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REVIEW ARTICLE

Treatable Ataxias: How to Find the Needle in the Haystack?

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ABSTRACT

Treatable ataxias are a group of ataxic disorders with specific treatments. These disorders include genetic and metabolic disorders, immune-mediated ataxic disorders, and ataxic disorders associated with infectious and parainfectious etiology, vascular causes, toxins and chemicals, and endocrinopathies. This review provides a comprehensive overview of different treatable ataxias. The major metabolic and genetic treatable ataxic disorders include ataxia with vitamin E deficiency, abetalipoproteinemia, cerebrotendinous xanthomatosis, Niemann-Pick disease type C, autosomal recessive cerebellar ataxia due to coenzyme Q10 deficiency, glucose transporter type 1 deficiency, and episodic ataxia type 2. The treatment of these disorders includes the replacement of deficient cofactors and vitamins, dietary modifications, and other specific treatments. Treatable ataxias with immune-mediated etiologies include gluten ataxia, anti-glutamic acid decarboxylase antibody-associated ataxia, steroid-responsive encephalopathy associated with autoimmune thyroiditis, Miller-Fisher syndrome, multiple sclerosis, and paraneoplastic cerebellar degeneration. Although dietary modification with a gluten-free diet is adequate in gluten ataxia, other autoimmune ataxias are managed by short-course steroids, plasma exchange, or immunomodulation. For autoimmune ataxias secondary to malignancy, treatment of tumor can reduce ataxic symptoms. Chronic alcohol consumption, antiepileptics, anticancer drugs, exposure to insecticides, heavy metals, and recreational drugs are potentially avoidable and treatable causes of ataxia. Infective and parainfectious causes of cerebellar ataxias include acute cerebellitis, postinfectious ataxia, Whipple's disease, meningoencephalitis, and progressive multifocal leukoencephalopathy. These disorders are treated with steroids and antibiotics. Recognizing treatable disorders is of paramount importance when dealing with ataxias given that early treatment can prevent permanent neurological sequelae.

Keywords Acquired ataxia; Cerebellar ataxia; Genetic ataxia; Movement disorders; Treatable ataxia.

INTRODUCTION

Neurological disorders may manifest with ataxia as a standalone symptom or in conjunction with other neurological features. The term "ataxic disorder" is generally reserved for conditions with ataxia as a major clinical symptom. These disorders can be acute, subacute, or chronic in their onset. In general, acute and subacute presentations are related to vascular, infectious, or autoimmune disorders, whereas chronic ataxias are genetic and neurodegenerative in origin.[1] Irrespective of the underlying cause, ataxia has a catastrophic consequence on the quality of life, and its emergence is often regarded as a herald of "permanent" dysfunction. However, this notion is not true in all conditions. In most acute or subacute ataxia disorders, early treatment of the underlying cause can stabilize or improve ataxia.

The clinical use of next-generation sequencing (NGS) has increased our understanding of the genetic basis of cerebellar ataxias. Novel variants and atypical phenotypes of known diseases are being identified more frequently, and mutations in hitherto unknown ataxia-causing genes are also being reported. Despite

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these advances, innovation on the treatment front is moving at a snail's pace. In most cases, the treatment, if any, is aimed at relieving ataxic symptoms, with no significant effect on disease progression whatsoever. However, few genetic ataxias have specific treatments available.

The diagnosis of ataxic disorders is not always straightforward due to overwhelming clinical heterogeneity. This is particularly true for autoimmune and genetic ataxias. In acute, subacute, or chronic ataxic disorders, early identification of treatable causes of ataxia can prevent permanent damage. This review discusses how to identify and manage ataxic disorders with specific treatment under four broad classes: 1) genetic and metabolic ataxia, 2) ataxic disorders associated with autoimmunity, 3) infectious and parainfectious ataxias, and 4) other miscellaneous ataxic disorders.

Genetic and metabolic treatable ataxias

There are few treatable causes of genetic and metabolic ataxias. In general, these disorders tend to manifest earlier and represent chronic progressive disorders. These disorders tend to have a multitude of neurological and non-neurological features, but ataxic manifestations are usually at the forefront.

Ataxia with vitamin E deficiency

Ataxia with vitamin E deficiency (AVED) is a neurogenetic disorder due to biallelic variations in the *TTPA* (alpha tocopherol transfer protein) gene (8q13).[2,3] AVED is inherited by an autosomal recessive mode with almost complete penetrance.[4] The normal protein product of the gene is necessary for the retention of vitamin E and very low-density lipoproteins.[5] The deficiency of vitamin E increases the vulnerability of cerebellar Purkinje cells to death, which leads to clinical manifestations of AVED.[6] The prevalence is estimated to range from 0.6 to 9 per 1,000,000 population.[7]

Clinical features: the clinical symptoms usually begin between the ages of 5 and 20 years.[4] The neurological features include a Friedreich's ataxia-like phenotype, which is most commonly reported in the literature and manifests with cerebellar ataxia, dysarthria, features of incoordination, loss of proprioception and vibration sense, a decrease in vision and retinitis pigmentosa, loss of deep tendon reflexes, and extensor plantar response.[4,8] In several cases, dystonia has been reported, and approximately one-third of patients have a characteristic tremor in head/titubation.[4,9] Systemic clinical features include cardiomyopathy and skeletal deformities in a few patients.[4,10] The affected members from the same family have a uniform age at onset and disease course. Probands with the p.His101Gln variant present with late-onset ataxia (age > 30 years) with a mild course but with a higher risk for pigmentary retinopathy and visual loss. On the other hand, the c.744delA variant exhibits a severe clinical course with early onset of disease and an increased risk of cardiomyopathy.[11,12]

Diagnostic evaluation: diagnosis is confirmed by identifying the biallelic or pathogenic compound heterozygous variation of *TTPA* on molecular testing.[13] The biochemical evaluation shows a very low concentration of plasma α-tocopherol (vitamin E) with normal lipid and lipoprotein profiles.[13] Neuroimaging in the initial stages may show very mild or no discernable cerebellar atrophy.[14] Nerve conduction studies commonly reveal pure sensory neuronopathy or ganglionopathy.[15]

Treatment: life-long, daily vitamin E supplementation at high doses (800 mg/day) can reduce disease progression. If started early, many symptoms may reverse or improve. Untreated patients become wheelchair-bound within 8−20 years of the onset of clinical symptoms.[4,16]

Practical point: AVED should be suspected when Friedreich's-like phenotype is clinically observed with low plasma vitamin E levels and normal lipoproteins without any malabsorption. Vitamin E levels should be monitored every six months to ensure that the level is maintained in a normal range.

Abetalipoproteinemia

Abetalipoproteinemia is a rare metabolic disease caused by biallelic variations in the *MTTP* gene (microsomal triglyceride transfer protein) on chromosome 4q22-24.[1] Abetalipoproteinemia has an autosomal recessive mode of inheritance. Greater than 75 mutations in the *MTTP* gene are known to cause apolipoproteinemia.[17] The penetrance is variable and incomplete. The normal product of the *MTTP* gene is essential for the formation of very-low-density lipoprotein and chylomicron.[17] *MTTP* gene abnormalities lead to the absence of apolipoprotein B-containing lipoproteins and causes malabsorption of fats and fat-soluble vitamins.[18] Abetalipoproteinemia has an estimated prevalence of less than 1 in a population of 1,000,000.[19] *APOB* gene mutations can cause hypobetalipoproteinemia with clinical features indistinguishable from abetalipoproteinemia.[20]

Clinical features: the onset of neurological symptoms usually occurs before the age of 20 years. The neurological symptoms are due to malabsorption of vitamin E and therefore resemble AVED. The first sign is usually a reduced deep tendon reflex, which is noted as early as the first few years, followed by reduced proprioception and vibratory sense (positive Romberg's sign).[18,21] Other signs include cerebellar ataxia, incoordination, muscle weakness, and musculoskeletal deformities. Deficiency in vitamins A and E causes retinitis pigmentosa, a decrease in vision acuity, night blindness and color blindness, annular scotoma sparing the macula, and constricted visual fields.[17] If left untreated, complete visual loss may occur. Ptosis, nystagmus, anisocoria, and strabismus represent rare manifestations.[20,22] Systemic clinical features

include gastrointestinal symptoms and failure to thrive with onset in infancy. Cardiomyopathy if present is usually lethal.[22,23] Anemia and jaundice are reported in a minority of patients.[17,22]

Diagnostic evaluation: the definitive test for diagnosis is genetic confirmation of variation in the MTTP gene.[21] Biochemical tests show an abnormal lipid profile with minimal low-density lipoprotein C levels and a variable decrease in apolipoprotein B, triglycerides, total cholesterol, and high density lipoprotein (performed after at least 12 hours of fasting).[17] Hematological abnormalities include acanthocytosis, low erythrocyte sedimentation rate, anemia, hemolysis, indirect hyperbilirubinemia, and prolonged international normalized ratio (INR). An ultrasound scan may reveal a fatty liver, and MRI brain commonly reveals degeneration affecting the spinocerebellar region.[17,18]

Treatment: restriction of fat intake to less than 15 to 20 g per day is useful to prevent steatorrhea and subsequent oxalate urolithiasis. Adequate calorie intake is also an important step to avoid growth retardation. Administration of medium-chain triglycerides is useful to correct malnutrition in infants but can cause hepatic fibrosis in the context of long-term treatment. The daily requirement of essential fatty acids should be provided in the form of polyunsaturated fatty acid-rich oils, such as soybean or olive oil.[17,18,22]

A high-dose vitamin E supplement of 100−300 mg/kg/day can delay disease progression. Monitoring serum vitamin E levels is not clinically significant as it does not reflect tissue vitamin E levels. High-dose vitamin A (100 to 400 IU/kg/day) can prevent ophthalmic sequelae but can cause toxicity in some cases. Vitamin D deficiency should be corrected using supplementation at 800 to 1,200 IU/day. If prothrombin time/INR is prolonged, vitamin K should be administered at a dose of 5−35 mg/week.[17,20,22] If anemia is present, iron, folate, and vitamin B12 supplements should be administered. The prognosis is variable and depends on the timing of management. Few symptoms may partly reverse. If untreated, the prognosis is poor.[17,19,20,22]

Practical point: abetalipoproteinemia should be suspected in patients with Friedreich's ataxia- or AVED-like phenotype with abnormal lipid profiles and acanthocytes in blood.

