

Acute cerebellar ataxia: differential diagnosis and clinical approach

Ataxia cerebelar aguda: diagnóstico diferencial e abordagem clínica

José Luiz Pedroso*¹, Thiago Cardoso Vale*², Pedro Braga-Neto^{3,4}, Lívia Almeida Dutra^{1,5}, Marcondes Cavalcante França Jr⁶, Hélio A. G. Teive⁷, Orlando G. P. Barsottini¹

ABSTRACT

Cerebellar ataxia is a common finding in neurological practice and has a wide variety of causes, ranging from the chronic and slowly-progressive cerebellar degenerations to the acute cerebellar lesions due to infarction, edema and hemorrhage, configuring a true neurological emergency. Acute cerebellar ataxia is a syndrome that occurs in less than 72 hours, in previously healthy subjects. Acute ataxia usually results in hospitalization and extensive laboratory investigation. Clinicians are often faced with decisions on the extent and timing of the initial screening tests, particularly to detect treatable causes. The main group of diseases that may cause acute ataxias discussed in this article are: stroke, infectious, toxic, immune-mediated, paraneoplastic, vitamin deficiency, structural lesions and metabolic diseases. This review focuses on the etiologic and diagnostic considerations for acute ataxia.

Keywords: Cerebellar ataxia; cerebellum; cerebellar diseases.

RESUMO

A ataxia cerebelar é um achado comum na prática neurológica e tem uma grande variedade de causas, desde a degeneração cerebelar crônica e lentamente progressiva à lesão cerebelar aguda devido a infarto, edema ou hemorragia, configurando uma verdadeira emergência neurológica. Ataxia cerebelar aguda é uma síndrome que ocorre em menos de 72 horas em indivíduos previamente saudáveis. A ataxia aguda geralmente resulta em hospitalização e extensa investigação laboratorial. Os clínicos são frequentemente confrontados com a decisão sobre a extensão e o momento dos testes de rastreio iniciais, em particular para detectar as causas tratáveis. O principal grupo de doenças que podem causar ataxias agudas discutidas neste artigo são: acidente vascular cerebral, infecciosas, tóxicas, imunomediadas, paraneoplásicas, deficiência de vitaminas, lesões estruturais e doenças metabólicas. Esta revisão enfoca a etiologia e considerações diagnósticas para a ataxia aguda.

Palavras-chave: Ataxia cerebelar; cerebelo; doenças cerebelares.

Cerebellar ataxia is a term that comprises a wide spectrum of neurological disorders with ataxia as the main symptom, and clinically denotes loss of balance and coordination. Furthermore, ataxia may be caused by disturbances in several

parts of the nervous system (e.g., cerebellum, brainstem, spinal cord, and peripheral nerves)¹.

Cerebellar ataxia is a common finding in neurological practice and has a wide variety of causes. Ataxias can

¹Universidade Federal de São Paulo, Departamento de Neurologia e Neurocirurgia, Unidade de Neurologia Geral e de Ataxias, São Paulo SP, Brasil;

²Universidade Federal de Juiz de Fora, Departamento de Clínica Médica, Serviço de Neurologia do Hospital Universitário, Juiz de Fora MG, Brasil;

³Universidade Federal do Ceará, Departamento de Medicina Clínica, Divisão de Neurologia, Fortaleza CE, Brasil;

⁴Universidade Estadual do Ceará, Centro de Ciências da Saúde, Fortaleza CE, Brasil;

⁵Faculdade Israelita de Ciências da Saúde Albert Einstein, Hospital Israelita Albert Einstein, São Paulo SP, Brasil;

⁶Universidade Estadual de Campinas, Departamento de Neurologia, Campinas SP, Brasil;

⁷Universidade Federal do Paraná, Hospital de Clínicas, Departamento de Medicina Interna, Serviço de Neurologia, Setor de Distúrbios do Movimento, Curitiba PR, Brasil.

Hélio Teive  <https://orcid.org/0000-0003-2305-1073>; Orlando Barsottini  <https://orcid.org/0000-0002-0107-0831>; Pedro Braga-Neto 

<https://orcid.org/0000-0001-9186-9243>; Lívia Dutra  <https://orcid.org/0000-0001-6309-9077>; Marcondes  <https://orcid.org/0000-0003-0898-2419>;

José Luiz Pedroso  <https://orcid.org/0000-0002-1672-8894>; Thiago Cardoso Vale  <https://orcid.org/0000-0001-6145-9868>

*These authors contributed equally to this work.

Correspondence: Orlando Barsottini; Departamento de Neurologia e Neurocirurgia, Unidade de Neurologia Geral e de Ataxias da UNIFESP; São Paulo, SP, Brasil. E-mail: orlandobarsottini@gmail.com

Conflict of interest: There is no conflict of interest to declare.

Received 18 September 2018; Received in final form 23 November 2018; Accepted 02 December 2018.

be subdivided into six major groups: autosomal dominant spinocerebellar ataxias, autosomal recessive ataxias, congenital ataxias, mitochondrial ataxias, X-linked cerebellar ataxias and sporadic or acquired ataxias^{1,2}. Acute cerebellar syndromes are usually acquired, non-genetic and often a neurological emergency. There is little medical literature on acute cerebellar syndromes, mainly due to their heterogeneity. Although the exact incidence is unknown, acute ataxia usually results in hospitalization and extensive laboratory investigation. Clinicians are often faced with deciding the extent and timing of initial screening tests in order to detect treatable causes³.

Acute cerebellar ataxias (ACA) are more common in childhood, often presenting as a post-infectious disorder⁴. The main group of diseases that may cause ACA discussed in this article are listed in Table 1 and include: stroke, infectious, toxic, immune-mediated, paraneoplastic, vitamin deficiency, structural and metabolic diseases³.

As a methodology for this review, we performed a search for the following terms in the PubMed library: “acute ataxias”, “acute cerebellar syndrome”, “adult sporadic ataxias”, “toxic ataxias”, “immune-mediated ataxias”, “acquired ataxias”, “cerebellitis” and “infection of the cerebellum”. The most relevant reviews, original articles and case reports were used

Table 1. The main group of diseases that may cause acute cerebellar ataxias.

