immune-mediated cerebellar ataxias. Cerebellum Ataxias 2015;2(01):14 [PubMed: 26561527]
62. Payer J, Petrovic T, Lisy L, Langer P. Hashimoto encephalopathy: a rare intricate syndrome. Int J Endocrinol Metab 2012;10(02): 506–514 [PubMed: 23843812]
63. Rao RS, Sheshadri S, Bhattacharjee D, Patil N, Rao K. Progressive non-familial adult onset cerebellar degeneration: an unusual occurrence with Hashimoto's thyroiditis. Psychopharmacol Bull 2018;48(03):42–46 [PubMed: 29713105]
64. Selim M, Drachman DA. Ataxia associated with Hashimoto's disease: progressive non-familial adult onset cerebellar degeneration with autoimmune thyroiditis. J Neurol Neurosurg Psychiatry 2001;71(01):81–87 [PubMed: 11413268]
65. Ferracci F, Moretto G, Candeago RM, et al. Antithyroid antibodies in the CSF: their role in the pathogenesis of Hashimoto's encephalopathy. Neurology 2003;60(04):712–714 [PubMed: 12601119]
66. Nakagawa H, Yoneda M, Fujii A, Kinomoto K, Kuriyama M. Hashimoto's encephalopathy presenting with progressive cerebellar ataxia. J Neurol Neurosurg Psychiatry 2007;78(02): 196–197 [PubMed: 17229749]
67. Castillo P, Woodruff B, Caselli R, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. Arch Neurol 2006;63(02):197–202 [PubMed: 16476807]
68. Cornejo R, Venegas P, Goñi D, Salas A, Romero C. Successful response to intravenous immunoglobulin as rescue therapy in a patient with Hashimoto's encephalopathy. BMJ Case Rep 2010; 2010:bcr0920103332
69. Miske R, Hahn S, Rosenkranz T, et al. Autoantibodies against glutamate receptor d2 after allogenic stem cell transplantation. Neurol Neuroimmunol Neuroinflamm 2016;3(04):e255 [PubMed: 27458598]
70. Shiihara T, Kato M, Konno A, Takahashi Y, Hayasaka K. Acute cerebellar ataxia and consecutive cerebellitis produced by glutamate receptor delta2 autoantibody. Brain Dev 2007;29(04): 254–256 [PubMed: 17049194]
71. Aly R, Emmady PD. Paraneoplastic cerebellar degeneration. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022
72. McKeon A, Tracy JA, Pittock SJ, Parisi JE, Klein CJ, Lennon VA. Purkinje cell cytoplasmic autoantibody type 1 accompaniments: the cerebellum and beyond. Arch Neurol 2011;68(10): 1282–1289 [PubMed: 21670387]
73. Rydz D, Lin CY, Xie T, Cortes E, Vonsattel JP, Kuo SH. Pathological findings of anti-Yo cerebellar degeneration with Holmes tremor. J Neurol Neurosurg Psychiatry 2015;86(01):121–122 [PubMed: 24876186]
74. Jarius S, Wildemann B. 'Medusa head ataxia': the expanding spectrum of Purkinje cell antibodies in autoimmune cerebellar ataxia. Part 3: anti-Yo/CDR2, anti-Nb/AP3B2, PCA-2, anti--Tr/DNER, other antibodies, diagnostic pitfalls, summary and outlook. J Neuroinflammation 2015;12(01):168 [PubMed: 26377319]
75. Peter E, Do LD, Hannoun S, et al. Cerebellar ataxia with anti-DNER antibodies: outcomes and immunologic features. Neurol Neuroimmunol Neuroinflamm 2022;9(05):e200018 [PubMed: 35940913]
76. Dade M, Berzero G, Izquierdo C, et al. Neurological syndromes associated with anti-GAD antibodies. Int J Mol Sci 2020;21(10): 3701 [PubMed: 32456344]
77. Joubert B, Belbezier A, Haesebaert J, et al. Long-term outcomes in temporal lobe epilepsy with glutamate decarboxylase antibodies. J Neurol 2020;267(07):2083–2089 [PubMed: 32221776]
78. Malter MP, Helmstaedter C, Urbach H, Vincent A, Bien CG. Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. Ann Neurol 2010;67(04):470–478 [PubMed: 20437582]
79. Honnorat J, Saiz A, Giometto B, et al. Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies: study of 14 patients. Arch Neurol 2001;58(02):225–230 [PubMed: 11176960]
80. Ariño H, Gresa-Arribas N, Blanco Y, et al. Cerebellar ataxia and glutamic acid decarboxylase antibodies: immunologic profile and long-term effect of immunotherapy. JAMA Neurol 2014;71 (08):1009–1016 [PubMed: 24934144]