Cerebrotendinous xanthomatosis

Cerebrotendinous xanthomatosis (CTX) is caused by homozygous or compound heterozygous mutations in the CYP27A1 gene, leading to the absence of the mitochondrial sterol 27-hydroxylase enzyme. CTX has an autosomal recessive inheritance pattern.[18,21] CTX mutations affect the conversion of cholesterol to chenodeoxycholic acid and cholic acid during bile synthesis and lead to low levels of bile acid and excess cholestanol, which accumulates in tissues. The prevalence varies in different populations, and a higher prevalence is noted in the Asian population.[24]

Clinical features: the initial symptoms of CTX begin in infancy as nonspecific systemic clinical manifestations, such as cholestatic jaundice, diarrhea, and failure to thrive. Approximately 92% of patients develop childhood-onset cataracts before the onset of neurological symptoms and tendon xanthomas.[25] Due to the deposition of cholestanol, 71% of patients develop xanthomas in the Achilles tendon, fingers, triceps, or tibial tuberosity during the first three decades.[25] Pes cavus deformity, pulmonary insufficiency, osteoporosis, endocrinopathies, renal and hepatic calculi, chronic diarrhea, cardiac involvement, and premature atherosclerosis are also observed in CTX. Neuropsychiatric symptoms appear in patients in their late teens or early third decade. These symptoms include cognitive and intellectual impairment ranging from mild impairment to dementia; psychiatric symptoms, such as depression, hallucinatory behavior, suicidal tendency, and agitation; pyramidal involvement; cerebellar dysfunction (80%); extrapyramidal symptoms (parkinsonism, myoclonus, tremor, dystonia: 20%); seizures (50%); myopathy; and peripheral neuropathy.[26] Although neurological symptoms appear in patients in their late teens and early 20s, the diagnosis is usually confirmed in the 3rd decade of life when the patient is disabled.[27,28]

Diagnostic evaluation: the definitive diagnosis of CTX is achieved by genetic confirmation of the mutation. The biochemical assay showed elevated levels of serum and urine cholestanol and bile alcohols. The MRI classically shows bilateral cerebellar dentate microcalcifications and T2-weighted hyperintensity in supratentorial and deep gray matter (Figure 1B).[25] Electromyography (EMG) reveals axonal neuropathy. Multimodal evoked potentials show delayed central conduction times, and electoencephalography (EEG) shows diffuse slowing with paroxysmal discharges.[29]

Treatment: Oral chenodeoxycholic acid is a bile acid replacement that induces feedback inhibition of bile acid production. Chenodeoxycholic acid normalizes the cholestanol levels and improves symptoms except for established neurological involvement and juvenile cataract. In a study of 56 patients by Stelten et al.,[26] cerebellar and pyramidal signs improved when chenodeoxycholic acid was initiated before the age of 24 years, and new neurological symptoms did not develop when patients were adherent to treatment. If treated later, 61% of patients continued to worsen and develop treatment-resistant parkinsonism. The dose is 250 mg three times daily and 15 mg/kg/day in divided doses in children.[30] Cholic acid and HMG-CoA reductase inhibitors (statins) are also useful in combination. Xanthomas are often surgically excised for cosmetic reasons.

Practice point: Clinicians should suspect and screen for CTX when early cataract and nonspecific gastrointestinal symptoms are observed in a child or young adult with or without neurolog-

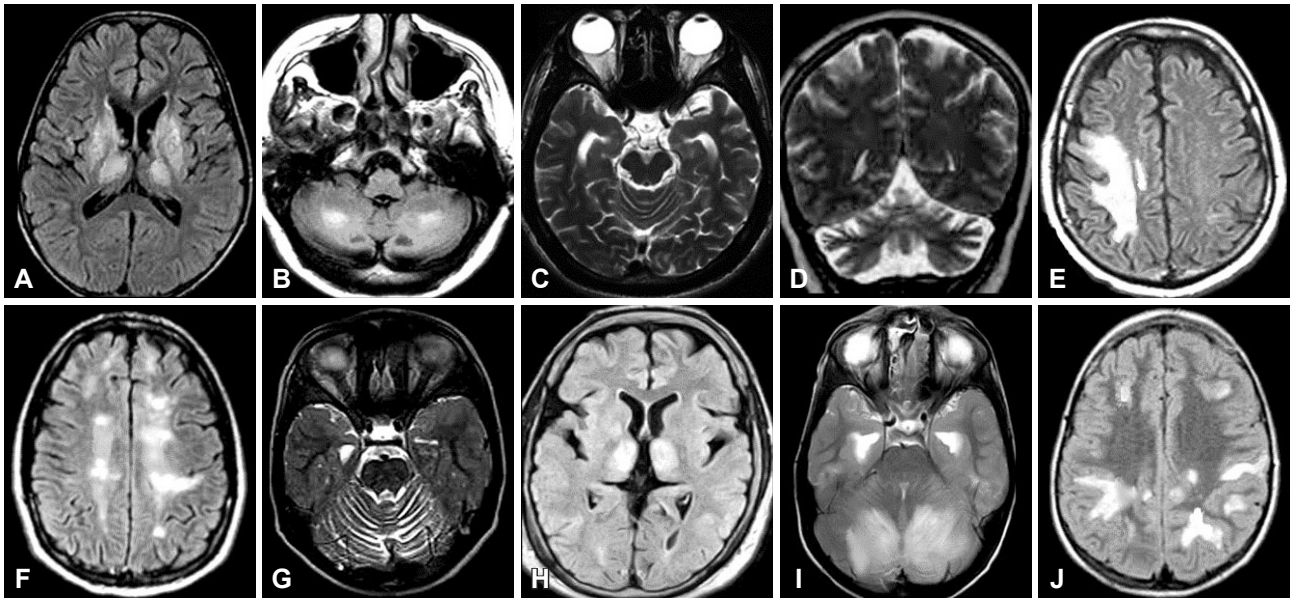

Figure 1. Representative MRI images of treatable disorders that manifest with ataxia. A: Axial FLAIR image showing hyperintense signals in the thalamus and basal ganglia in a patient with Wilson disease. B: Axial FLAIR images showing hyperintense signals in the dentate and surrounding cerebellar white matter in a patient with cerebrotendinous xanthomatosis. C: Axial T2-weighted image showing mild cerebellar atrophy in a patient with Niemann-Pick C disease. D: Coronal T2-weighted image showing cerebellar atrophy in a patient with Sjogren's syndrome. E: Axial FLAIR images show multifocal, asymmetric hyperintense signals in a patient with progressive multifocal leukoencephalopathy. F: Axial FLAIR image shows multifocal, asymmetric hyperintense signals in a patient with multiple sclerosis. G: Axial T2-weighted image showing cerebellar atrophy in a patient with alcohol-induced cerebellar ataxia. H: Axial FLAIR image showing hyperintense signals in the bilateral dorsomedial thalami in a patient with Wernicke encephalopathy. I: Axial T2 FLAIR image showing hyperintense signals in the bilateral cerebellum in a patient with acute cerebellitis. J: Axial T2 FLAIR image showing asymmetric and multifocal hyperintensity in a patient with acute disseminated encephalomyelitis (ADEM). FLAIR, fluid-attenuated inversion recovery.

ical symptoms.

Niemann-Pick disease type C

Niemann-Pick disease type C (NPC) is caused by biallelic or compound heterozygous mutations in the *NPC-1* (95%) and *NPC-2* (5%) genes and has an autosomal recessive inheritance pattern. NPC is a neurovisceral disease characterized by sequestration of non-esterified cholesterol in lysosomes. The prevalence of the disease is estimated to be 1 in 150,000 population.