Infectious
Acute cerebellitis (Epstein-Barr virus, influenza A and B, mumps, varicella-zoster, coxsackie virus, rotavirus, echovirus, Mycoplasma and immunization)
Bacterial infection (<i>Mycoplasma pneumoniae</i> , <i>Listeria monocytogenes</i>)
Acquired immunodeficiency syndromes (<i>Mycoplasma pneumoniae</i> , Epstein-Barr virus, herpes simplex virus, and toxoplasmosis)
Other infectious (Lyme disease, Whipple disease, Aspergillus, JC virus, syphilis and Creutzfeldt-Jakob disease)
Toxic causes
Alcoholic cerebellar degeneration
Anticonvulsants (particularly phenytoin)
Antineoplastics (5-fluorouracil and cytosine arabinoside)
Lithium
Amiodarone
Environmental exposure (toluene, benzene derivate and heavy metals – mercury, thallium and manganese)
Metronidazole and polymyxins
Immune-mediated
Steroid responsive encephalopathy associated with autoimmune thyroiditis
Celiac disease
Anti-GAD (glutamic acid decarboxylase) ataxia
Miller-Fisher syndrome
Paraneoplastic cerebellar degeneration
Multiple sclerosis
Vitamin deficiency
Vitamin B1 deficiency (Wernicke encephalopathy)
Vitamin B12 deficiency
Vitamin E deficiency
Structural and vascular causes
Cerebellar stroke (ischemic and hemorrhagic)
Tumors (primary and metastasis)
Abscesses
Chiari malformation
Metabolic and genetic causes
Biotinidase deficiency
Maple syrup urine Disease
Hartnup disease
Mitochondrial disorders (Leigh syndrome)
Episodic ataxias
Other causes
Childhood periodic syndromes
Benign paroxysmal torticollis
Psychogenic ataxia
Migraine with brainstem aura and other vestibular disorders

as references for this paper. On the whole, this review serves as a diagnostic approach for the clinical neurologist, and focuses on the etiology of acute ataxias.

INFECTIOUS ACUTE CEREBELLAR ATAXIAS

Acute cerebellar ataxias secondary to infectious diseases most commonly involve the posterior fossa. In the pediatric population, the most frequent cause of acute ataxia is cerebellitis³. Infectious pathogens that frequently or preferentially affect the cerebellum include *Listeria monocytogenes*, varicella-zoster virus, John Cunningham (JC) virus, and Creutzfeldt-Jakob disease⁵.

Acute cerebellitis

Acute cerebellitis represents an inflammatory disorder that results from para-infectious, post-infectious, or post-vaccination cerebellar immune-mediated inflammation. Evidence of direct central nervous system infection is rarely found⁶. Acute post-infectious cerebellitis is more common in children and young adults. It is a pure cerebellar syndrome with normal or abnormal brain magnetic resonance imaging (MRI) at onset. Previously reported infections include: Epstein-Barr virus, influenza A and B, mumps, varicella-zoster virus, coxsackie virus, rotavirus, echovirus, *Mycoplasma pneumoniae* and immunization. In a large series of 73 patients with acute cerebellar ataxia, 19 had a previous varicella infection, two had Epstein-Barr virus infection, and 36 had other, presumed but unproven, viral illnesses. Fourteen cases were termed idiopathic and two were thought to be related to a vaccine. Overall, 91% recovered completely, including all children with varicella⁷. Other infections that may be related to ACA include hepatitis A, human herpesvirus 7, mumps and human parvovirus B19³. Severe cases of acute cerebellitis may present with clinical manifestations related to increased intracranial pressure resulting from cerebellar swelling and acute hydrocephalus, which overshadow manifestations of cerebellar dysfunction and may need urgent neurosurgical decompression³.

Bacterial infection

Any bacterial infection that causes meningoencephalitis can result in cerebellar signs and symptoms, including ACA. *Mycoplasma pneumoniae* has also been associated with a cerebellar syndrome during, or just after, the acute illness. Considering rhombencephalitis, *Listeria monocytogenes* is the most common causative agent².

Acute ataxia in acquired immunodeficiency syndromes

In patients with acquired immunodeficiency syndromes, ACA may be related to *M. pneumoniae*, Epstein-Barr virus, herpes simplex virus, and toxoplasmosis.

Other infectious agents causing acute ataxia

Patients with Lyme disease, Whipple disease, and Creutzfeldt-Jakob disease may also develop ataxia, and this may be the initial manifestation³. Fungi, in particular the *Aspergillus* species, can also cause ACA due to its tendency to cause posterior fossa invasive parenchymal disease⁵. Meningovascular syphilitic infection has also been reported to cause ACA in the setting of a bilateral inferior cerebellar infarction³. Subacute ataxia and abnormalities in brain MRI (Figure 1) may be caused by JC virus infection.

ACUTE CEREBELLAR ATAXIA RELATED TO TOXIC CAUSES

Alcoholic cerebellar degeneration

The cerebellum, particularly the Purkinje cells, are susceptible to a large number of toxic agents, alcohol being the most common. Alcohol may cause toxic effects on the central and peripheral nervous systems. Alcoholic cerebellar degeneration is related either to a direct toxic alcoholic effect on the Purkinje cells and vitamin B1 deficiency (see section of vitamin deficiency)⁸. Ataxia usually has a rapid progression (weeks or months), but slower progression may occur. Neurological features usually include severe ataxia of gait and lower limbs with relatively mild involvement of the upper limbs. Interestingly, speech and ocular motility are usually preserved. Brain imaging in alcoholic cerebellar degeneration typically shows vermis atrophy. Alcoholic cerebellar degeneration can often be accompanied by, and exacerbate, coexisting peripheral neuropathy and degeneration of posterior columns. Treatment of alcoholic cerebellar degeneration consists of abstinence from alcohol and vitamin B1 supplementation^{2,8}.

Antibiotic-induced acute ataxia

Weeks after initiation of metronidazole, an encephalopathy accompanied by cerebellar signs and brain MRI abnormalities may occur. It is characterized by cerebellar dysfunction, rare seizures, and non-specific EEG abnormalities. Metronidazole toxicity results in characteristic reversible MRI signal abnormalities in the cerebellar dentate nuclei, dorsal brainstem, or splenium of the corpus callosum. Both increased and decreased diffusivity have been observed in MRI, suggesting the variable presence of both vasogenic and cytotoxic edema, respectively⁹.

The interaction of polymyxins with neurons, which have a high lipid content, has been associated with the occurrence of several neurotoxic events. The most common is paresthesia, but ataxia may also occur in isolation or combined with dizziness, generalized muscle weakness, partial deafness, visual disturbances, vertigo, confusion, hallucinations, seizures, and neuromuscular blockade¹⁰.