81. Kuchling J, Shababi-Klein J, Nümann A, Gerischer LM, Harms L, Prüss H. GAD antibody-associated late-onset cerebellar ataxia in two female siblings. Case Rep Neurol 2014;6(03): 264–270 [PubMed: 25566057]
82. Saiz A, Blanco Y, Sabater L, et al. Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. Brain 2008;131(Pt 10):2553–2563 [PubMed: 18687732]
83. Espay AJ, Chen R. Rigidity and spasms from autoimmune encephalomyelopathies: stiff-person syndrome. Muscle Nerve 2006; 34(06):677–690 [PubMed: 16969837]
84. McKeon A, Robinson MT, McEvoy KM, et al. Stiff-man syndrome and variants: clinical course, treatments, and outcomes. Arch Neurol 2012;69(02):230–238 [PubMed: 22332190]
85. Rosin L, DeCamilli P, Butler M, et al. Stiff-man syndrome in a woman with breast cancer: an uncommon central nervous system paraneoplastic syndrome. Neurology 1998;50(01):94–98 [PubMed: 9443464]
86. Silverman IE. Paraneoplastic stiff limb syndrome. J Neurol Neurosurg Psychiatry 1999;67(01):126–127 [PubMed: 10454877]
87. Tanaka H, Matsumura A, Okumura M, Kitaguchi M, Yamamoto S, Iuchi K. Stiff man syndrome with thymoma. Ann Thorac Surg 2005;80(02):739–741 [PubMed: 16039251]
88. Thomas S, Critchley P, Lawden M, et al. Stiff person syndrome with eye movement abnormality, myasthenia gravis, and thymoma. J Neurol Neurosurg Psychiatry 2005;76(01):141–142 [PubMed: 15608018]
89. Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome. N Engl J Med 2001;345(26):1870–1876 [PubMed: 11756577]
90. Georgieva Z, Parton M. Cerebellar ataxia and epilepsy with anti-GAD antibodies: treatment with IVIG and plasmapheresis. BMJ Case Rep 2014;2014:bcr2013202314
91. Jones AL, Flanagan EP, Pittock SJ, et al. Responses to and outcomes of treatment of autoimmune cerebellar ataxia in adults. JAMA Neurol 2015;72(11):1304–1312 [PubMed: 26414229]
92. Sawaishi Y, Takada G. Acute cerebellitis. Cerebellum 2002;1(03): 223–228 [PubMed: 12879984]
93. Salas AA, Nava A. Acute cerebellar ataxia in childhood: initial approach in the emergency department. Emerg Med J 2010;27 (12):956–957 [PubMed: 20581406]
94. Bozzola E, Bozzola M, Tozzi AE, et al. Acute cerebellitis in varicella: a ten year case series and systematic review of the literature. Ital J Pediatr 2014;40:57 [PubMed: 24942129]
95. Malayala SV, Jaidev P, Vanaparthy R, Jolly TS. Acute COVID-19 cerebellitis: a rare neurological manifestation of COVID-19 infection. Cureus 2021;13(10):e18505 [PubMed: 34754665]
96. O'Neill KA, Polavarapu A. Acute cerebellar ataxia associated with COVID-19 infection in a 5-year-old boy. Child Neurol Open 2021; 8:X211066755
97. Povlow A, Auerbach AJ. Acute cerebellar ataxia in COVID-19 infection: a case report. J Emerg Med 2021;60(01):73–76 [PubMed: 33208227]
98. Tomar LR, Shah DJ, Agarwal U, Batra A, Anand I. Acute postinfectious cerebellar ataxia due to COVID-19. Mov Disord Clin Pract (Hoboken) 2021;8(04):610–612 [PubMed: 33981797]
99. Werner J, Reichen I, Huber M, Abela IA, Weller M, Jelcic I. Subacute cerebellar ataxia following respiratory symptoms of COVID-19: a case report. BMC Infect Dis 2021;21(01):298 [PubMed: 33761897]
100. Altmann K, Koziol K, Palaver A, et al. Cytotoxic edema involving the corpus callosum and middle cerebellar peduncles in a young patient with mild COVID-19. Neurology 2022 (e-pub ahead of print). Doi: 10.1212/WNL.0000000000200816
101. van Gaalen J, Kerstens FG, Maas RP, Härmark L, van de Warrenburg BP. Drug-induced cerebellar ataxia: a systematic review. CNS Drugs 2014;28(12):1139–1153 [PubMed: 25391707]
102. Gürkov R Amiodarone: a newly discovered association with bilateral vestibulopathy. Front Neurol 2018;9:119 [PubMed: 29559948]
103. Sarrazin S, Hein C, Delrieu J, et al. Amiodarone-induced ataxia: a case report of severe cerebellar dysfunction and review of literature. J Nutr Health Aging 2021;25(03):284–286 [PubMed: 33575717]

104. Belli LS, De Carlis L, Romani F, et al. Dysarthria and cerebellar ataxia: late occurrence of severe neurotoxicity in a liver transplant recipient. Transpl Int 1993;6(03):176–178 [PubMed: 8499072]
105. Kaleyias J, Faerber E, Kothare SV. Tacrolimus induced subacute cerebellar ataxia. Eur J Paediatr Neurol 2006;10(02):86–89 [PubMed: 16530436]
106. Teimouri A, Ahmadi SR, Anavri Ardakani S, Foroughian M. Cyclosporine-A-based immunosuppressive therapy-induced neurotoxicity: a case report. Open Access Emerg Med 2020; 12:93–97 [PubMed: 32431553]
107. Thompson CB, June CH, Sullivan KM, Thomas ED. Association between cyclosporin neurotoxicity and hypomagnesaemia. Lancet 1984;2(8412):1116–1120 [PubMed: 6150182]
108. Graves TD, Condon M, Loucaidou M, Perry RJ. Reversible metro-nidazole-induced cerebellar toxicity in a multiple transplant recipient. J Neurol Sci 2009;285(1–2):238–240 [PubMed: 19560788]
109. Woodruff BK, Wijdicks EF, Marshall WF. Reversible metronidazole-induced lesions of the cerebellar dentate nuclei. N Engl J Med 2002;346(01):68–69 [PubMed: 11778010]
110. Hamberg P, De Jong FA, Brandsma D, Verweij J, Sleijfer S. Irinotecan-induced central nervous system toxicity. Report on two cases and review of the literature. Acta Oncol 2008;47(05): 974–978 [PubMed: 17924208]
111. Hamberg P, Donders RC, ten Bokkel Huinink D. Central nervous system toxicity induced by irinotecan. J Natl Cancer Inst 2006;98 (03):219 [PubMed: 16449682]
112. Vaughn DJ, Jarvik JG, Hackney D, Peters S, Stadtmauer EA. High-dose cytarabine neurotoxicity: MR findings during the acute phase. AJNR Am J Neuroradiol 1993;14(04):1014–1016 [PubMed: 8352140]
113. Adityanjee, Munshi KR, Thampy A. The syndrome of irreversible lithium-effectuated neurotoxicity. Clin Neuropharmacol 2005; 28(01):38–49 [PubMed: 15714160]
114. Decker BS, Goldfarb DS, Dargan PI, et al. ; EXTRIP Workgroup. Extracorporeal treatment for lithium poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin J Am Soc Nephrol 2015;10(05):875–887 [PubMed: 25583292]
115. Moon HJ, Jeon B. Can therapeutic-range chronic phenytoin administration cause cerebellar ataxia? J Epilepsy Res 2017;7 (01):21–24 [PubMed: 28775951]
116. Lin CR, Viswanathan A, Chen TX, et al. Clinicopathological correlates of pyramidal signs in multiple system atrophy. Ann Clin Transl Neurol 2022;9(07):988–994 [PubMed: 35593123]
117. Tu PH, Galvin JE, Baba M, et al. Glial cytoplasmic inclusions in white matter oligodendrocytes of multiple system atrophy brains contain insoluble alpha-synuclein. Ann Neurol 1998;44 (03):415–422 [PubMed: 9749615]
118. Revuelta GJ, Benatar M, Freeman A, et al. Clinical subtypes of anterocollis in parkinsonian syndromes. J Neurol Sci 2012;315 (1–2):100–103 [PubMed: 22133481]
119. Cortelli P, Calandra-Buonaura G, Benarroch EE, et al. Stridor in multiple system atrophy: consensus statement on diagnosis, prognosis, and treatment. Neurology 2019;93(14):630–639 [PubMed: 31570638]
120. Miki Y, Foti SC, Asi YT, et al. Improving diagnostic accuracy of multiple system atrophy: a clinicopathological study. Brain 2019;142(09):2813–2827 [PubMed: 31289815]
121. Wenning GK, Stankovic I, Vignatelli L, et al. The Movement Disorder Society criteria for the diagnosis of multiple system atrophy. Mov Disord 2022;37(06):1131–1148 [PubMed: 35445419]
122. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008;71(09):670–676 [PubMed: 18725592]
123. Koga S, Aoki N, Uitti RJ, et al. When DLB, PD, and PSP masquerade as MSA: an autopsy study of 134 patients. Neurology 2015;85 (05):404–412 [PubMed: 26138942]
124. Braune S, Reinhardt M, Schnitzer R, Riedel A, Lücking CH. Cardiac uptake of [123I]MIBG separates Parkinson's disease from multiple system atrophy. Neurology 1999;53(05):1020–1025 [PubMed: 10496261]
125. Donadio V, Incensi A, Rizzo G, et al. Skin biopsy may help to distinguish multiple system atrophy-Parkinsonism from Parkinson's disease with orthostatic hypotension. Mov Disord 2020;35 (09):1649–1657 [PubMed: 32557839]