Clinical features: clinical features may appear anytime from the neonatal period to late adulthood. The most prevalent forms of the disease include juvenile and adult-onset variants. The visceral signs as well as psychiatric and neurological symptoms and signs in NPC may follow a different course independent of each other, leading to significant heterogeneity in symptoms.[31,32] However, in most cases, systemic symptoms appear before the neurological symptoms. The most common systemic clinical features include an enlarged spleen and pulmonary involvement with respiratory failure secondary to alveolar proteinosis and aspiration pneumonia. Neurological symptoms include cerebellar ataxia, vertical supranuclear palsy, cerebellar dysarthria, cognitive impairment, and abnormal movements, such as dystonia, myoclonus, parkinsonism, and chorea. Vertical supranuclear palsy is often not easily discernible until late in the disease.[18,21] Nonspecific psychiatric symptoms and seizures are noted in a minority of patients. A characteristic finding in several patients is laughter-induced cataplexy.[32]

Diagnostic evaluation: according to the revised diagnostic algorithm for NPC, if the suspicion index for NPC is high, a biomarker profile consisting of oxysterols (oxidation products of cholesterol), such as olestane-3β,5α,6β-triol (C-triol) and 7-ketocholesterol; lysosphingolipids, such as lysosphingomyelin-509 (Lyso-SM-509); or bile acids, specifically 3β,5α,6β-trihydroxycholanoyl-glycine, may be used.[18,33] However, these tests are not available widely. Diagnosis can also be confirmed by the characterization of NPC genes and can be used either for confirmation after the biomarker profile or as the first-line if the clinical suspicion is very high. The filipin staining test on skin fibroblasts is no longer favored as the initial screening test. This test is currently used to assess whether novel variants of NPC mutations have functional significance.[18,33,34] Brain MRI may show nonspecific changes, such as cerebral (predominantly frontal) and cerebellar atrophy, T2 signal hyperintensities in white matter, particularly of parietooccipital periventricular regions, deep gray matter atrophy of the thalamus, hippocampus, putamen, caudate, cerebellum, and insular region (Figure 1C).[32] MR spectroscopy may detect changes earlier, but only limited data are available.[31]

Treatment: no treatment has conclusively been demonstrated

to benefit patients with NPC. However, some may benefit from the use of miglustat. Studies have shown that miglustat may delay the progression of neurological manifestations when started as soon as neurological symptoms appear. The miglustat dose is 600 mg daily in three divided doses for adults and adolescents.[35] For children, the dose must be calculated based on body surface area. The adverse effects are mostly limited to gastrointestinal symptoms, weight loss, and tremors. The use of cholesterol-lowering agents does not change the clinical course. Cyclodextrin and arimoclomol show clinical benefit in preliminary studies but have yet to be confirmed in clinical trials.[36]

Practical point: clinicians should suspect and screen for NPC in young people with progressive cerebellar ataxia and vertical supranuclear gaze palsy. A high index of suspicion is required for the early diagnosis of NPC.

Refsum's disease

Refsum's disease is caused by mutations of the peroxisomal phytanoyl-CoA hydroxylase (*PHYH*) gene and is rarely due to *PEX7* gene mutations. Refsum's disease is also called hereditary motor and sensory neuropathy IV. Phytanoyl-CoA hydroxylase is involved in the alpha oxidation of phytanic acid, whereas the *PEX7* gene product is a signal receptor for the transport of peroxisomal proteins from the cytoplasm into peroxisomes. Phytanic acid is a branched-chain fatty acid produced from chlorophyll in the diet. The mutation causes the phytanic acid level to increase and be stored in body fat. It produces toxicity to neuronal tissues by unknown mechanisms. It is inherited as an autosomal recessive disorder and has an estimated prevalence of 1 in 1,000,000 people.[37,38]

Clinical features: onset typically occurs in adolescents and young adults. The first reported symptom is deteriorating vision, which presents as night blindness due to retinitis pigmentosa and anosmia. Other systemic clinical features include ichthyotic skin lesions, sensorineural hearing loss, skeletal abnormalities, arrhythmia, and renal failure. Approximately one decade after the onset of clinical symptoms, neurological involvement begins in the form of polyneuropathy and cerebellar ataxia.[39,40] The ataxic symptoms are most commonly due to peripheral polyneuropathy until late in the disease when cerebellar ataxia also appears. No appreciable cognitive impairment is noted. Periodic worsening and clinical presentation similar to Guillain−Barre syndrome (GBS) is observed when phytanic acid is mobilized rapidly into peripheral blood during stress, rapid weight loss or illness.[18,21,40]

Diagnostic evaluation: in patients with a high index of suspicion, clinical diagnosis can be complemented by measuring the plasma phytanic acid levels, which are typically > 200 μmol/L (normal < 15 μmol/L). Mutation analysis of the gene by Sanger sequencing or NGS techniques is diagnostic. There is albuminocytological dissociation is noted, and the cerebrospinal fluid (CSF) protein concentration is usually between 100 and 600 mg/dL. In people with polyneuropathy, nerve conduction studies show slowed conduction velocity. Biopsy of the peripheral nerve shows hypertrophy with onion bulb formation.[18,21,38,41]

Treatment: dietary restriction, such as reducing the daily intake of phytanic acid (meat, dairy products, animal fats) to less than 10 mg per day, halts disease progression. Green vegetables have fewer free phytols and may be included in the diet. For acute symptoms, plasma exchange of chronic lipid apheresis is used in conjunction with diet changes. Plasmapheresis removes phytanic acid from the blood and not from adipose or other tissues.[42-44] Strict controls lead to improvement in peripheral neuropathy and ataxia first followed by ichthyosis. Retinitis pigmentosa, hearing, and olfactory disturbances usually do not improve.[38,39]

Practical point: a tetrad of cerebellar ataxia, polyneuropathy, retinitis pigmentosa, and albuminocytological dissociation should prompt evaluation for Refsum's disease.

Glucose transporter type 1 deficiency

Glucose transporter type 1 (GLUT1) deficiency syndrome is an autosomal dominant disorder caused by mutations in the GLUT1 transporter (*SLC2A1*). The condition causes a disturbance in glucose transport across the blood−brain barrier, resulting in an "energy crisis" in the brain.[45]

Clinical features: GLUT1 deficiency presents with heterogeneous clinical manifestations, and atypical presentations are very common. The most frequent clinical features include intellectual disability, dysarthria, ataxia, limb and face dystonia, treatment-resistant infantile-onset seizures (multiple types), and a decrease in head circumference. An age-specific pattern is recognized in GLUT1. In infancy, seizures and paroxysmal eye-head movements are observed. The impairment in growth and development becomes noticeable as the child ages. This feature is usually followed by ataxia (70%), spasticity and dystonia. During the adolescent period, these movement disorders may predominate the clinical picture. Chorea and tremor are also observed.[46] Movement disorders may be paroxysmal in a few individuals and are precipitated by fatigue, physical activity, anxiety, fasting, anxiety, and poor compliance with the diet. Other paroxysmal symptoms include behavioral disturbances, cyclical vomiting, migraines, and sleep episodes.[45,47,48]

Diagnostic evaluation: the diagnosis is established by a lumbar puncture with low CSF glucose and low to normal CSF lactate levels with normal glucose and lactate levels in blood and a CSF/blood glucose ratio of 0.4. Lumbar puncture should be performed after a minimum of 4 to 6 hours of fasting, and blood glucose should be measured immediately before lumbar punc-

ture.[18,21] An erythrocyte glucose uptake assay showing impaired 3-O-methyl-D-glucose uptake is also a sensitive test for GLUT1 deficiency. MRI scans are useful to exclude the causes of other epileptic encephalopathies and movement disorders.[21] An fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan shows hypometabolism from the thalamus, cerebellum, and cerebral cortex with an increase in glucose accumulation in the caudate nucleus.[47,49,50] Identification of the underlying genetic variation is also useful in the diagnosis. However, according to the latest recommendations of the International Glut1DS study group, although the identification of pathogenic variants of *SLC2A1* is confirmatory, its absence does not exclude GLUT1 deficiency given that variations, such as deletions, duplications, noncoding RNA and downstream defects in Glut1 transcription, translation, processing, activation and trafficking, can also cause GLUT1 deficiency.[47]

Treatment: a ketogenic diet improves clinical symptoms by 40%−70% and halts disease progression. Development delay and movement disorders respond only partially to the ketogenic diet. The use of antiepileptics remains controversial, but levetiracetam, valproic acid, and lamotrigine have been used in different centers. For paroxysmal events unresponsive to seizure medication, alpha-lipoic acid triheptanoin and acetazolamide have been tested with variable responses.[49,50] Patients on a ketogenic diet should be monitored regularly for long-term side effects, such as kidney stones, growth retardation, and cardiovascular disease.[47-50]

Practical point: GLUT1 deficiency should be assessed in individuals with unexplained movement disorders, early-onset drug-resistant epilepsy of multiple types of seizures, and paroxysmal motor and nonmotor events at any age.

Episodic ataxia type 2

Episodic ataxia 2 (EA2) is an autosomal dominant disorder caused by *CACNA1A* gene mutations. Sporadic cases with de novo mutations are also known. This gene encodes the alpha subunit of the P/Q-type calcium channel.[51]

Clinical features: the clinical features of EA2 begin in early childhood (< 20 years) but may also manifest late (> 50 years). EA2 is characterized by recurrent episodes of ataxia lasting hours to days and may have a frequency of a few times per year to more than four episodes per week. In addition to ataxia, attacks may be characterized by symptoms, such as downbeat nystagmus, nausea, dysarthria, vertigo, and truncal ataxia.[18,21] Approximately 50% of patients may complain of vestibular migraine. Rarely, patients may also present with myasthenic symptoms. Episodes are usually precipitated by alcohol intake and stress due to physical or emotional causes. During the interictal period, the patient may be asymptomatic or may have interictal nystagmus, impaired suppression of the vestibulo-ocular reflex, gaze-holding deficits, saccadic pursuits, and bilateral internuclear ophthalmoplegia. A few patients may also have subtle ataxic and postural symptoms, and dystonia is also rarely observed.[52-54]

Diagnostic evaluation: in suspected clinical cases, confirmation should be performed by identifying the underlying genetic mutation. In long-standing cases of EA2, brain MRI may show midline anterior cerebellar vermis atrophy.[51]

Treatment: A majority of EA2 patients show a good response to acetazolamide at a dose of 250 to 1,000 mg/day. The use of the potassium channel blocker 4-aminopyridine at a dose of 5 mg thrice daily reduces the frequency of attacks.[18,21]

Practice points: EA2 should be suspected in patients with paroxysmal ataxia with or without brainstem symptoms.