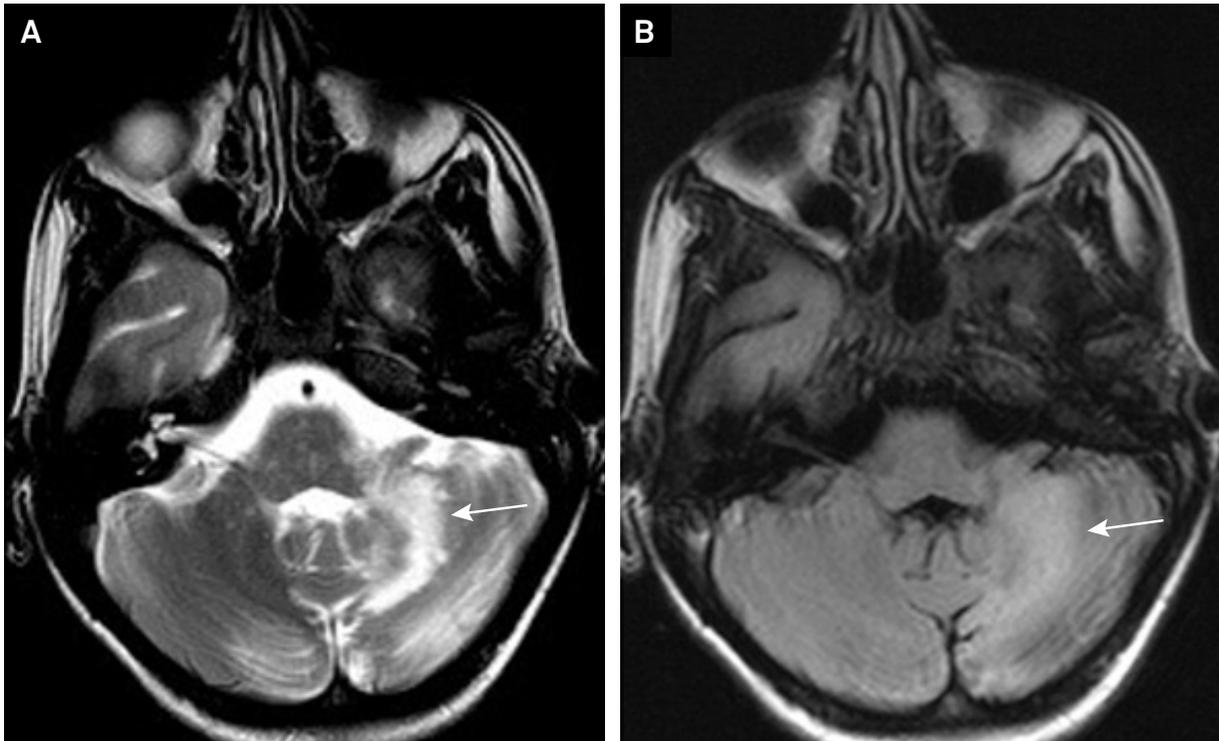


Figure 1. Patient with HIV and subacute cerebellar ataxia. Cerebrospinal fluid PCR confirmed John Cunningham virus infection (cerebellar form of progressive multifocal leukoencephalopathy). (A) Axial T2-weighted and (B) axial FLAIR-weighted brain MRI shows asymmetric hyperintense signal in the cerebellum evolving to the left cerebellar hemisphere and middle cerebellar peduncle.

Other toxic agents causing acute ataxia

Several drugs may cause toxic ataxia, dependent on the dosing and timing of use. The main agents include anticonvulsants (carbamazepine, phenobarbital, vigabatrin, gabapentin, lamotrigine and phenytoin), antineoplastics (5-fluorouracil, cytosine arabinoside, capecitabine, methotrexate), lithium and amiodarone. It is important to mention that interaction between medications can increase the plasmatic level of these agents^{2,8}. Chemical toxins related to environmental exposure may also cause acute ataxia and include: carbon dioxide, scorpion sting, insecticides/herbicides (organophosphate), toluene, benzene derivate and heavy metals (mercury, thallium, manganese, lead and copper)^{2,11}. Drug abuse such as cocaine, heroin, methadone and phencyclidine are also important causes of toxic ataxias¹¹.

IMMUNE-MEDIATED CAUSES OF ACUTE CEREBELLAR ATAXIA

Immune-mediated ataxias may cause acute, subacute or chronic ataxia. In this topic, we will focus on the acute and subacute autoimmune ataxias not related to a demyelinating disease, such as multiple sclerosis.

Steroid responsive encephalopathy associated with autoimmune thyroiditis

Steroid responsive encephalopathy associated with autoimmune thyroiditis is an autoimmune disorder characterized

by behavioral abnormalities, seizures, ataxia, myoclonus, stroke-like episodes and high serum levels of thyroid antibodies¹². Steroid responsive encephalopathy associated with autoimmune thyroiditis hardly ever presents with a pure ataxia syndrome and is usually associated with a more complex phenotype with encephalopathy. Brain MRI may show focal or diffuse abnormalities in 50% of patients. These patients are managed with steroids and refractory cases may be treated with immunosuppressive medications¹³.

Celiac disease or gluten ataxia

Celiac disease is chronic immune-mediated enteropathy precipitated by gluten exposure in patients carrying HLA-DQ2 and/or DQ8 alleles¹⁴. Patients may develop antibodies against transglutaminase and endomysium. Cerebellar ataxia is the most common neurological manifestation, but other symptoms may occur, such as neuropathy, brain calcifications, seizures, myelopathy and dementia. Nonetheless, a recent study reported that an alternative diagnosis for neurological manifestation was found in 57% of patients with suspected celiac disease¹⁵. However, this condition is hardly ever observed in our Brazilian population (personal observation of the authors).

Anti-GAD ataxia

Glutamic acid decarboxylase antibody (GAD-Ab) neurological syndromes comprise cerebellar ataxia, limbic encephalitis, stiff-person syndrome and autoimmune epilepsy^{16,17}.

The clinical spectrum of ataxia associated with anti-GAD-Ab comprises subacute or chronic cerebellar ataxia syndrome evolving over months or years, associated with cerebellar atrophy on brain MRI. Cerebrospinal fluid analysis frequently depicts oligoclonal bands. Treatment with immunoglobulin might be considered in these cases. In some patients, particularly those with diseases that are associated with GAD autoimmunity (e.g., type 1 diabetes mellitus), the development of ataxia should lead to GAD65-Ab testing¹⁸.

Autoimmune encephalitis

Acute and subacute ataxia is a frequent symptom in patients with autoimmune encephalitis. Metabotropic glutamate receptor 1 (mGluR1) is a G-protein-coupled receptor, involved in long-term depression of parallel fiber–Purkinje cell synapses. Patients with anti-mGluR1 encephalitis typically present with cerebellar ataxia, and almost half of the patients may present with dysgeusia^{19,20}. Patients with anti-CAPSR-2 encephalitis may present with ataxia, limbic encephalitis and/or peripheral nerve hyperexcitability. Anti-GABA(B) encephalitis may present as acute ataxia coupled or not with limbic encephalitis and seizures. Other antibodies associated with ataxia include anti-GABA(A), anti-dipeptidyl-peptidase-like protein-6 and antibodies against IgLON family member 5 protein²¹.