126. Haga R, Sugimoto K, Nishijima H, et al. Clinical utility of skin biopsy in differentiating between Parkinson's disease and multiple system atrophy. Parkinsons Dis 2015;2015:167038 [PubMed: 25945280]

127. Shahnawaz M, Mukherjee A, Pritzkow S, et al. Discriminating α-synuclein strains in Parkinson's disease and multiple system atrophy. Nature 2020;578(7794):273–277 [PubMed: 32025029]

128. Eschlböck S, Wenning G, Fanciulli A. Evidence-based treatment of neurogenic orthostatic hypotension and related symptoms. J Neural Transm (Vienna) 2017;124(12):1567–1605 [PubMed: 29058089]

129. Jordan J, Shibao C, Biaggioni I. Multiple system atrophy: using clinical pharmacology to reveal pathophysiology. Clin Auton Res 2015;25(01):53–59 [PubMed: 25757803]

130. Perez-Lloret S, Flabeau O, Fernagut PO, et al. Current concepts in the treatment of multiple system atrophy. Mov Disord Clin Pract (Hoboken) 2015;2(01):6–16 [PubMed: 30363880]

131. Pérez-Lloret S, Quarracino C, Otero-Losada M, Rascol O. Droxidopa for the treatment of neurogenic orthostatic hypotension in neurodegenerative diseases. Expert Opin Pharmacother 2019;20 (06):635–645 [PubMed: 30730771]

132. Wenning GK, Colosimo C, Geser F, Poewe W. Multiple system atrophy. Lancet Neurol 2004;3(02):93–103 [PubMed: 14747001]

133. Cortese A, Reilly MM, Houlden H. RFC1 CANVAS / Spectrum Disorder. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. GeneReviews(®). Seattle, WA: University of Washington Seattle Copyright © 1993–2022; 1993

134. Sullivan R, Yau WY, Chelban V, et al. *RFC1*-related ataxia is a mimic of early multiple system atrophy. J Neurol Neurosurg Psychiatry 2021;92(04):444–446 [PubMed: 33563805]

135. Leehey MA. Fragile X-associated tremor/ataxia syndrome: clinical phenotype, diagnosis, and treatment. J Investig Med 2009;57 (08):830–836

136. Kamm C, Healy DG, Quinn NP, et al. ; European Multiple System Atrophy Study Group. The fragile X tremor ataxia syndrome in the differential diagnosis of multiple system atrophy: data from the EMSA study group. Brain 2005;128 (Pt 8):1855–1860 [PubMed: 15947063]

137. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996;47(01):1–9 [PubMed: 8710059]

138. Höglinger GU, Respondek G, Stamelou M, et al. ; Movement Disorder Society-endorsed PSP Study Group. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. Mov Disord 2017;32(06):853–864 [PubMed: 28467028]

139. Ishizawa K, Lin WL, Tiseo P, Honer WG, Davies P, Dickson DW. A qualitative and quantitative study of grumose degeneration in progressive supranuclear palsy. J Neuropathol Exp Neurol 2000; 59(06):513–524 [PubMed: 10850864]

140. Sawa N, Kataoka H, Kiriyama T, et al. Cerebellar dentate nucleus in progressive supranuclear palsy. Clin Neurol Neurosurg 2014; 118:32–36 [PubMed: 24529226]

141. Shirota Y, Hamada M, Hanajima R, et al. Cerebellar dysfunction in progressive supranuclear palsy: a transcranial magnetic stimulation study. Mov Disord 2010;25(14):2413–2419 [PubMed: 20818672]

142. Iwasaki Y, Mori K, Ito M, Tatsumi S, Mimuro M, Yoshida M. An autopsied case of progressive supranuclear palsy presenting with cerebellar ataxia and severe cerebellar involvement. Neuropathology 2013;33(05):561–567 [PubMed: 23320789]

143. Kanazawa M, Shimohata T, Toyoshima Y, et al. Cerebellar involvement in progressive supranuclear palsy: a clinicopathological study. Mov Disord 2009;24(09):1312–1318 [PubMed: 19412943]

144. Koga S, Josephs KA, Ogaki K, et al. Cerebellar ataxia in progressive supranuclear palsy: an autopsy study of PSP-C. Mov Disord 2016; 31(05):653–662 [PubMed: 26841329]

145. Ando S, Kanazawa M, Onodera O. Progressive supranuclear palsy with predominant cerebellar ataxia. J Mov Disord 2020;13(01): 20–26 [PubMed: 31847511]

146. CDC's diagnostic criteria for Creutzfeldt-Jakob disease (CJD). 2018 Accessed February 8, 2023 at: https://www.cdc.gov/prions/cjd/diagnostic-criteria.html