Other disorders in this class include ataxias due to coenzyme Q10 deficiency, guanidoacetate methyltransferase deficiency, biotinidase deficiency, cerebral folate deficiency, pyruvate dehydrogenase complex deficiency, Wilson disease, aceruloplasminemia, riboflavin transporter deficiency neuronopathy, and thiamine transporter deficiency. The salient clinical features, diagnosis, and treatment are provided in Table 1.

Treatable ataxias associated with autoimmunity

Ataxic disorders associated with autoimmunity encompass a large, heterogeneous group of acute to subacute ataxias that occur due to neuronal dysfunction or cell death caused by immune-mediated mechanisms. Many of these disorders have known triggers (e.g., GBS), have well-characterized anti-neuronal antibodies, or are characterized as primary autoimmune cerebellar ataxia.

Guillain−Barre syndrome

Variants of GBS, such as the Miller Fisher (MF) variant and Bickerstaff encephalitis (BE), can present with noncerebellar ataxia. GBS is triggered by an antecedent infection that evokes an immune response to myelin or axons of the peripheral nerve due to molecular mimicry by cross-reacting epitopes. The most common cause of antecedent infection is *Campylobacter* infection. GBS has an annual incidence of 1−2 per 100,000 persons. It affects men more often than women.[55,56]

Clinical features: the clinical presentation is usually acute to subacute after an infection of the respiratory or gastrointestinal system. The MF variant presents with ataxia, ophthalmoplegia with retained pupillary reflexes, areflexia, and weakness. In many patients, the clinical picture may be incomplete, and patients may present with ophthalmoplegia without ataxia or acute ataxia without ophthalmoplegia. The BE variant usually presents with encephalopathy, hyperreflexia, ophthalmoplegia, and ataxia.[55-58]

Diagnostic evaluation: the diagnosis is based on clinical examination with supportive evidence from investigations. There

J Mov Disord 2022;15(3):206-226

Table 1. Genetic and metabolic causes of treatable ataxias

Number	Condition and gene	Clinical feature	Diagnostic evaluation	Treatment
1	CoQ10 deficiency[111-113] Gene(s): *APTX*, *ADCK3*, or *ANO10*	Autosomal recessive inheritance. Cerebellar ataxia, myopathy, nephropathy, encephalomyopathy, severe infantile multisystemic disease. Pyramidal signs and eye movement abnormalities develop later.	Measurement of CoQ10 in skeletal muscle by high-performance liquid chromatography.	CoQ10 supplement at 30 mg/kg/day in three divided doses. Replacement of CoQ10 has variable responses ranging from good response to lack of any clinical benefit.
2	GAMT deficiency[114-116] Gene: *GAMT*	Autosomal recessive inheritance Developmental delay, intellectual disability, speech impairment, and behavioural disturbances such as aggression, hyperactivity, autistic features, and self-mutilation in the first year of life. Pyramidal signs, multiple seizure types, ataxia, dystonia, chorea, hemiballism. and hypotonia is seen. Leigh syndrome and mitochondrial encephalopathy-like presentations are reported.	Sequencing of the *GAMT* gene is diagnostic Measurement of the creatine signal in the brain by proton magnetic resonance spectroscopy is used for screening. MRI shows T1 hypointensity and T2 hyperintensity in the basal ganglia, especially the globus pallidus. Higher levels of guanidinoacetate, and low levels of creatine in the urine, plasma, and/or CSF. Electoencephalography changes are non-specific with high-amplitude background activities and multifocal spikes.	Creatine (400 to 800 mg/kg/day, orally or enterally), L-ornithine (400 to 800 mg/kg/day orally or enterally), Arginine-restricted diet (less than 250 mg/kg/day) to decrease the levels of GAA. Early treatment has a beneficial effect on intellectual and behavioural outcomes, seizures, extrapyramidal symptoms, and MRI changes.
3	Biotinidase deficiency[117-119] Gene: *BTD*	Autosomal recessive inheritance. Ataxia, hypotonia, seizures, eczematous skin rash, alopecia, feeding problems, developmental delay, hearing loss, optic atrophy, conjunctivitis, susceptibility to viral and fungal infections.	Low biotinidase activity in serum, plasma, fibroblasts, leukocytes and other tissue by radioassay. High serum ammonia and lactate levels. 3-hydroxypropionate in urine organic acid analysis. MRI shows cerebral atrophy, calcifications of basal ganglia, subdural effusions, T2 and FLAIR hyperintensities in bilateral hippocampi and parahippocampal gyri. Late-onset biotinidase deficiency has spinal cord involvement on MRI. Sequencing of *BTD* gene.	Biotin at a dose of 5–20 mg/day Rapid improvement in seizures, cutaneous symptoms, ataxia, alopecia, skin rash, and developmental delay. Auditory and visual defects usually do not resolve despite treatment.
4	Cerebral folate deficiency[120-123] Gene: *FOLR1*; auto-antibodies against folate receptors	Autosomal recessive inheritance. Ataxia, hypotonia, developmental delay, psychomotor retardation, deceleration of head growth, irritability, spasticity, chorea, dystonia, seizure.	Lower levels of 5MTHF in CSF with normal folate levels in serum and red blood cells. MRI may be normal or show frontotemporal atrophy and/or T2 hyperintensity in periventricular and subcortical white matter. Sequencing of *FOLR1* gene.	Folinic acid at a dose of 1mg/kg body weight for at least a year improves clinical symptoms and normalize the 5-MTHF in the CSF. A milk-free diet also improves clinical symptoms if started early.
5	Pyruvate dehydrogenase complex deficiency[124-126] Gene (s): *PDHA1*, *PDHX*, *PDHB*, *DLAT*, *PDP1* and *DLD*	X linked recessive (*PDHA1*), Autosomal recessive (*PDHX*, *PDHB*, *DLAT*, *PDP1* and *DLD*) inheritance. Intermittent or continuous ataxia, microcephaly, developmental delay, seizures, hypotonia, peripheral neuropathy, dystonia, paroxysmal exertional dyskinesia.	Low pyruvate dehydrogenase complex enzyme activity in, lymphocytes, skeletal muscle, and cultured fibroblast. MRI brain shows cerebral atrophy, asymmetric ventriculomegaly, corpus callosum dysgenesis, T2 hyperintensity in basal ganglia and brainstem. High lactate, pyruvate, alanine in plasma and CSF with normal lactate to pyruvate ratio. Sequencing of Pyruvate dehydrogenase complex related genes.	Ketogenic diet and restriction of branched-chain amino acid, oral thiamine (300–1000 mg/day), oral riboflavin (220–400 mg/day).
6	Wilson disease[127-129] Gene: *ATP7B*	Autosomal recessive inheritance. Dystonia, parkinsonism, tremor, liver disease, cognitive dysfunction, ataxia. Kayser Fleischer ring may be present. A pure cerebellar syndrome is usually uncommon.	Low to low normal ceruloplasmin and copper levels. High level of hepatic copper. Kayser-Fleisher ring on slit-lamp examination. MRI brain showed bilateral T2 hyperintensity involving putamen, thalami, and brainstem (Figure 1A). Gene sequencing in inconclusive cases.	D-penicillamine, trientine, zinc, dietary restriction of copper-rich, hepatic transplantation.

Table 1. Genetic and metabolic causes of treatable ataxias (continued)

Number	Condition and gene	Clinical feature	Diagnostic evaluation	Treatment
7	Aceruloplasminemia[130,131] Gene: *CP*	Cognitive dysfunction, ataxia, dystonia, chorea, dysarthria, developmental delay, parkinsonism, retinal degeneration, diabetes mellitus, anaemia.	Low serum ceruloplasmin and serum copper. Higher serum ferritin, iron and hepatic iron. MRI shows decreased T2 signal intensity in the basal ganglia.	Iron chelating agents and fresh-frozen human plasma
8	Riboflavin transporter deficiency neuronopathy[132,133] Gene(s): *SLC52A2*, *SLC52A3*	Ataxia, tongue fasciculations, nystagmus, muscle weakness, failure to thrive, developmental delay, respiratory insufficiency, nystagmus, sensorineural deafness, optic atrophy.	Abnormal acylcarnitine profile (elevated short, medium or long-chain species). MRI may be normal or show cerebellar atrophy. Increased T2 intensity in the brainstem and cerebellum.	Riboflavin (220–400 mg/day)
9	Thiamine transporter deficiency[134,135] Gene(s): *SLC19A2*, *SLC19A3*	Recurrent ataxia, dystonia, dysarthria, nystagmus, external ophthalmoplegia, seizures, spasticity, eye movement abnormalities, encephalopathy, dysphagia, facial palsy, developmental delay.	CSF and blood lactate may be high. MRI brain shows atrophy of caudate and putamen and swelling of the pons.	Biotin (5–20 mg/day), thiamine (300–1,000 mg/day)

CoQ10, coenzyme Q10; GAMT, guanidoacetate methyltransferase; FLAIR, fluid-attenuated inversion recovery; CSF, cerebrospinal fluid; 5-MTHF, 5-methyltetrahydrofolate.

is no one specific test that can conclusively diagnose GBS. CSF analysis shows albuminocytological dissociation. Electrodiagnostic tests show features of demyelination, and brainstem auditory evoked potentials show peripheral and central conduction defects. MRI may show spinal root and cauda equina thickening and enhancement but is used only to exclude alternate pathologies. The presence of serum IgG antibodies to GQ1b is useful for the diagnosis of MF and BE.[18,21,55,58-60]

Treatment: plasma exchange and intravenous immunoglobulins have some value in the treatment of MF and BE, although no randomized control trial studies have been performed. MF and BE without complications, such as respiratory disease and dysphagia, do not usually require immunotherapy. Recently, clinical trials have established the safety and efficacy of eculizumab, and eculizumab can be used along with IVIg. Greater than 87% of patients have a favorable prognosis and recover.[55,59,61,62]

Practical point: GBS should be suspected in cases presenting with acute or subacute onset of ataxia, weakness, or ophthalmoparesis.