Miller-Fisher syndrome

Miller-Fisher syndrome is a variant of Guillain-Barré syndrome, characterized by acute ataxia, areflexia and ophthalmoplegia, usually with a preceding infection. Cerebrospinal fluid shows protein cytological dissociation, brain MRI is normal and the anti-GQ1b antibody may be positive. Current evidence suggests that a dorsal root antibody attack may explain the cerebellar ataxia²².

Paraneoplastic cerebellar degeneration causing acute cerebellar ataxia

Paraneoplastic cerebellar degeneration (PCD) has an association with tumors of the ovary and breast, small cell lung cancer and Hodgkin's lymphoma, but has also been reported in association with many other types of tumors. Paraneoplastic cerebellar degeneration is seen in about 20% of paraneoplastic neurological syndromes and typically affects more females than males. The disease usually has an acute or subacute onset, with vertigo, dizziness, vomiting, and nausea, and evolves rapidly, over weeks to months, to gait ataxia, truncal and limb ataxia, dysarthria and nystagmus. Also, PCD usually reaches its peak and then stabilizes. Other signs and symptoms may be present, including dysphagia, brisk reflexes, hearing loss, extrapyramidal signs, peripheral neuropathy and cognitive impairment²²⁻²⁴. In patients with rapid onset ataxia (acute or subacute), clinicians should suspect a paraneoplastic disorder. Ataxia symptoms may be part of opsoclonus-myoclonus syndrome. In

this syndrome, opsoclonus is associated with truncal ataxia, diffuse or focal myoclonus, vertigo, dysarthria and encephalopathy. In children, it may be associated with neuroblastoma or ganglioneuroma, and in adults with lung cancer or ovarian teratoma. The disorder is paraneoplastic in about 30–40% of children²⁵. Onconeural antibodies are generated against tumor antigens and are cross-reactive with cerebellar tissue antigens, especially those expressed by Purkinje cells. Pathology includes loss and degeneration of Purkinje cells and other cerebellar structures. Brain MRI is usually normal, particularly in the early course of the disease (Figure 2). Later, during the disease progression, diffuse cerebellar atrophy may occur. Cerebrospinal fluid usually contains a lymphocytic pleocytosis. Paraneoplastic cerebellar degeneration has been reported with most onconeural antibodies (Table 2)²⁶. Paraneoplastic cerebellar degeneration, without classical onconeural antibodies (seronegative PCD), is thought to represent up to 50% of patients with PCD and the clinical characteristics of seronegative and seropositive PCD are similar but the spectrum of associated tumors is different²⁷.

Treatment is commonly unsuccessful, although an improvement or stabilization of neurological symptoms after surgical resection of the tumor may occur. Other treatment options are immunosuppressive therapies with corticosteroids, intravenous immunoglobulin, cyclophosphamide, tacrolimus, mycophenolate and, more recently, rituximab (anti-CD20)²⁸.

Vitamin deficiency causing acute cerebellar ataxia

Vitamin B1 (thiamine) and B12 deficiencies may cause ACA or subacute ataxia. Thiamine deficiency may cause Wernicke encephalopathy (ataxia, confusion and ophthalmoparesis), a condition usually observed in alcoholics. Besides, thiamine deficiency is also involved in the pathophysiology of alcoholic cerebellar degeneration²⁹. Vitamin B12 deficiency causes sensory ataxia and patients present with impaired proprioception, peripheral neuropathy and pyramidal signs. Serum levels of B12 are usually decreased, and high levels of serum homocysteine and methylmalonic acid are also useful to suggest the diagnosis. The MRI may disclose a hyperintense signal in the posterior column of the cervical or thoracic spinal cord (Figure 3)³⁰. Symptomatic treatment comprises intramuscular B12 replacement. Vitamin E deficiency is usually related to a genetic cause and has a chronic course similar to Friedreich's ataxia³¹.

Vascular causes of acute cerebellar ataxia

Cerebellar stroke accounts for approximately 2% to 3% of all strokes. Acute cerebellar stroke may manifest with ataxia, vertigo, dysarthria, nausea, vomiting and, often, a prominent headache. Cerebellar infarction or hemorrhage may initially manifest in a clinically indolent manner only later to deteriorate into a life-threatening neurologic catastrophe, leading to a comatose state. These complications are mostly due