147. Sequeira D, Nihat A, Mok T, et al. Prevalence and treatments of movement disorders in prion diseases: a longitudinal cohort study. Mov Disord 2022;37(09):1893–1903 [PubMed: 35841311]
148. Cooper SA, Murray KL, Heath CA, Will RG, Knight RS. Sporadic Creutzfeldt-Jakob disease with cerebellar ataxia at onset in the UK. J Neurol Neurosurg Psychiatry 2006;77(11): 1273–1275 [PubMed: 16835290]
149. Lin CY, Kuo SH. Cerebellar ataxia and hearing impairment. JAMA Neurol 2017;74(02):243–244 [PubMed: 27918770]
150. Waliszewska-Prosół M, Obara K, Szewczyk P, Śniatowska M, Budrewicz S. Cerebellar ataxia as a first manifestation of Creutzfeldt-Jakob disease in two cousins. Postgrad Med J 2018;94 (1112):360 [PubMed: 29434023]
151. Heckmann JG, Vachalova I, Vynogradova I, Schwab S. Dressing apraxia as initial manifestation of Creutzfeldt-Jakob disease. Tremor Other Hyperkinet Mov (N Y) 2020;10:14 [PubMed: 32775028]
152. Green AJE. RT-QuIC: a new test for sporadic CJD. Pract Neurol 2019;19(01):49–55 [PubMed: 30282760]
153. McGuire LI, Peden AH, Orrú CD, et al. Real time quaking-induced conversion analysis of cerebrospinal fluid in sporadic Creutzfeldt-Jakob disease. Ann Neurol 2012;72(02):278–285 [PubMed: 22926858]
154. Fogel BL, Perlman S. An approach to the patient with late-onset cerebellar ataxia. Nat Clin Pract Neurol 2006;2(11):629–635, quiz 1, 635 [PubMed: 17057750]
155. van Gaalen J, van de Warrenburg BPC. A practical approach to late-onset cerebellar ataxia: putting the disorder with lack of order into order. Pract Neurol 2012;12(01):14–24 [PubMed: 22258168]
156. Perlman S. Evaluation and Management of Ataxic Disorders: An Overview for Physicians. Minneapolis, MN: National Ataxia Foundation; 2016
157. Klockgether T Sporadic ataxia with adult onset: classification and diagnostic criteria. Lancet Neurol 2010;9(01):94–104 [PubMed: 20083040]
158. Klockgether T, Schroth G, Diener HC, Dichgans J. Idiopathic cerebellar ataxia of late onset: natural history and MRI morphology. J Neurol Neurosurg Psychiatry 1990;53(04):297–305 [PubMed: 2341843]
159. Tsuji S Idiopathic late onset cerebellar ataxia (ILOCA), and cerebellar plus syndrome. In: Manto M, Schmahmann JD, Rossi F, Gruol DL, Koibuchi N, eds. Handbook of the Cerebellum and Cerebellar Disorders. Dordrecht: Springer Netherlands; 2013: 2143–2150
160. van Swieten JC, Brusse E, de Graaf BM, et al. A mutation in the fibroblast growth factor 14 gene is associated with autosomal dominant cerebellar ataxia [corrected]. Am J Hum Genet 2003; 72(01):191–199 [PubMed: 12489043]
161. Groth CL, Berman BD. Spinocerebellar ataxia 27: a review and characterization of an evolving phenotype. Tremor Other Hyperkinet Mov (N Y) 2018;8:534 [PubMed: 29416937]
162. 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;110(01): 105–119 [PubMed: 36493768]
163. Pellerin D, Danzi MC, Wilke C, et al. Deep intronic FGF14 GAA repeat expansion in late-onset cerebellar ataxia. N Engl J Med 2023;388(02):128–141 [PubMed: 36516086]
164. Arkadir D, Louis ED. The balance and gait disorder of essential tremor: what does this mean for patients? Ther Adv Neurol Disord 2013;6(04):229–236 [PubMed: 23858326]
165. Rao AK, Louis ED. Ataxic gait in essential tremor: a disease-associated feature? Tremor Other Hyperkinet Mov (N Y) 2019; 9:9
166. Louis ED, Bares M, Benito-Leon J, et al. Essential tremor-plus: a controversial new concept. Lancet Neurol 2020;19(03):266–270 [PubMed: 31767343]
167. Wu YC, Louis ED, Gionco J, Pan MK, Faust PL, Kuo SH. Increased climbing fiber lateral crossings on purkinje cell dendrites in the cerebellar hemisphere in essential tremor. Mov Disord 2021;36 (06):1440–1445 [PubMed: 33497495]

168. Gionco JT, Hartstone WG, Martuscello RT, Kuo SH, Faust PL, Louis ED. Essential tremor versus "ET-plus": a detailed postmortem study of cerebellar pathology. Cerebellum 2021;20(06):904–912 [PubMed: 33768479]
169. Louis ED, Galecki M, Rao AK. Four essential tremor cases with moderately impaired gait: how impaired can gait be in this disease? Tremor Other Hyperkinet Mov (N Y) 2013;3:3
170. Dowd H, Zdrodowska MA, Radler KH, et al. Prospective longitudinal study of gait and balance in a cohort of elderly essential tremor patients. Front Neurol 2020;11:581703 [PubMed: 33304305]
171. Gan SR, Wang J, Figueroa KP, et al. Postural tremor and ataxia progression in spinocerebellar ataxias. Tremor Other Hyperkinet Mov (N Y) 2017;7:492 [PubMed: 29057148]
172. Lai RY, Tomishon D, Figueroa KP, et al. Tremor in the degenerative cerebellum: towards the understanding of brain circuitry for tremor. Cerebellum 2019;18(03):519–526 [PubMed: 30830673]
173. Bracchi M, Savoiardo M, Triulzi F, et al. Superficial siderosis of the CNS: MR diagnosis and clinical findings. AJNR Am J Neuroradiol 1993;14(01):227–236 [PubMed: 8427096]
174. Fearnley JM, Stevens JM, Rudge P. Superficial siderosis of the central nervous system. Brain 1995;118(Pt 4):1051–1066 [PubMed: 7655881]
175. Meshkat S, Ebrahimi P, Tafakhori A, et al. Idiopathic superficial siderosis of the central nervous system. Cerebellum Ataxias 2021;8(01):9 [PubMed: 33632336]
176. Demos MK, van Karnebeek CD, Ross CJ, et al. ; FORGE Canada Consortium. A novel recurrent mutation in ATP1A3 causes CAPOS syndrome. Orphanet J Rare Dis 2014;9:15 [PubMed: 24468074]
177. Maas RP, Schieving JH, Schouten M, Kamsteeg EJ, van de Warrenburg BP. The genetic homogeneity of CAPOS syndrome: four new patients with the c.2452G>A (p.Glu818Lys) mutation in the ATP1A3 gene. Pediatr Neurol 2016;59:71.e1–75.e1 [PubMed: 27091223]
178. Nicolaides P, Appleton RE, Fryer A. Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS): a new syndrome. J Med Genet 1996;33(05):419–421 [PubMed: 8733056]
179. Kumar V, Vincent D, Butler JS, Xu Y. Ataxia in long term survivors of lung cancer after whole brain radiation therapy (WBRT). J Clin Oncol 2016;34(15_Suppl):e20656
180. Renard D, Collombier L, Castelnovo G, Fourcade G, Debrigode C, Labauge P. Radiation therapy-related ataxia associated with FDG-PET cerebellar hypometabolism. Acta Neurol Belg 2010; 110(01):100–102 [PubMed: 20514935]
181. Joaquim AF. Severe cerebellar degeneration and Chiari I malformation - speculative pathophysiology based on a systematic review. Rev Assoc Med Bras 2020;66(03):375–379 [PubMed: 32520161]
182. Gardiner SL, Boogaard MW, Trompet S, et al. Prevalence of carriers of intermediate and pathological polyglutamine disease-associated alleles among large population-based cohorts. JAMA Neurol 2019;76(06):650–656 [PubMed: 30933216]
183. Corral-Juan M, Casquero P, Giraldo-Restrepo N, et al. New spinocerebellar ataxia subtype caused by *SAMD9L* mutation triggering mitochondrial dysregulation (SCA49). Brain Commun 2022;4(02):fcac030 [PubMed: 35310830]
184. Leone M, Bottacchi E, D'Alessandro G, Kustermann S. Hereditary ataxias and paraplegias in Valle d'Aosta, Italy: a study of prevalence and disability. Acta Neurol Scand 1995;91(03):183–187 [PubMed: 7793232]
185. Ruano L, Melo C, Silva MC, Coutinho P. The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. Neuroepidemiology 2014;42(03): 174–183 [PubMed: 24603320]
186. van de Warrenburg BP, Sinke RJ, Verschuuren-Bemelmans CC, et al. Spinocerebellar ataxias in the Netherlands: prevalence and age at onset variance analysis. Neurology 2002;58(05):702–708 [PubMed: 11889231]
187. Schöls L, Bauer P, Schmidt T, Schulte T, Riess O. Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. Lancet Neurol 2004;3(05):291–304 [PubMed: 15099544]
188. Ashizawa T, Öz G, Paulson HL. Spinocerebellar ataxias: prospects and challenges for therapy development. Nat Rev Neurol 2018; 14(10):590–605 [PubMed: 30131520]

189. Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. Nat Rev Dis Primers 2019;5(01):24 [PubMed: 30975995]

190. Paulson HL, Shakkottai VG, Clark HB, Orr HT. Polyglutamine spinocerebellar ataxias - from genes to potential treatments. Nat Rev Neurosci 2017;18(10):613–626 [PubMed: 28855740]

191. Iwaki A, Kawano Y, Miura S, et al. Heterozygous deletion of ITPR1, but not SUMF1, in spinocerebellar ataxia type 16. J Med Genet 2008;45(01):32–35 [PubMed: 17932120]

192. Misceo D, Fannemel M, Barøy T, et al. SCA27 caused by a chromosome translocation: further delineation of the phenotype. Neurogenetics 2009;10(04):371–374 [PubMed: 19471976]

193. McInnis MG. Anticipation: an old idea in new genes. Am J Hum Genet 1996;59(05):973–979 [PubMed: 8900222]

194. Donis KC, Mattos EP, Silva AA, et al. Infantile spinocerebellar ataxia type 7: case report and a review of the literature. J Neurol Sci 2015;354(1–2):118–121 [PubMed: 25972113]

195. Brooker SM, Edamakanti CR, Akasha SM, Kuo SH, Opal P. Spinocerebellar ataxia clinical trials: opportunities and challenges. Ann Clin Transl Neurol 2021;8(07):1543–1556 [PubMed: 34019331]

196. Yang CY, Lai RY, Amokrane N, et al. Dysphagia in spinocerebellar ataxias type 1, 2, 3 and 6. J Neurol Sci 2020;415:116878 [PubMed: 32454319]

197. Figueroa KP, Gan SR, Perlman S, et al. C9orf72 repeat expansions as genetic modifiers for depression in spinocerebellar ataxias. Mov Disord 2018;33(03):497–498 [PubMed: 29193335]

198. Lo RY, Figueroa KP, Pulst SM, et al. Depression and clinical progression in spinocerebellar ataxias. Parkinsonism Relat Disord 2016;22:87–92 [PubMed: 26644294]

199. Chen SJ, Lee NC, Chien YH, Hwu WL, Lin CH. Heterogeneous nonataxic phenotypes of spinocerebellar ataxia in a Taiwanese population. Brain Behav 2019;9(10):e01414 [PubMed: 31523939]

200. Gwinn-Hardy K, Singleton A, O'Suilleabhain P, et al. Spinocerebellar ataxia type 3 phenotypically resembling parkinson disease in a black family. Arch Neurol 2001;58(02): 296–299 [PubMed: 11176969]

201. Kuo MC, Tai CH, Tseng SH, Wu RM. Long-term efficacy of bilateral subthalamic deep brain stimulation in the parkinsonism of SCA 3: a rare case report. Eur J Neurol 2022;29(08):2544–2547 [PubMed: 35837753]

202. Ashizawa T, Figueroa KP, Perlman SL, et al. Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US; a prospective observational study. Orphanet J Rare Dis 2013;8:177 [PubMed: 24225362]

203. Jacobi H, Bauer P, Giunti P, et al. The natural history of spinocerebellar ataxia type 1, 2, 3, and 6: a 2-year follow-up study. Neurology 2011;77(11):1035–1041 [PubMed: 21832228]

204. Jacobi H, du Montcel ST, Bauer P, et al. Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study. Lancet Neurol 2015;14(11): 1101–1108 [PubMed: 26377379]

205. Gan SR, Figueroa KP, Xu HL, et al. The impact of ethnicity on the clinical presentations of spinocerebellar ataxia type 3. Parkinsonism Relat Disord 2020;72:37–43 [PubMed: 32105964]

206. Iannuzzelli K, Shi R, Carter R, et al. The association between educational attainment and SCA 3 age of onset and disease course. Parkinsonism Relat Disord 2022;98:99–102 [PubMed: 35635856]

207. Choi KD, Choi JH. Episodic ataxias: clinical and genetic features. J Mov Disord 2016;9(03):129–135 [PubMed: 27667184]

208. Garone G, Capuano A, Travaglini L, et al. Clinical and genetic overview of paroxysmal movement disorders and episodic ataxias. Int J Mol Sci 2020;21(10):3603 [PubMed: 32443735]

209. Graves TD, Cha YH, Hahn AF, et al. ; CINCH Investigators. Episodic ataxia type 1: clinical characterization, quality of life and geno-type-phenotype correlation. Brain 2014;137(Pt 4):1009–1018 [PubMed: 24578548]

210. Strupp M, Zwergal A, Brandt T. Episodic ataxia type 2. Neurotherapeutics 2007;4(02):267–273 [PubMed: 17395137]

211. Jen J, Kim GW, Baloh RW. Clinical spectrum of episodic ataxia type 2. Neurology 2004;62(01):17–22 [PubMed: 14718690]

212. Imbrici P, Eunson LH, Graves TD, et al. Late-onset episodic ataxia type 2 due to an in-frame insertion in CACNA1A. Neurology 2005;65(06):944–946 [PubMed: 16186543]

213. Guterman EL, Yurgionas B, Nelson AB. Pearls & Oy-sters: episodic ataxia type 2: case report and review of the literature. Neurology 2016;86(23):e239–e241 [PubMed: 27272039]

214. Jen JC, Graves TD, Hess EJ, Hanna MG, Griggs RC, Baloh RWCINCH investigators. Primary episodic ataxias: diagnosis, pathogenesis and treatment. Brain 2007;130(Pt 10):2484–2493 [PubMed: 17575281]