Multiple sclerosis

Multiple sclerosis (MS) is an immune-mediated, autoinflammatory disorder caused by autoreactive lymphocytes and microglial activation, leading to demyelination and degeneration. MS more commonly affects women than men. Greater than 200 genetic loci are associated with a higher risk for MS.[63] The most frequent gene polymorphism associated with MS is major histocompatibility complex class 1 and II (*HLA-DRB1*).[64] The prevalence and incidence vary depending on the geographical region, latitude, race, sunlight exposure, and vitamin D levels.[18,21,65]

Clinical features: MS is a clinically heterogeneous disease and has variable clinical symptoms. Ataxic manifestations are observed in 50% of children < 5 years and less than 20% of adolescents.[21,66,67] Cerebellitis may manifest as a clinically isolated syndrome or may be part of the progressive or relapsing forms of MS. Acute symptoms are initially noted and may last for a few months.[18,21,66,67]

Diagnostic evaluation: the diagnosis is mostly clinical and based on supportive investigations.[68] A brain MRI with contrast shows T2-weighted hyperintense lesions with/without enhancement in the brainstem, periventricular white matter, cerebellum, and spinal cord (Figure 1F).[69] CSF shows oligoclonal bands with a modest increase in protein and white blood cell levels in several patients.[68]

Treatment: patients with ataxic manifestations may benefit from a short course of intravenous glucocorticoids in the acute phase. Other disease-modifying agents, such as beta interferons, glatiramer acetate, or intravenous immunoglobulin, may delay progression.[70]

Practical point: subacute onset of ataxia with clinical features of MS should prompt the consideration of MS as a differential diagnosis.

Gluten ataxia

Gluten ataxia is an idiopathic ataxic disorder associated with gluten sensitivity and is related to celiac disease. Antibodies are formed against gliadin in gluten, which cross-reacts with the cerebellum. Gluten ataxia is more prevalent in people with northern European ancestry.[71]

Clinical features: gluten ataxia presents with slowly progressive gait and limb ataxia, dysarthria, and ocular signs, such as gaze-evoked nystagmus and saccade and pursuit eye movement abnormalities. Clinical onset is typically noted in the fifth or sixth decade. The majority of people (approximately 90%) with gluten ataxia do not have gastrointestinal symptoms, although they may have histopathological features of gluten enteropathy. Few patients may also report symptoms suggestive of peripheral neuropathy, seizures, headache, anxiety, and depression. People with celiac disease may also have chronic malabsorption-related ataxic features due to hypovitaminosis.[18,21,71,72]

Diagnostic evaluation: an MRI or CT of the brain shows cerebellar atrophy in greater than 60% of patients. Elevated serum levels of antigliadin, tissue transglutaminase type 2, or tissue transglutaminase type 6 may be observed in many patients but are controversial. In patients with additional features of enteropathy, immunoglobulins against transglutaminase type 2 may be detected in small bowel biopsy specimens.[18,21,71,73] None of these diagnostic evaluations are highly sensitive or specific, and the diagnosis is confirmed on the basis of stabilization or improvement of symptoms through a gluten-free diet.[72-74]

Treatment: a strict gluten-free diet can improve neurological symptoms. However, if significant cerebellar atrophy has been established, partial to no recovery is expected. If present, treatment of hypovitaminosis is recommended.[18,21,72-74]

Practical point: gluten ataxia should be suspected in late-onset sporadic ataxia with or without enteropathy.

Hashimoto encephalopathy/steroid-responsive encephalopathy associated with autoimmune thyroiditis

Hashimoto encephalopathy/steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is a steroid-responsive disorder that may present with an uncommon ataxic syndrome. The exact cause is not known, but evidence points toward autoimmune vasculitis or immune complex deposition with resultant disruption of the cerebral microvasculature.[75,76]

Clinical features: the clinical presentation is usually heterogeneous with subacute onset of cognitive dysfunction with altered consciousness, psychiatric symptoms, myoclonus, tremor, seizures, and ataxia. The clinical picture may be confused with Creutzfeldt Jakob disease (CJD). A slowly progressive, sporadic, predominantly cerebellar phenotype mimicking spinocerebellar ataxia has also been reported.[18,21]

Diagnostic evaluation: elevated serum levels of thyroid peroxidase (TPO) and thyroglobulin antibodies are noted. However, the patient may be euthyroid on thyroid function tests. Antibodies against the neuronal alpha-enolase-NH2 terminal are a highly specific marker of ataxic variants of SREAT but have not yet been verified in large series.[77] An MRI brain may or may not reveal cerebellar atrophy. When present, atrophy is only minimal.[18,21,75,76]

Treatment: intravenous, high-dose methylprednisolone followed by a tapering dose of oral prednisone is the most common treatment protocol. Steroid sparing immunomodulators are also found to be useful in some patients.[21,75]

Practical point: in patients presenting with symptoms of CJD, SREAT should be assessed.

Glutamic acid decarboxylase antibody-associated ataxia

Glutamic acid decarboxylase (GAD) antibody-associated ataxia is a rare, sporadic ataxic disorder characterized by high titers of anti-GAD antibodies (anti-GAD 65). GAD antibody-associated ataxia mainly affects women more than men and is associated with other autoimmune disorders, such as type 1 diabetes mellitus, autoimmune thyroiditis, and pernicious anemia. GAD antibody-associated ataxia is typically diagnosed after the age of 20 years.[18,78]

Clinical features: The onset of symptoms is usually subacute or chronic. Gait ataxia is the most common feature. Large studies on people with high anti-GAD levels showed ataxia to be the most common neurological feature. Other cerebellar symptoms, such as limb incoordination, dysarthric speech, and ocular nystagmus, are also observed. In most cases, patients may have had episodes of double vision, speech dysarthria, or vertigo before cerebellar ataxia. Elevated titers of anti-GAD are also noted in stiff-person syndrome and refractory epilepsy with myoclonus.[79-81]

Diagnostic evaluation: the diagnosis is obtained by detecting high titers of anti-GAD antibodies in the serum or CSF. Despite the lack of a clear consensus, abnormal values are usually defined in studies as values greater than 2,000 U/mL (by radioimmunoassay), greater than 1,000 IU/mL or 20 nmol/L (by enzyme-linked immunosorbent assay [ELISA]) or by strong positivity at low dilutions (by immunohistochemistry). The presence of anti-GAD antibodies in CSF has more diagnostic significance for gluten ataxia than when noted in serum. ELISA and radioimmunoassay are also associated with more false-positive results; therefore, caution should be exercised when titers are low in a patient with

classical symptoms. In general, a titer of < 5 U/ml is considered normal. Imaging studies are usually normal or may show cerebellar atrophy. CSF analysis shows oligoclonal bands in two-thirds of patients.[79-81]

Treatment: previous studies suggest a good clinical response to plasmapheresis, glucocorticoids, intravenous immunoglobulin, mycophenolate, and azathioprine. A gluten-free diet is also recommended by a few experts. In general, people with subacute presentation respond better to immunotherapy and have a good long-term response and functional status.[18,79-81]

Practical point: anti-GAD antibodies should be assessed in individuals with ataxia with autoimmune disorders and stiff-person spectrum disorders.

Paraneoplastic cerebellar degeneration

Paraneoplastic cerebellar degeneration (PCD) is caused by anti-neuronal antibodies against tumor antigens that cross-react with intracellular neuronal proteins. The common malignancies associated with PCD include cancers of the female reproductive system and small cell carcinoma of the lung. Although all paraneoplastic antibodies are associated with cerebellar ataxia, only anti-metabotropic glutamate receptor 1 (mGluR1), anti-Yo, and anti-Tr (anti-Delta/Notch-like epidermal growth factor-related receptor) are consistently associated with cerebellar dysfunction.[82,83]

Clinical features: approximately 60% to 70% of patients with PCD do not have a cancer diagnosis at the onset of their neurologic symptoms. PCD is characterized by progressive ataxia (gait, truncal and appendicular ataxia), oscillopsia, diplopia, opsoclonus, nystagmus, dizziness, vertigo, nausea, vomiting, and dysarthria. Symptoms usually begin acutely or subacutely and continue to worsen for weeks to months. The symptoms are often severely disabling, and patients have almost no functional independence.[82-85]

Diagnostic evaluation: paraneoplastic antibodies should be assessed in blood and CSF. However, not all antibodies are available for commercial testing. Furthermore, a negative result does not exclude a paraneoplastic disorder. Evaluation should be performed to identify occult malignancy. Occasionally, despite rigorous evaluation, the primary malignancy is not found. An MRI brain is rarely useful for a positive diagnosis of PCD but helps exclude metastatic and cerebrovascular disease. In later disease, diffuse cerebellar atrophy is present. In some cases, contrast enhancement may be observed in the cerebellar folia during the acute phases. PET scans may reveal hypermetabolism in the cerebellum. CSF analysis may show mild pleocytosis and elevation of protein. Some patients may exhibit higher levels of 14-3-3 protein on immunoblotting as well as a double band as opposed to a single band in CJD.[18,21]

Treatment: the treatment is individualized and includes treatment of malignancy and immunomodulation using cyclophosphamide (preferred drug due to underlying cytotoxic T-cell mechanism of injury), corticosteroids, plasma exchange, tacrolimus, rituximab, or mycophenolate.[86-89] Improvement is variable and usually incomplete.

Practical point: PCD should be suspected in patients with underlying malignancies and cerebellar syndrome.