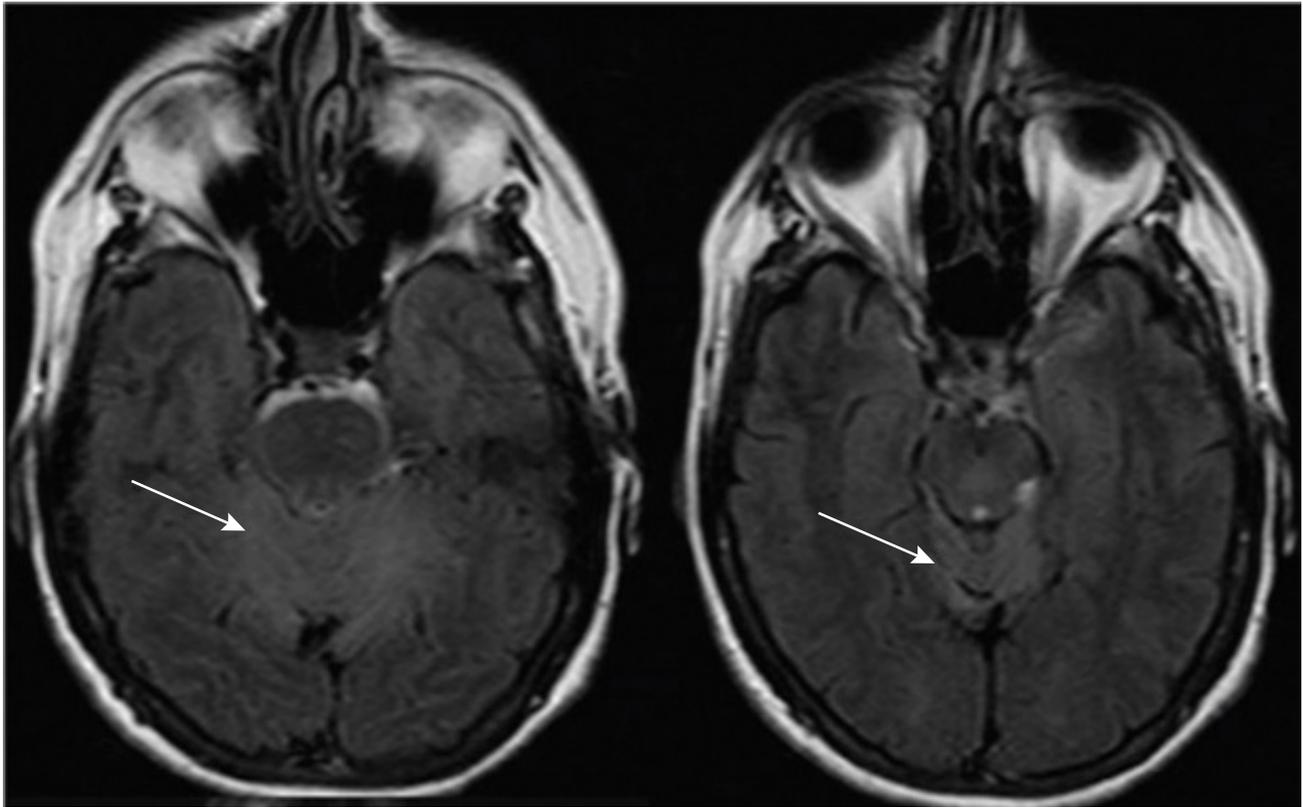


Figure 2. Patient with acute ataxia and breast cancer. Paraneoplastic cerebellar degeneration was diagnosed. Axial FLAIR-weighted brain MRI disclosed marked hyperintense signal in the superior vermis.

Table 2. Paraneoplastic cerebellar degeneration: autoantibodies, related tumors and clinical syndromes.

Antibody	Related cancer
Anti-Yo	Breast, gynecological tumors
Anti-Hu	Small cell lung cancer
Anti-Tr ¹	Hodgkin's lymphoma
Anti-CV2 ²	Small cell lung cancer, thymoma
Anti-Ri	Breast, ovaries, small cell lung cancer, neuroblastoma
Anti-Ma2	Testicles, lung cancer
Anti-VGCC	Small cell lung cancer
Anti-SOX1	Small cell lung cancer
Anti-ZIC4	Small cell lung cancer

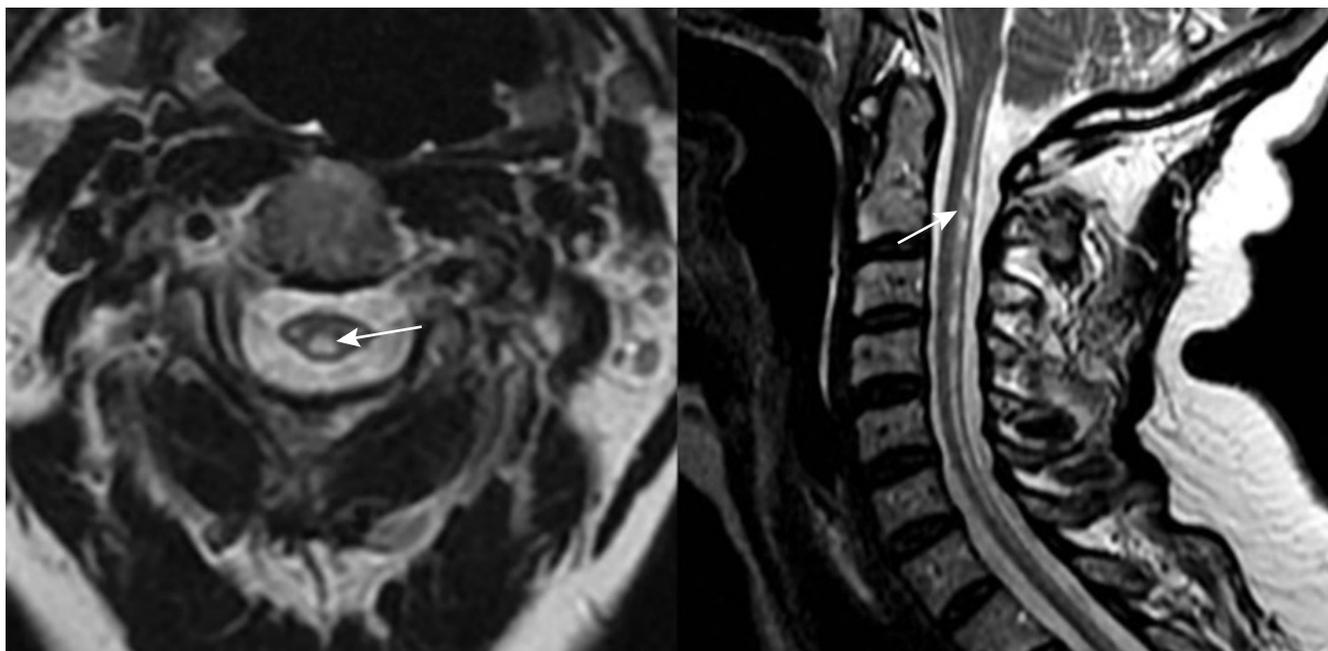
¹Anti-Tr is also known as anti-DNER (delta/notch-like epidermal growth factor-related receptor); ² anti-CV2 is also known as CRMP-5 (collapsin response mediator protein 5); Other antibodies: PCA-2 (the antigen was characterized as being the microtubule-associated protein [MAP1B]), anti-Homer 3, anti-CARP VIII, anti-GAD65, antibodies targeting septin-5 and GluD2 receptor antibody.

to hydrocephalus, brainstem compression by mass effect, or irreversible brainstem infarction (Figure 4)³². Approximately 20% of the patients with cerebellar stroke develop signs of clinical and radiographic deterioration due to mass effect. Cerebellar ischemia commonly occurs because of embolism, large vessel atherosclerosis or vertebrobasilar dissection in

one of its three major vascular beds: posterior inferior cerebellar artery, anterior inferior cerebellar artery and superior cerebellar artery³³. Ischemia of the cerebellum may coexist with ischemia of the brainstem due to pathologic abnormality in the vertebrobasilar vasculature. Thus, cranial nerve abnormalities may coexist with acute ataxia. Cerebellar hemorrhage accounts for approximately 9% to 10% of all intracranial hemorrhages. Hypertension and small vessel disease are considered the most common causes. It is frequently seen in middle-aged to older patients (usually beyond the fifth decade). The clinical spectrum of cerebellar hemorrhage is determined by its size and perilesional edema³⁴. Patients with small cerebellar strokes can present with classic cerebellar symptoms and those with larger strokes may become comatose and may develop other brainstem features and hydrocephalus.