215. Kotagal V Acetazolamide-responsive ataxia. Semin Neurol 2012; 32(05):533–537 [PubMed: 23677664]

216. Strupp M, Kalla R, Claassen J, et al. A randomized trial of 4-aminopyridine in EA2 and related familial episodic ataxias. Neurology 2011;77(03):269–275 [PubMed: 21734179]

217. Anheim M, Tranchant C, Koenig M. The autosomal recessive cerebellar ataxias. N Engl J Med 2012;366(07):636–646 [PubMed: 22335741]

218. Synofzik M, Németh AH. Recessive ataxias. Handb Clin Neurol 2018;155:73–89 [PubMed: 29891078]

219. Synofzik M, Puccio H, Mochel F, Schöls L. Autosomal recessive cerebellar ataxias: paving the way toward targeted molecular therapies. Neuron 2019;101(04):560–583 [PubMed: 30790538]

220. Renaud M, Tranchant C, Martin JVT, et al. ; RADIAL Working Group. A recessive ataxia diagnosis algorithm for the next generation sequencing era. Ann Neurol 2017;82(06): 892–899 [PubMed: 29059497]

221. Beaudin M, Matilla-Dueñas A, Soong BW, et al. The classification of autosomal recessive cerebellar ataxias: a consensus statement from the Society for Research on the Cerebellum and Ataxias Task Force. Cerebellum 2019;18(06):1098–1125 [PubMed: 31267374]

222. Aranca TV, Jones TM, Shaw JD, et al. Emerging therapies in Friedreich's ataxia. Neurodegener Dis Manag 2016;6(01):49–65 [PubMed: 26782317]

223. Zesiewicz TA, Hancock J, Ghanekar SD, Kuo SH, Dohse CA, Vega J. Emerging therapies in Friedreich's ataxia. Expert Rev Neurother 2020;20(12):1215–1228 [PubMed: 32909841]

224. Indelicato E, Nachbauer W, Eigentler A, et al. ; EFACTS (European Friedreich's Ataxia Consortium for Translational Studies) Onset features and time to diagnosis in Friedreich's ataxia. Orphanet J Rare Dis 2020;15(01):198 [PubMed: 32746884]

225. Bürk K Friedreich ataxia: current status and future prospects. Cerebellum Ataxias 2017;4:4 [PubMed: 28405347]

226. Strawser C, Schadt K, Hauser L, et al. Pharmacological therapeutics in Friedreich ataxia: the present state. Expert Rev Neurother 2017;17(09):895–907 [PubMed: 28724340]

227. Koeppen AH, Qian J, Travis AM, Sossei AB, Feustel PJ, Mazurkiewicz JE. Microvascular pathology in Friedreich cardiomyopathy. Histol Histopathol 2020;35(01):39–46 [PubMed: 31166002]

228. Koeppen AH, Ramirez RL, Becker AB, Feustel PJ, Mazurkiewicz JE. Friedreich ataxia: failure of GABA-ergic and glycinergic synaptic transmission in the dentate nucleus. J Neuropathol Exp Neurol 2015;74(02):166–176 [PubMed: 25575136]

229. Morral JA, Davis AN, Qian J, Gelman BB, Koeppen AH. Pathology and pathogenesis of sensory neuropathy in Friedreich's ataxia. Acta Neuropathol 2010;120(01):97–108 [PubMed: 20339857]

230. Cook A, Giunti P. Friedreich's ataxia: clinical features, pathogenesis and management. Br Med Bull 2017;124(01):19–30 [PubMed: 29053830]

231. Rummey C, Corben LA, Delatycki M, et al. Natural history of Friedreich's ataxia: heterogeneity of neurological progression and consequences for clinical trial design. Neurology 2022;99 (14):e1499–e1510 [PubMed: 35817567]

232. Cortese A, Simone R, Sullivan R, et al. Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. Nat Genet 2019;51(04):649–658 [PubMed: 30926972]

233. Currò R, Salvalaggio A, Tozza S, et al. RFC1 expansions are a common cause of idiopathic sensory neuropathy. Brain 2021; 144(05):1542–1550 [PubMed: 33969391]

234. Traschütz A, Cortese A, Reich S, et al. ; RFC1 Study Group. Natural history, phenotypic spectrum, and discriminative features of multi-systemic RFC1 disease. Neurology 2021;96(09):e1369–e1382 [PubMed: 33495376]

235. Kuo PH, Lo RY, Tanji K, Kuo SH. Clinical reasoning: a 58-year-old man with progressive ptosis and walking difficulty. Neurology 2017;89(01):e1–e5 [PubMed: 28674165]

236. Shi H, Waldman G, Tobochnik S, Kuo SH, Pack A. Clinical reasoning: refractory status epilepticus in a primigravida. Neurology 2019;92(20):968–972 [PubMed: 31085725]

237. Chaudhary MW, Al-Baradie RS. Ataxia-telangiectasia: future prospects. Appl Clin Genet 2014;7:159–167 [PubMed: 25258552]

238. Lavin MF. Radiosensitivity and oxidative signalling in ataxia telangiectasia: an update. Radiother Oncol 1998;47(02):113–123 [PubMed: 9683357]

239. Byrd PJ, Srinivasan V, Last JI, et al. Severe reaction to radiotherapy for breast cancer as the presenting feature of ataxia telangiectasia. Br J Cancer 2012;106(02):262–268 [PubMed: 22146522]

240. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, McGrath-Morrow SA, Crawford TO, Lederman HM. Ataxia telangiectasia: a review. Orphanet J Rare Dis 2016;11(01):159 [PubMed: 27884168]

241. Bras J, Alonso I, Barbot C, et al. Mutations in PNKP cause recessive ataxia with oculomotor apraxia type 4. Am J Hum Genet 2015;96 (03):474–479 [PubMed: 25728773]

242. Paucar M, Malmgren H, Taylor M, et al. Expanding the ataxia with oculomotor apraxia type 4 phenotype. Neurol Genet 2016;2(01): e49 [PubMed: 27066586]

243. Coutinho P, Barbot C, Coutinho P. Ataxia with oculomotor apraxia type 1. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. GeneReviews(®). Seattle, WA: University of Washington Seattle Copyright © 1993–2022; 1993

244. Moreira MC, Koenig M. Ataxia with oculomotor apraxia type 2. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. GeneReviews (®). Seattle, WA: University of Washington Seattle Copyright © 1993–2022; 1993

245. Patterson M Niemann-Pick disease type C. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. GeneReviews(®). Seattle, WA: University of Washington Seattle Copyright © 1993–2022; 1993

246. Gupta DK, Blanco-Palmero VA, Chung WK, Kuo SH. Abnormal vertical eye movements as a clue for diagnosis of Niemann-Pick type C. Tremor Other Hyperkinet Mov (N Y) 2018;8:560 [PubMed: 29971198]