Other disorders in this class, such as sarcoidosis, systemic lupus erythematosus, Behcet's syndrome, Sjogren syndrome, autoimmune encephalitis, and paraneoplastic ataxias, are given in Table 2.

Infectious and parainfectious ataxias

Many infections can directly or indirectly affect the cerebellum. These infections can present acutely in the setting of an illness (e.g., meningoencephalitis and acute cerebellitis) or may have a subacute presentation (postinfectious ataxia) after a few days or weeks. Furthermore, some infections can cause slow evolution, such as Whipple's disease (WD).

Whipple's disease

WD is caused by *Tropheryma whipplei*, a non-acid fast, periodic acid-Schiff (PAS)-positive, rod-shaped, and Gram-positive bacillus. *T. whipplei* is a ubiquitous organism that rarely causes diseases in humans. Most previous reports of WD are from men of European ancestry and in people with occupational exposure to soil or animals. An unconfirmed increased association of WD with HLA-B27, HLA DRB1*13, and HLA DQB1*06 has been reported.

Clinical features: classic WD is a slowly evolving disease that presents with systemic features, such as migratory arthralgia followed by intermittent diarrhea, colicky abdominal pain, and wasting syndrome. Neurological involvement is observed in only 10% to 40% of classic WD cases and includes cognitive dysfunction, memory impairment, confusion, vertical supranuclear gaze palsy, oculomasticatory myorhythmia, and oculofacial-skeletal myorhythmia. Other neurological findings reported include seizure, myoclonus, peripheral neuropathy, hemiparesis, and upper motor neuron disorders.[90-94]

Diagnostic evaluation: endoscopic biopsy of the small intestine for *T. whipplei* testing is preferred. If the result was indeterminate, additional testing on specimens from other sites, such as synovial fluid, lymph nodes, and CSF, was also performed. Endoscopy should be performed even when gastrointestinal symptoms are absent.[91] The testing protocol should include histology with PAS-positive macrophages, immunohistochemistry, and polymerase chain reaction (PCR).[95] MRI or CT scans of the brain show nonspecific focal lesions that gradually resolve with treatment.[96] CSF analysis shows lymphocytic or monocytic pleocy-

Table 2. Treatable ataxias associated with autoimmunity

Number	Condition and classification	Clinical feature	Diagnostic evaluation	Treatment
1	Sarcoidosis [136,137]			
	Neurosarcoidosis	Neurosarcoidosis is the presenting feature in 5% of patients. Ataxic symptoms are seen in 13% of patients with neurosarcoidosis. Other presentations are cranial mononeuropathy, myelopathy, focal or multifocal encephalopathy, neuroendocrine dysfunction, aseptic meningitis, hydrocephalus, peripheral neuropathy, or myopathy. The course can be monophasic (approximately two-thirds of patients), relapsing-remitting type, or progressive disease.	MRI with contrast: meningeal or parenchymal enhancement, parenchymal or meningeal masses, and occasionally hydrocephalus are seen. CSF study: elevated proteins, mononuclear cell pleocytosis, normal glucose, elevated CSF ACE concentration (non-specific) and soluble interleukin 2 receptor (sIL-2r) levels. Elevated serum angiotensin-converting enzyme (ACE) levels. Biopsy shows characteristic lesions (naked granuloma).	Glucocorticoid therapy, immunomodulators such as mycophenolate mofetil, azathioprine, methotrexate, cyclophosphamide, infliximab, or adalimumab. Radiation can be attempted if sarcoidosis is refractory to medicines.
2	Systemic immune disorders and vasculitis[138,139]			
	Behçet syndrome	1) Behcet syndrome presents with headaches, cranial nerve palsies, seizures, cerebrovascular insufficiency, brainstem syndrome, cerebellar ataxia, and pseudobulbar palsy.	Behcet disease: pathergy test	Steroid pulse therapy and long-term immunosuppression with steroid-sparing agents.
	Sjögren syndrome	2) Sjogren's syndrome presents with polyneuropathy, spinal cord involvement, motor neurone symptoms, cognitive dysfunction, cerebellar ataxia.	Sjogren's syndrome: anti-Ro/SSA or La/SSB, salivary gland biopsy	
	Systemic lupus erythematosus	3) Systemic lupus erythematosus presents with psychiatric symptoms, dementia, seizures, long tract signs, cranial nerve abnormalities, peripheral neuropathy, cerebellar ataxia.	Systemic lupus erythematosus: ANA and anti-double-stranded DNA (anti-dsDNA)	
		In these disorders, ataxia is usually not reflective of sensory ataxia and does not occur secondary to stroke or seizure.	MRI may be normal or show cerebellar atrophy, T2 hyperintensity of the cerebellum and subcortical white matter of frontal and parietal lobes (Figure 1D).	
3	Autoimmune encephalitis [140-144]			
	Anti-mGluR2	Episodic ataxia, cerebellar syndrome (100%).	Testing for surface receptor antibodies in serum and CSF is necessary. Negative results do not rule out autoimmune encephalitis. Non-specific signals may cause false-positive results. The use of steroids may interfere with the test. All patients with autoimmune encephalitis should be screened for tumours. MRI findings are non-specific in different types of autoimmune encephalitis.	Methylprednisolone 1 g IV for 3–5 days and intravenous immunoglobulin (0.4 g/kg/day) for five days. Methylprednisolone and plasmapheresis are preferred in unresponsive seizures and autonomic dysfunction. Associated tumours if suspected should be identified and treated to improve the clinical condition. If there is no improvement, second-line treatment such as rituximab or cyclophosphamide should be given
	Anti-mGluR1	Cerebellar symptoms (100%), cognitive and psychiatric symptoms, peripheral neuropathy, myoclonus, and dysgeusia. Associated with Lymphoproliferative disorders.		
	Anti-DPPX	Cerebellar symptoms (77%), diarrhoea, weight loss, myoclonus, hyperekplexia, tremor, seizures, and progressive encephalomyelitis with rigidity and myoclonus (PERM). Associated with B-cell neoplasm.		
	Anti-glycine receptor	Cerebellar symptoms (47%), movement disorders, epilepsy, visual disturbances, demyelination, and cognitive dysfunction. Associated with thymoma, lymphoma, small cell lung cancer, and breast cancer.		
	Anti-IgLON5	Cerebellar symptoms (40%), cognitive decline, gait instability, parasomnia, bulbar dysfunction, and facial spasms.		
	Anti-CASPR2	Cerebellar symptoms (36%), neuropathic pain, cognitive impairment, autonomic dysfunction, Morvan syndrome, and tremors.		

Table 2. Treatable ataxias associated with autoimmunity (continued)

Number	Condition and classification	Clinical feature	Diagnostic evaluation	Treatment
	Anti-NMDAR	Cerebellar ataxia (5%), orofacial dyskinesia, psychiatric symptoms, dystonia, seizures, language difficulty, dysautonomia. Associated with ovarian teratoma, small cell lung cancer, testis teratoma, other solid tumours.		
	Anti-GABABR	Cerebellar ataxia (5%), limbic encephalitis, seizures, opsoclonus-myoclonus. Associated with small cell lung cancer.		
	Anti-GABAAR	Cerebellar ataxia (5%), refractory seizures, status epilepticus, opsoclonus-myoclonus, stiff-person syndrome. Associated with thymoma.		
		Antibodies against synaptic antigens or intraneuronal antigens lead to a neurological syndrome that may present as pure ataxia or ataxia with additional symptoms. The clinical course may be either acute, subacute, or chronic progressive		
4	Paraneoplastic ataxia [145-148]			
	Anti-Yo (Purkinje cell antibody type 1-PCA1)	Paraneoplastic cerebellar degeneration. Associated with breast, gynaecological tumours.	Antibodies should be assessed in blood and cerebrospinal fluid. A negative result does not exclude a paraneoplastic disorder. Evaluation should be done to identify the occult malignancy.	Treatment of underlying malignancy. Immunomodulation using cyclophosphamide, corticosteroids, plasma exchange, tacrolimus, rituximab, or mycophenolate.
	Purkinje cell antibody type 2 (PCA2)	Limbic and brainstem encephalitis, paraneoplastic cerebellar degeneration, Lambert-Eaton syndrome, peripheral neuropathy, autonomic neuropathy. Associated with small cell lung cancer		
	Anti-Hu (anti-neuronal nuclear antibody 1 - ANNA1)	Sensory neuropathy, brainstem encephalitis, paraneoplastic cerebellar degeneration, limbic encephalitis, encephalomyelitis, gastrointestinal pseudo-obstruction. Associated with small cell lung cancer.		
	Anti-Ri (ANNA2)	Brainstem encephalitis, opsoclonus myoclonus, paraneoplastic cerebellar degeneration. Associated with breast, gynaecological, small cell lung cancer.		
	Anti-CV2 (CRMP5)	Mixed neuropathies, isolated myelopathy, optic neuropathy, paraneoplastic cerebellar degeneration, limbic and diffuse encephalitis. Associated with small cell lung cancer, thymoma.		
	Anti-Ma 2	Limbic encephalitis, paraneoplastic cerebellar degeneration. Associated with testicular tumours.		
	Anti-Tr	Paraneoplastic cerebellar degeneration. Associated with Hodgkin's lymphoma.		
	Anti-glutamic acid decarboxylase 65 (GAD65)	Stiff-person syndrome, ataxia, limbic encephalitis, brainstem encephalitis, parkinsonism, myelopathy. Associated with thymoma, renal cell, breast and colon adenocarcinoma		
	Anti-ZIC4	Paraneoplastic cerebellar degeneration. Associated with small cell lung cancer.		
	Anti-mGluR1 (metabotropic glutamate receptor 1)	Paraneoplastic cerebellar degeneration. Associated with Hodgkin's lymphoma		
	Anti-Ma 1	Paraneoplastic cerebellar degeneration, Brainstem encephalitis. Associated with testicular, non-small cell lung cancer.		