STRUCTURAL LESIONS CAUSING ACUTE CEREBELLAR ATAXIA

Primary brain tumors, such as meningiomas and gliomas, as well as metastatic tumors secondary to melanoma, breast and lung cancer, may present with acute ataxia (Figure 5)³. Likewise, other pediatric posterior fossa brain tumors, including cerebellar astrocytoma and medulloblastoma, may present with ACA and



Dr. Victor Hugo Rocha Marussi (Medimagem, Beneficência Portuguesa de São Paulo).

Figure 3. Patient with acute sensory ataxia related to vitamin B12 deficiency. T2-weighted spine MRI shows hyperintense signal in the posterior column of the spinal cord.

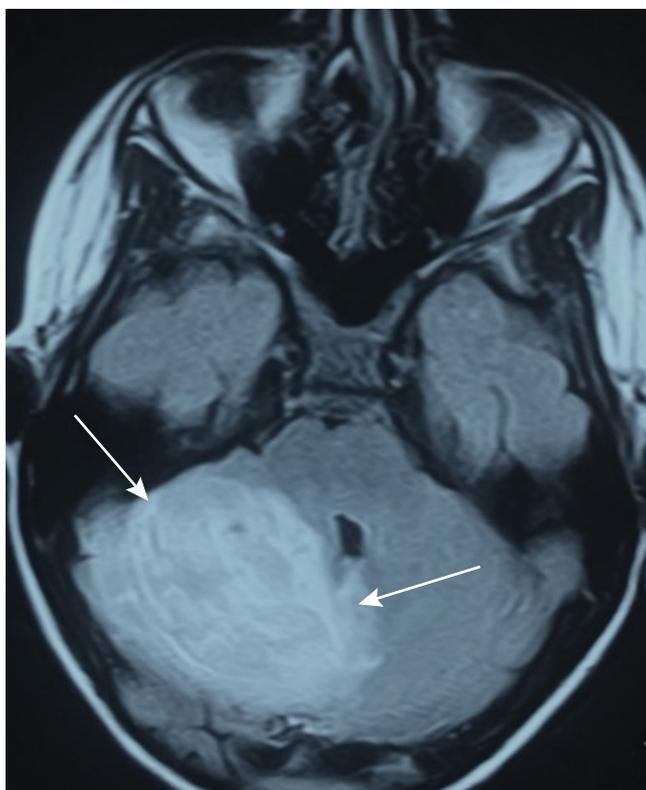


Figure 4. Patient with sudden ataxia. Axial FLAIR-weighted brain MRI disclosed acute ischemic stroke in the territory of the superior cerebellar artery, with compression of the fourth ventricle.

hydrocephalus from fourth ventricle outlet obstruction³⁵. Other space-occupying lesions, such as cerebellar lesions, abscesses and arteriovenous malformations that undergo hemorrhagic

transformation, may manifest with acute ataxia. Less common etiologies for space-occupying cerebellar lesions include giant multiple sclerosis plaques and tumefactive multiple sclerosis lesions, traumatic subdural hematoma, and progressive multifocal leukoencephalopathy. All patients found to have cerebellar space-occupying lesions, with the potential for caudal and rostral herniation of cerebellum, need immediate attention, as these can be life-threatening events^{3,35}. Worrisome premonitory clinical manifestations of cerebellar herniation include ataxia, intractable headache, nausea and vomiting, photophobia, and decreased consciousness. As the pathologic process progresses, patients may evolve into stupor and then coma, along with an ataxic respiratory pattern. In Chiari malformation, caudal displacement of the cerebellar tonsils enter through the foramen magnum and clinical manifestation are diverse, depending on the severity: headache, ataxia, radicular limb pain, weakness, paresthesia, vestibular symptoms, diplopia, tinnitus, hearing loss, syncope, slurred speech, dysphagia, urinary incontinence and sleep disturbance³⁶. Patients with Chiari hardly ever present with acute or subacute ataxia. Brain MRI is the gold standard method for diagnosis.

METABOLIC AND GENETIC DISEASES ASSOCIATED WITH ACUTE CEREBELLAR ATAXIA

Metabolic and genetic diseases associated with acute ataxias are more commonly observed in children, and hardly ever occur in adults. Biotinidase deficiency is an inherited disorder associated with the presence of seizures, hypotonia, respiratory