247. Orsini A, Valetto A, Bertini V, et al. The best evidence for progressive myoclonic epilepsy: a pathway to precision therapy. Seizure 2019;71:247–257 [PubMed: 31476531]

248. Hagerman RJ, Hagerman P. Fragile X-associated tremor/ataxia syndrome - features, mechanisms and management. Nat Rev Neurol 2016;12(07):403–412 [PubMed: 27340021]

249. Fay-Karmon T, Hassin-Baer S. The spectrum of tremor among carriers of the FMR1 premutation with or without the fragile X-associated tremor/ataxia syndrome (FXTAS). Parkinsonism Relat Disord 2019;65:32–38 [PubMed: 31126791]

250. Apartis E, Blancher A, Meissner WG, et al. FXTAS: new insights and the need for revised diagnostic criteria. Neurology 2012;79 (18):1898–1907 [PubMed: 23077007]

251. Shelton AL, Cornish KM, Godler D, Bui QM, Kolbe S, Fielding J. White matter microstructure, cognition, and molecular markers in fragile X premutation females. Neurology 2017;88(22): 2080–2088 [PubMed: 28476762]

252. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. Lancet Neurol 2008;7(04):327–340 [PubMed: 18339348]

253. Hara M, Ariño H, Petit-Pedrol M, et al. DPPX antibody-associated encephalitis: Main syndrome and antibody effects. Neurology 2017;88(14):1340–1348 [PubMed: 28258082]

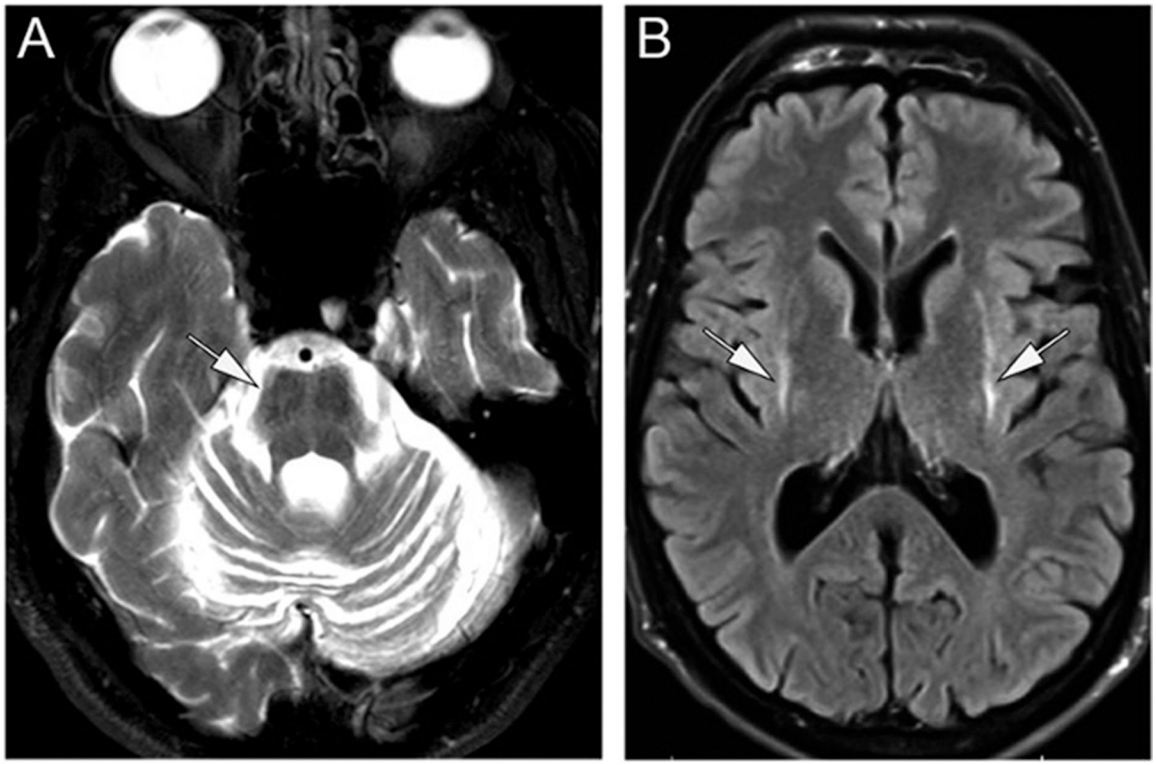

Fig. 1.

Characteristic structural MRI features of multiple system atrophy. The hot crossed bun sign in multiple system atrophy cerebellar type, a feature as a result of the olivopontocerebellar system degeneration (A), and T2 hyperintense external striatal signals, implying putaminal degeneration in multiple system atrophy parkinsonian type (B). MRI, magnetic resonance imaging.

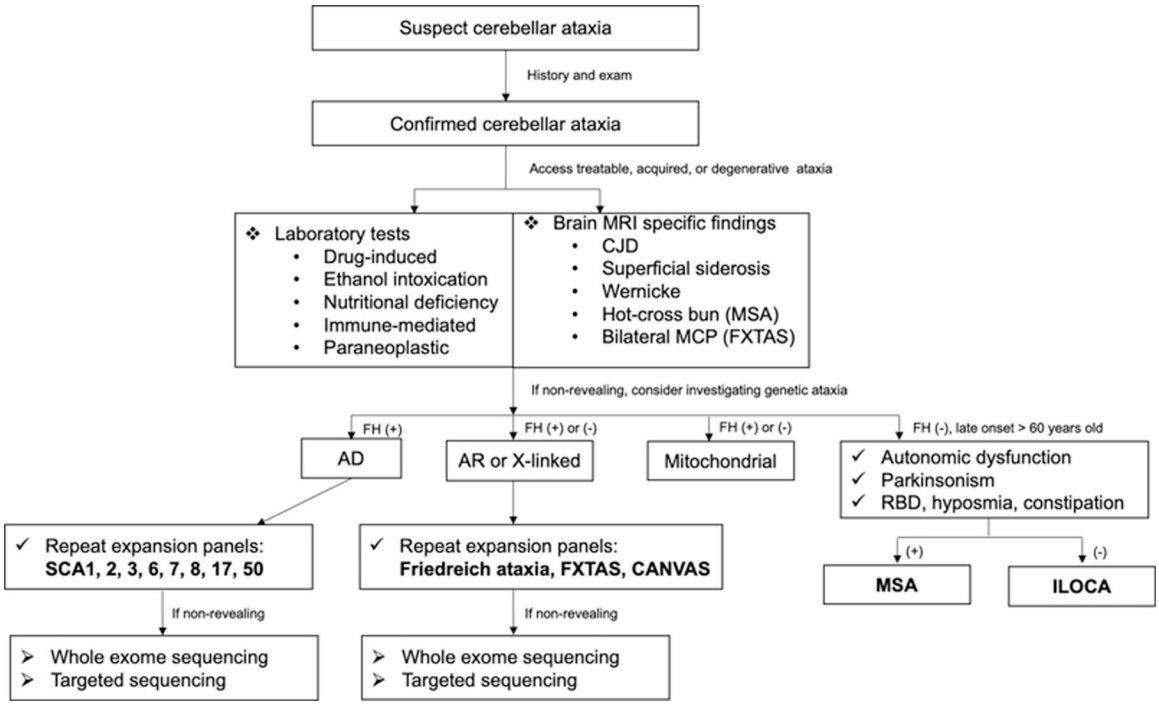

Fig. 2.