SSA, anti-Sjogren's syndrome A; SSB, anti-Sjogren's syndrome B.

tosis and elevated protein levels. Occasionally, PAS-positive macrophages are also observed. In addition, protein levels may be elevated, and oligo-clonal bands may be present.[90,92,94,95]

Treatment: for WD with central nervous system involvement, ceftriaxone (2 g IV once daily) or penicillin G (4 MU IV every 4 hours) for two weeks followed by oral trimethoprim-sulfamethoxazole (one double-strength tablet (160/800 mg twice a day) for one year is the preferred regimen. An alternative regimen of doxycycline, hydroxychloroquine, and sulfonamide is also used.[91,97-99]

Practical point: WD should be suspected in patients with neurological involvement with four other cardinal manifestations (arthralgias, diarrhea, abdominal pain, and weight loss).

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) results from JC virus reactivation in immunocompromised people. PML is usually seen in patients with HIV-AIDS and MS on treatment with natalizumab. As the name suggests, it is progressive and multifocal and involves the white matter of the brain.[100]

Clinical features: it has a subacute clinical presentation with cerebellar ataxia, altered mental status, hemiparesis or monoparesis, hemianopia, and diplopia. The JC virus can also cause JC virus granule cell neuronopathy that can lead to cerebellar atrophy and ataxic symptoms.[101,102] Diagnostic evaluation: MRI brain shows multifocal lesions limited to white matter (Figure 1E). The lesions are not confined to vascular territories and do not show mass effects or contrast enhancement. Often, a pontine cruciate hyperintensity (termed the hot-cross bun sign) is appreciable in axial T2 and FLAIR sequences. The diagnosis of PML is confirmed by the detection of JC virus DNA by PCR assay on CSF. Other CSF findings are nonspecific in PML.[100-103]

Treatment: management is aimed at reversing the immunocompromised state. In PML with HIV infection, initiation and optimization of highly active antiretroviral therapy may stabilize or improve symptoms and prolong survival. If PML is associated with non-HIV related immunocompromise (e.g., natalizumab, calcineurin inhibitors, glucocorticoids, transplant recipients), it may be beneficial to stop the responsible agent. PML may be associated with immune reconstitution inflammatory syndrome, which causes marked neurologic deterioration and swelling of the brain and requires treatment with high-dose glucocorticoids.[101-104]

Practical point: PML should be suspected in immunocompromised hosts with ataxic symptoms.

Infectious and parainfectious ataxia due to meningoencephalitis, acute disseminated encephalomyelitis, acute cerebellitis, and acute postinfectious ataxia are provided in Table 3.

Miscellaneous ataxias

There are many other causes of ataxia that do not have an underlying genetic, infectious/parainfectious or immune-mediated etiology, including vascular causes of ataxia, toxins and chemicals, and endocrinopathies. Ataxia secondary to cerebellar ischemia, hemorrhage, and hematoma as well as nutritional causes, such as vitamin E, pernicious anemia, vitamin B12, copper, and tryptophan deficiencies, are not included. Mimics of cerebellar ataxia, such as large fiber sensory neuropathy, migraine headache with ataxic symptoms, normal pressure hydrocephalus, and functional ataxia, are also not included in this review.

Superficial siderosis

Superficial siderosis (SS) is a condition that results from hemosiderin deposition in the subpial layers of the cerebellum, brainstem, cranial nerves, and spinal cord due to chronic or intermittent extravasation of blood into the subarachnoid space.[105] The cerebellar ataxia type of presentation is observed in infratentorial SS and most likely due to exudation of blood from engorged, friable, or damaged intradural or epidural vessels.[105,106] SS is more commonly observed in men in the fourth to sixth decades of life.[105] Onset in young people may occur after intradural surgery.[107]

Clinical features: patients with SS have various combinations of gait and appendicular ataxia, myelopathy, or sensorineural hearing impairment. As the disease progresses, patients may also develop cerebellar dysarthria. Nystagmus is typically absent. Rare presentations include dementia, seizures, isolated lower motor neuron involvement, anosmia or hyposmia, and palatal tremor.[18,21]

Diagnostic evaluation: contrast-enhanced MRI of the brain and spinal cord is the investigation of choice in the initial work-up in patients with SS. The source of bleeding is identified in only approximately 50% of cases despite detailed imaging of the neuraxis.[105,107] The characteristic MRI findings are T2-weighted hyperintensities in the affected regions. Other changes include atrophy of cerebellum or cerebellar peduncles, hypertrophy and hyperintense inferior olivary nucleus, and T2 echo due to hemosiderin deposition.[108,109] Lumbar puncture is rarely performed to assess for active subarachnoid bleeding.

Treatment: identifying the source of the bleeding and its repair will prevent further disease progression. Iron chelators, such as deferiprone at a dose of 30 mg/kg/d, have shown clinical improvement in a few studies.[107] However, this response was not consistently reported.[105] Chelators should not be used routinely in SS due to the risk of neutropenic sepsis and agranulocytosis.[107] Cochlear implants are useful to improve hearing only when SS is less severe and stable.[110]

Practice point: screens for typical MRI findings should be performed in all patients with cerebellar syndrome and sensorineu-

Table 3. Infectious and parainfectious ataxias

Number	Condition	Clinical feature	Diagnostic evaluation	Treatment
1	Acute post-infectious ataxia[149-151]	Previous history of varicella, measles (children), Epstein-Barr or other viral infections and vaccinations (adolescents, young adults) about 6 to 8 weeks prior to the onset of symptoms. Symptoms include ataxia, vomiting, headache, fever, somnolence/lethargy, seizure, and irritability. The mechanism is through auto-antibodies and molecular mimicry.	MRI brain may show diffusion restriction and T2-weighted abnormalities in cerebellar hemispheres. It may also be normal in some patients.	Monophasic illness can spontaneously resolve. If complicated by oedema, additional intervention and treatment using glucocorticoids, surgical decompression, or ventriculoperitoneal shunting for hydrocephalus.
2	Meningoencephalitis[149,152]	Viruses such as varicella-zoster virus, Epstein-Barr virus, bacteria such as Streptococcus pneumoniae and Neisseria meningitidis are typical underlying causes. Atypical organisms such as Lyme, listeria, mycoplasma, tuberculosis, malaria can also cause meningoencephalitis. Symptoms include cerebellar ataxia with or without encephalopathy, headache, neck stiffness, and fever.	CSF examination shows characteristic changes depending on aetiology. Non-contrast CT may show if there is a risk of brain herniation and increased intracranial pressure. MRI may show a distended subarachnoid space, widening of interhemispheric fissure, leptomeningeal enhancement and complications such as hydrocephalus, cerebral edema, or stroke. Polymerase chain reaction assay can be used for rapid detection of causative pathogens. EEG may be useful to differentiate focal encephalitis from generalized encephalopathy (diffuse bihemispheric slowing).	Treatment and recovery are dependent on the underlying infectious agent.
3	ADEM[153-155]	Viruses: Epstein-Barr virus, cytomegalovirus, herpes simplex virus, human herpes-virus-6, influenza virus, hepatitis A, human immunodeficiency virus. Bacteria: Leptospira, beta-hemolytic streptococci, Borrelia burgdorferi, and mycoplasma. Vaccines and vaccine-preventable infections were previously common causes of ADEM. Symptoms include multifocal neurologic symptoms with encephalopathy with rapid deterioration. Symptoms include monoparesis, paraparesis, or quadriparesis. Sensory deficits and brainstem involvement with oculomotor deficits and dysarthria, headache, malaise, meningismus, ataxia, aphasia, optic neuritis, nystagmus, extrapyramidal movement disorders, seizures, and increased intracranial pressure.	MRI shows hyperintense lesions on T2-weighted, FLAIR, proton-density, and echo-planar trace diffusion MRI are typical. Lesions can be a single lesion or multiple lesions in the white and grey matter of the brain. Lesions are widespread, asymmetric, and bilateral and have indistinct margins. Infratentorial lesions of the cerebellum, brainstem, and spinal cord (Figure 1J). EEG may show a focal or generalized slowing of electrical activity.	Acyclovir or antibiotics on the initial patient presentation is recommended. Immunosuppression with high-dose intravenous glucocorticoids, intravenous immune globulin, plasma exchange, or cyclophosphamide.
4	Acute cerebellitis[156-159]	It is caused by direct infection of the cerebellum or following a systemic illness caused by rotavirus, mycoplasma, and human herpes virus. Symptoms include features of raised intracranial pressure, altered sensorium, irritability, cerebellar dysfunction.	MRI brain show features of cerebellar oedema, leptomeningeal enhancement, diffuse bihemispheric signal change (Figure 1I). Lumbar puncture is dangerous due to high risk of coning.	High-dose glucocorticoids, osmotic therapy, temporary CSF diversion, and rarely decompressive craniectomy to decrease CSF pressures.

ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; EEG, electoencephalography.