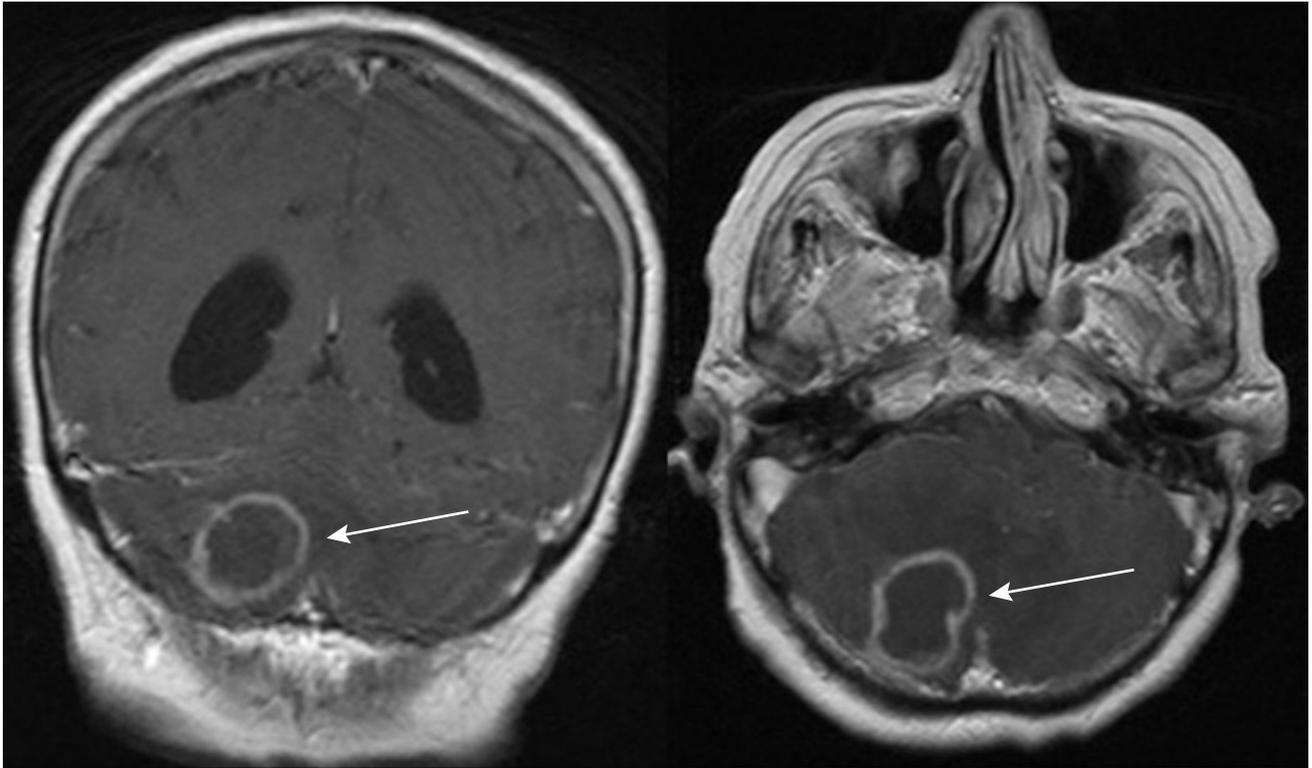


Figure 5: Kidney transplant recipient patient with acute ataxia. Brain MRI shows an expansive lesion with gadolinium enhancement in the cerebellum. Biopsy confirmed central nervous system post-transplant lymphoproliferative disorders.

problems, hearing loss and optic atrophy. Other clinical findings are skin rash, hair loss and conjunctivitis. Patients with late-onset biotinidase deficiency may present with ACA, especially after an acute stressor, such as prolonged infection³⁷. Maple syrup urine disease is an autosomal recessive aminoacidopathy. The disease is named for the presence of sweet-smelling urine and affected patients frequently present with intermittent events of acute ataxia, drowsiness and seizures³⁸. Treatment involves a protein-restricted diet and supplementation with essential amino acids and micronutrients. Hartnup disease is an autosomal recessive aminoaciduria characterized by abnormal gastrointestinal and renal transport of neutral amino acids. Patients may have light-sensitive dermatitis, emotional instability, psychotic symptoms, seizures and intermittent episodes of ataxia symptoms³⁹. Mitochondrial disorders like pyruvate dehydrogenase deficiency, pyruvate decarboxylase deficiency and Leigh syndrome may have intermittent or acute episodes of cerebellar ataxia, frequently associated with lactic acidosis³⁹. Episodic ataxias, particularly type 1 and type 2, which are the most common forms, may cause recurrent symptoms of ACA. Family history and genetic features are crucial for the diagnosis⁴⁰.

OTHER CAUSES OF ACUTE CEREBELLAR ATAXIA

Childhood periodic syndromes

Previously called “childhood periodic syndromes that are commonly precursors of migraine” in the International

Classification of Headache Disorders (ICHD)-II or colloquially “childhood periodic syndromes”, these disorders were renamed “episodic syndromes that may be associated with migraine” in the ICHD-III beta. Infant colic affects young babies, benign paroxysmal torticollis older infants, benign paroxysmal vertigo typically affects preschool-aged children, abdominal migraine and cyclical vomiting affects school-aged children around six or seven years of age⁴¹. An important feature of all these disorders is that, between attacks, the patients are healthy and have a normal neurologic examination. Acute episodes of ataxia can be an accompanying symptom of benign paroxysmal torticollis, which is characterized by periodic, stereotyped bouts of torticollis during infancy, typically beginning to improve by age two and resolving by age three or four. Drowsiness, irritability, apathy, pallor, vomiting or tortipelvis may also occur during the episodes. The etiology of benign paroxysmal torticollis is unknown. Some authors postulated it might be due to vestibular disorders or those in the central vestibular region or vestibulocerebellar connections, especially when associated with ataxia^{42,43}. The hypothesis of channelopathy was also raised, and this entity was recently linked to mutation of the *CACNA1A* gene.

Psychogenic ataxia

Psychogenic movement disorders may present with a broad spectrum of phenomenology that may resemble, but can be differentiated from, organic movement disorders by careful history and examination, sometimes

supplemented by ancillary tests⁴⁴. Psychogenic gait disorders may have various clinical presentations, such as ataxia. The most frequent pattern is atasia-abasia, characterized by bizarre contortions and side-to-side swaying of their bodies, usually accompanied by buckling at the knees, maintaining good balance and even being able to perform the tandem gait. Patients may have spontaneous improvement, but recurrence or a chronic psychogenic gait disorder may also occur⁴⁵.

Migraine with brainstem aura and other vestibular disorders

Migraine with brainstem aura, previously named basilar migraine or basilar-type migraine, is a subcategory of migraine with aura. Ataxia is listed among the brainstem symptoms that may occur during an attack, together with dysarthria, vertigo, tinnitus, hypoacusis, diplopia and decreased level of consciousness. A therapeutic response to a medication that prevents migraine headaches may assist to ratify the diagnosis of ACA secondary to basilar migraine⁴⁶. Brain MRI is usually normal. Vestibular neuritis is characterized by an acute onset of sustained rotatory vertigo combined with horizontal rotatory peripheral vestibular spontaneous

nystagmus toward the unaffected ear, which are typically suppressed by visual fixation. Examination reveals a pathological head-impulse test and postural imbalance. Ataxia may accompany the vestibular neuritis crisis, frequently associated with nausea and vomiting, without hearing loss and other neurologic abnormalities⁴⁷. We must consider the differential diagnosis of a minor brainstem stroke when ataxia is an important feature.

CONCLUSION

In conclusion, ACA is a syndrome that evolves in less than 72 hours, affecting previously-healthy individuals. Acute cerebellar ataxia is commonly seen in neurological practice and patients are initially seen by clinicians at the emergency department. There is a wide array of causes of ACA, including vascular, neoplastic, nutritional, metabolic, immune-mediated, infectious, toxic and paraneoplastic. Acute cerebellar ataxia usually results in hospitalization and extensive laboratory investigation. Clinicians are often faced with deciding the extent and timing of initial screening tests, particularly to detect treatable causes.