The recommended diagnostic algorithm for cerebellar ataxia. CANVAS, cerebellar ataxia, neuropathy, vestibular areflexia syndrome; CJD, Creutzfeldt–Jakob disease; FXTAS, fragile X tremor and ataxia associated syndrome; ILOCA, idiopathic late-onset cerebellar ataxia; MSA, multiple system atrophy.

Table 1

Reversible and treatable causes of cerebellar ataxia, recommended tests, and treatment

Disorders/diseases	Test	Treatment and management
Alcohol-induced ataxia	History[a]	Alcohol cessation
Wernicke encephalopathy	Whole blood thiamine level, brain MRI[b]	High-dose IV or oral thiamine supplementation[c]
Vitamin B12 deficiency	Serum vitamin B12 level	Vitamin B12 supplementation
Vitamin E deficiency	Serum vitamin E level	Vitamin E supplementation
Steroid-responsive encephalopathy[d]	Serum anti-TPO and anti-TG antibodies	IVMP
Gluten ataxia	Anti-gliadin antibody	Gluten-free diet, IVMP, IVIG, or plasmapheresis
Multiple sclerosis	Brain MRI, spine MRI, oligoclonal band of CSF	Immune-modulating therapy
Sjogren syndrome	Anti-Ro (SS-A) and anti-La (SS-B) antibodies	Immune-modulating therapy
Paraneoplastic ataxia	See [Table 2]	IVMP, IVIG, or plasmapheresis; cancer curative treatment If possible
Anti-GAD	GAD antibody	
Toxin-induced ataxia	History; brain MRI[f]	Lithium, amiodarone, metronidazole, cyclosporine, tacrolimus, and other chemotherapy agents[e]

Abbreviations: CSF, cerebrospinal fluid; GAD, glutamic acid decarboxylase; GluRd2, glucose receptor delta 2; IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; TG, thyroglobulin; TPO, thyroid peroxidase.

[a] > 140 g or 50 ounces of wine per day for more than 10 years. Individual susceptibility and other contributors need to be considered.

[b] The purpose of MRI is for supporting the diagnosis; lack of classic findings does not serve as evidence of diagnostic exclusion.

[c] 500 mg every 8 hours for 3 days, followed by 250 mg every day for 5 days.

[d] Hashimoto encephalopathy is the alternative name.

[e] Lithium, amiodarone, metronidazole, cyclosporine, tacrolimus, and other chemotherapy agents.

[f] Bilateral dentate hyperintensity can sometimes be seen on MRI.

Table 2

The onconeuronal antibodies related to paraneoplastic cerebellar degeneration and its underlying malignancy[252,253]

Antibody	Alternative name	Commonly reported tumor/malignancy
ANNA-1	Anti-Hu	Small cell lung cancer, prostate cancer, testicular seminoma
ANNA-2	Anti-Ri	Small cell lung cancer, breast cancer, ovarian cancer
ANNA-3		Small cell lung cancer
PCA-1	Anti-Yo	Breast cancer, ovarian cancer
PCA-2		Small cell lung cancer, breast cancer, ovarian cancer
PCA-Tr	Anti-DNER	Hodgkin lymphoma
mGluR1		Hodgkin lymphoma
CRMP-5	Anti-CV2	Small cell lung cancer, thymoma
Amphiphysin		Small cell lung cancer, breast cancer
DPPX		B cell lymphoma, mantle cell lymphoma, B cell lymphocytic leukemia
NMDA		Ovarian teratoma (malignant and nonmalignant), small cell lung cancer
LGI-1		Lung (squamous cell), thyroid, breast, kidney
CASPR2		Thymoma

Abbreviations: ANNA, antineuronal nuclear antibody; CASPRI2, contactin-associated protein-like 2; CRMP, collapsin response-mediator protein; CV, clathrin-coated vesicles; DNER, delta/notch like epidermal growth factor-related; DPPX, dipeptidyl-peptidase-like protein-6; LGI-1, leucine-rich glioma-inactivated 1; mGluR1, metabotropic glutamate receptor 1; NMDA, N-methyl-D-aspartate; PCA, Purkinje cytoplasmic antibody.

Table 3

Predominant clinical features and characteristics in cerebellar ataxia of autosomal dominant inheritance

Type	Gene	Predominant or characteristic clinical features	Note
SCA1	*ATXN1*	Pyramidal signs	Onset: 3rd or 4th decade
SCA2	*ATXN2*	Early ophthalmoparesis and slow saccade; pronounced truncal sway and proximal limb tremor	Onset: 4th decade; life span is shortened: between 10 and 15 years after onset.
SCA3	*ATXN3*	Extrapyramidal signs/parkinsonism; restless leg syndrome	Onset: highly variable between 2nd to 5th decade.
SCA6	*CACNA1A*	*Pure cerebellar ataxia*; may be very late onset without family history	Onset: 4th to 5th decade; mentation is generally not affected.
SCA7	*ATXN7*	Vision loss, especially early in adolescent onset	Due to macular pigmentary retinal degeneration
SCA8	*ATXN8 and ATXN8OS*	Pyramidal and extrapyramidal signs; slowly progressive	
SCA10	*ATXN10*	Epilepsy/recurrent generalized or complex partial seizures	
SCA12	*PPP2R2B*	Early tremor followed by dementia	
SCA17	*TBP*	Early dementia and neuropsychiatric symptoms (<50 years old); combined with chorea and dystonia	Cognitive and behavioral symptoms can be the initial manifestation
SCA23	*PDYN*	Sensory loss in distal limbs	
SCA26	*EEF2*	Pure cerebellar ataxia	
SCA28	*AFG3L2*	Early ophthalmoparesis, eyelid ptosis	
SCA34	*ELOVL4*	Papulosquamous erythematous skin lesions	
SCA38	*ELOVL5*	Pure cerebellar ataxia	
SCA40	*CCDC88*	Pyramidal signs	
SCA46	*PLD3*	Lower limb sensory ataxia in addition to cerebellar ataxia	
SCA47	*PUM1*	Early intellectual disability, epilepsy	
DRPLA	*ATN1*	Dementia, chorea, seizures	

Abbreviations: GI, gastrointestinal; SCA, spinocerebellar ataxia.