J Mov Disord 2022;15(3):206-226

Table 4. Miscellaneous treatable ataxias

Number	Condition	Clinical feature	Diagnostic evaluation	Treatment
1	Acquired hepatocerebral degeneration[160-162]	Acquired hepatocerebral degeneration is characterized by parkinsonism, ataxia, dystonia, chorea, orobuccal dyskinesia, and cognitive impairment, Sensorium is usually intact. It results from multiple episodes of decompensated liver failure.	MRI brain shows an increased signal of pallidum and other basal ganglia structures on T1-weighted images.	Liver transplantation improves neurologic manifestations
2	Hypothyroidism[163-165]	Severe and untreated hypothyroidism is associated with ataxia.	Thyroid function tests are abnormal.	Thyroid hormone replacement therapy
3	Wernicke encephalopathy[166,167]	Caused by a deficiency of thiamine and is associated with alcoholism, malnutrition, refeeding, and dialysis patients. It is characterized by a triad of ataxia, delirium, and ophthalmoplegia.	MRI brain shows hyperintense signal in the periventricular thalamus, mammillary bodies and periaqueductal gray matter (Figure 1H). Erythrocyte transketolase levels are low.	Parenteral thiamine
4	Hydrocephalus[168]	Intracranial mass lesions or haemorrhage may present with ataxia, headache, and vomiting with papilledema and paresis of lateral gaze.	MRI brain shows dilated ventricular system.	Emergent third ventriculostomy or external ventricular drainage and anti-cerebral oedema measures
5	Traumatic vertebral artery dissection[169-171]	Trauma may cause vertebral dissection and cause acute ataxia, headache, neck pain and vomiting. Trauma may worsen ataxic symptoms in certain conditions like vanishing white matter disease and episodic ataxia type 2.	Diffusion-weighted and MR angiography are non-invasive imaging tools that are useful. Digital subtraction angiography confirms the diagnosis.	Antiplatelet drugs
6	Pharmacological drugs[172-174]	Antiseizure medications: phenytoin, carbamazepine, oxcarbazepine, lacosamide, lamotrigine, rufinamide, and zonisamide, benzodiazepines, felbamate, phenobarbital, and valproic acid. Chemotherapeutic agents: cytarabine, vincristine, fluorouracil, capecitabine, procarbazine, hexamethylmelamine, cisplatin, methotrexate, and oxaliplatin	Urine and serum drug levels.	Decrease drug dose or change medicines
7	Toxins and chemicals[172-174]	Alcohol, carbon tetrachloride, heavy metals, phencyclidine, toluene, paraquat, phosphine, eucalyptus oil, shellfish poisoning, scorpion sting, cocaine, heroin, toluene, and phencyclidine may cause ataxic symptoms. In addition to cerebellar symptoms, there may be altered mentation, agitation, and seizures in cases of toxin exposure.	Urine and serum toxin levels. Non-specific cerebellar atrophy may be seen on MRI (Figure 1G).	Stop exposure to toxins and chemicals, use chelators, specific antidotes, hemodialysis

ral hearing loss.

Ataxic manifestations due to acquired hepatocerebral degeneration, hypothyroidism, hypoparathyroidism, Wernicke encephalopathy, hydrocephalus, traumatic vertebral dissection, drugs, and toxins are included in Table 4.

EVALUATION OF TREATABLE ATAXIAS

The heterogeneous presentations, poor knowledge of genotype-phenotype correlations, and rarity of these disorders make the diagnosis of specific ataxia a very challenging task. Although the diagnostic approach should be tailored to fit the clinical presentations of each patient, if everything fails, a shotgun approach of investigations can ensure that treatable ataxia is not missed. In resource-limited countries, a priority-based approach may help reduce the health care burden. A flowchart for narrowing down the clinical diagnosis is provided in Figure 2. This flowchart presents a simplified version of a tier-based approach to investigations followed by the authors of this review for diagnosis or to exclude treatable ataxic disorders. These investigations are classified into different tiers based on the authors' experience with the relative prevalence of different ataxic disorders and the cost and availability of investigations. We strongly suggest personalizing these tests in your practice.

Tier 1: MRI of the brain with contrast, complete blood count, renal function tests with electrolytes, liver function tests, fasting lipid profile, antinuclear antibody, vitamin E levels, copper and ceruloplasmin levels, HbA1c, thyroid stimulating hormone, anti-TPO antibodies, antithyroglobulin, vitamin B12/methylmalonic acid/homocysteine levels, and HIV tests.

Optional tests: nerve conduction tests/EMG (neuropathy), MRI spine (spasticity), EEG (seizures), and autonomic function testing.

Tier 2: cerebellar autoantibodies, antibodies associated with rheumatological disorders, alpha-fetoprotein, anti-GAD, ammo-

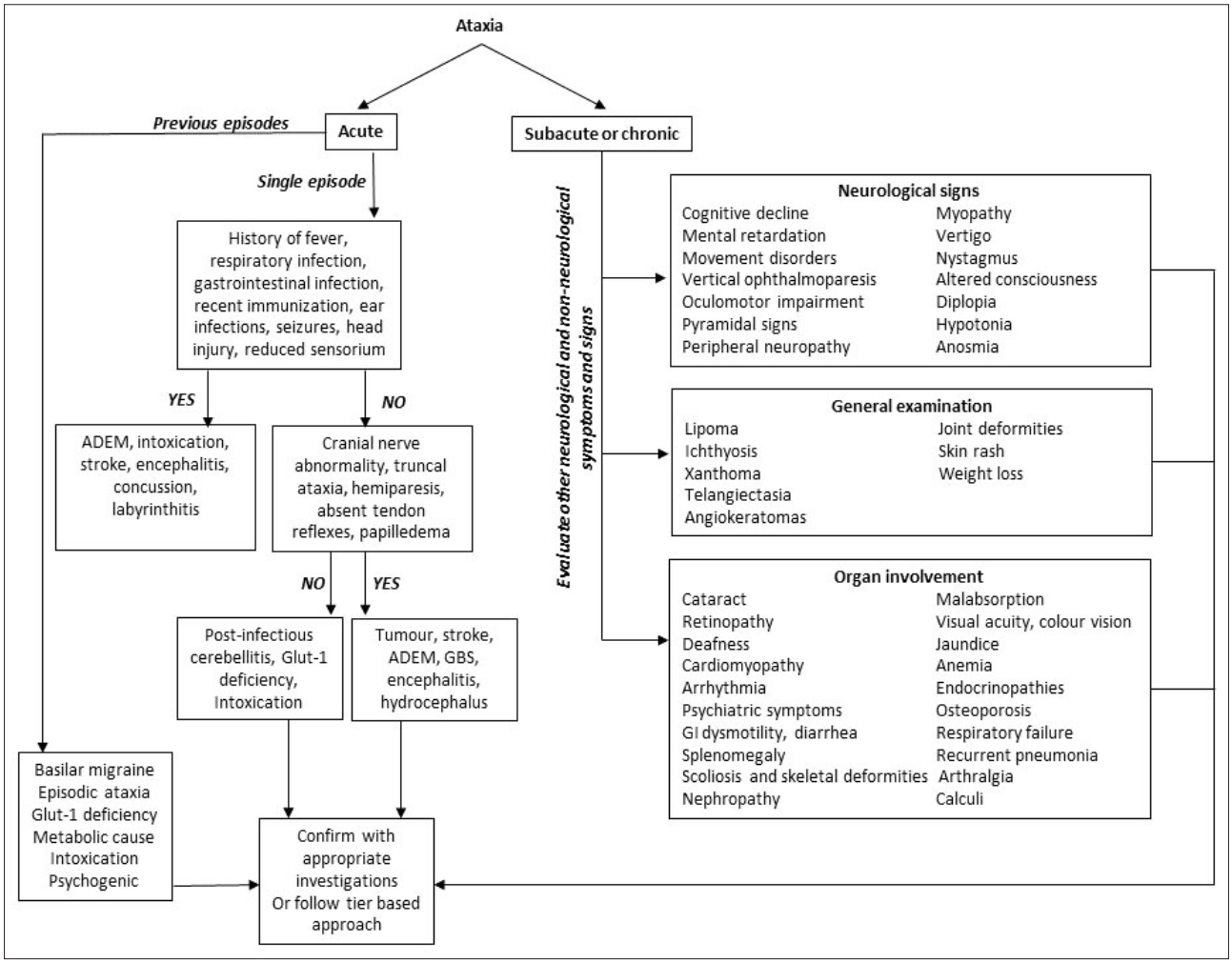

Figure 2. A diagnostic flowchart to identify treatable disorders that present with ataxic manifestations. ADEM, acute disseminated encephalomyelitis; GBS, Guillain–Barre syndrome.

nia, creatine kinase, ketones, lactate, pyruvate, blood or urine heavy metal screen, antigliadin antibody, serum and urine protein electrophoresis, urine for abnormal metabolites and organic acids. CSF tests are also performed in tier 2.

Optional tests: CT chest/abdomen/pelvis and PET scan (if positive cerebellar autoantibodies), anti-endomysial antibody and anti- tissue transglutaminase antibody (if positive celiac antibodies).

Tier 3: these tests are performed based on the presence of specific clinical signs, including lysosomal enzymes, plasma amino acids, skin biopsy, muscle biopsy, phytanic acid, and very long-chain fatty acids.

Optional tests: genetic tests (tier 1 if family history is present or if other biochemical tests for metabolic genetic diseases are unavailable), Sanger sequencing for specific genes, or NGS for full or targeted exome should be performed. NGS-based techniques are not useful to identify repeat expansion disorders. Genetic counseling session(s) are also recommended.

CONCLUSIONS

Identifying treatable ataxias is often likened to attempting to find a needle in a haystack. However, every attempt should be made not to miss treatable ataxias. This is especially pertinent because the timing of treatment can make a significant difference in the course of the disease and symptom reversal. Appropriate investigation can thus help find the 'needle' lost in the haystack and help institute specific treatments, which can help thread the needle (literally).

Conflicts of Interest

The authors have no financial conflicts of interest.

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