References

1. Klockgether T. Sporadic ataxia with adult onset: classification and diagnostic criteria. *Lancet Neurol*. 2010 Jan;9(1):94-104. [https://doi.org/10.1016/S1474-4422\(09\)70305-9](https://doi.org/10.1016/S1474-4422(09)70305-9)
2. Barsottini OG, Albuquerque MV, Braga-Neto P, Pedroso JL. Adult onset sporadic ataxias: a diagnostic challenge. *Arq Neuropsiquiatr*. 2014 Mar;72(3):232-40. <https://doi.org/10.1590/0004-282X20130242>
3. Javalakar V, Kelley RE, Gonzalez-Toledo E, McGee J, Minagar A. Acute ataxias: differential diagnosis and treatment approach. *Neurol Clin*. 2014 Nov;32(4):881-91. <https://doi.org/10.1016/j.ncl.2014.07.004>
4. Caffarelli M, Kimia AA, Torres AR. Acute ataxia in children: a review of the differential diagnosis and evaluation in the emergency department. *Pediatr Neurol*. 2016 Dec;65:14-30. <https://doi.org/10.1016/j.pediatrneurol.2016.08.025>
5. Pruitt AA. Infections of the cerebellum. *Neurol Clin*. 2014 Nov;32(4):1117-31. <https://doi.org/10.1016/j.ncl.2014.07.009>
6. Desai J, Mitchell WG. Acute cerebellar ataxia, acute cerebellitis, and opsoclonus-myoclonus syndrome. *J Child Neurol*. 2012 Nov;27(11):1482-8. <https://doi.org/10.1177/0883073812450318>
7. Connolly AM, Dodson WE, Prensley AL, Rust RS. Course and outcome of acute cerebellar ataxia. *Ann Neurol*. 1994 Jun;35(6):673-9. <https://doi.org/10.1002/ana.410350607>
8. Nachbauer W, Eigentler A, Boesch S. Acquired ataxias: the clinical spectrum, diagnosis and management. *J Neurol*. 2015 May;262(5):1385-93. <https://doi.org/10.1007/s00415-015-7685-8>
9. Bhattacharyya S, Darby RR, Raibagkar P, Gonzalez Castro LN, Berkowitz AL. Antibiotic-associated encephalopathy. *Neurology*. 2016 Mar;86(10):963-71. <https://doi.org/10.1212/WNL.0000000000002455>
10. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Crit Care*. 2006 Feb;10(1):R27. <https://doi.org/10.1186/cc3995>
11. Manto M, Perrotta G. Toxic-induced cerebellar syndrome: from the fetal period to the elderly. *Handb Clin Neurol*. 2018;155:333-52. <https://doi.org/10.1016/B978-0-444-64189-2.00022-6>
12. Grommes C, Griffin C, Downes KA, Lerner AJ. Steroid-responsive encephalopathy associated with autoimmune thyroiditis presenting with diffusion MR imaging changes. *AJNR Am J Neuroradiol*. 2008 Sep;29(8):1550-1. <https://doi.org/10.3174/ajnr.A1113>
13. Zhou JY, Xu B, Lopes J, Blamoun J, Li L. Hashimoto encephalopathy: literature review. *Acta Neurol Scand*. 2017 Mar;135(3):285-90. <https://doi.org/10.1111/ane.12618>
14. Briani C, Samaroo D, Alaedini A. Celiac disease: from gluten to autoimmunity. *Autoimmun Rev*. 2008 Sep;7(8):644-50. <https://doi.org/10.1016/j.autrev.2008.05.006>
15. Bürk K, Farecki ML, Lamprecht G, Roth G, Decker P, Weller M, et al. Neurological symptoms in patients with biopsy proven celiac disease. *Mov Disord*. 2009 Dec;24(16):2358-62. <https://doi.org/10.1002/mds.22821>
16. Pedroso JL, Braga-Neto P, Dutra LA, Barsottini OG. Cerebellar ataxia associated to anti-glutamic acid decarboxylase autoantibody (anti-GAD): partial improvement with intravenous immunoglobulin therapy. *Arq Neuropsiquiatr*. 2011 Dec;69(6):993. <https://doi.org/10.1590/S0004-282X2011000700030>
17. Vale TC, Pedroso JL, Alquéres RA, Dutra LA, Barsottini OG. Spontaneous downbeat nystagmus as a clue for the diagnosis of ataxia associated with anti-GAD antibodies. *J Neurol Sci*. 2015 Dec;359(1-2):21-3. <https://doi.org/10.1016/j.jns.2015.10.024>
18. Ariño H, Gresa-Arribas N, Blanco Y, Martínez-Hernández E, Sabater L, Petit-Pedrol M, et al. Cerebellar ataxia and glutamic acid decarboxylase antibodies: immunologic profile and long-term effect of immunotherapy. *JAMA Neurol*. 2014 Aug;71(8):1009-16. <https://doi.org/10.1001/jamaneurol.2014.1011>

19. Lopez-Chiriboga AS, Komorowski L, Kümpfel T, Probst C, Hinson SR, Pittock SJ, et al. Metabotropic glutamate receptor type 1 autoimmunity: clinical features and treatment outcomes. *Neurology*. 2016 Mar;86(11):1009-13. <https://doi.org/10.1212/WNL.0000000000002476>
20. Pedroso JL, Dutra LA, Espay AJ, Höftberger R, Barsottini OG. Video NeuroImages: head titubation in anti-mGluR1 autoantibody-associated cerebellitis. *Neurology*. 2018 Apr;90(16):746-7. <https://doi.org/10.1212/WNL.0000000000005338>
21. Heidbreder A, Philipp K. Anti-IgLON 5 disease. *Curr Treat Options Neurol*. 2018;20(8):29. <https://doi.org/10.1007/s11940-018-0515-4>
22. Kuwabara S. [Pathophysiology of ataxia in Fisher syndrome]. *Brain Nerve*. 2016 Dec;68(12):1411-4. Japanese. <https://doi.org/10.11477/mf.1416200610>
23. Vernino S. Paraneoplastic cerebellar degeneration. *Handb Clin Neurol*. 2012;103:215-23. <https://doi.org/10.1016/B978-0-444-51892-7.00013-9>
24. Leypoldt F, Wandinger KP. Paraneoplastic neurological syndromes. *Clin Exp Immunol*. 2014 Mar;175(3):336-48. <https://doi.org/10.1111/cei.12185>
25. Meena JP, Seth R, Chakrabarty B, Gulati S, Agrawala S, Naranje P. Neuroblastoma presenting as opsoclonus-myoclonus: A series of six cases and review of literature. *J Pediatr Neurosci*. 2016 Oct-Dec;11(4):373-7. <https://doi.org/10.4103/1817-1745.199462>
26. Höftberger R, Rosenfeld MR, Dalmau J. Update on neurological paraneoplastic syndromes. *Curr Opin Oncol*. 2015 Nov;27(6):489-95. <https://doi.org/10.1097/CCO.0000000000000222>
27. Ducray F, Demarquay G, Graus F, Decullier E, Antoine JC, Giometto B, et al. Seronegative paraneoplastic cerebellar degeneration: the PNS Euronetwork experience. *Eur J Neurol*. 2014 May;21(5):731-5. <https://doi.org/10.1111/ene.12368>
28. Mitoma H, Hadjivassiliou M, Honnorat J. Guidelines for treatment of immune-mediated cerebellar ataxias. *Cerebellum Ataxias*. 2015 Nov;2(1):14. <https://doi.org/10.1186/s40673-015-0034-y>
29. Spinazzi M, Angelini C, Patrini C. Subacute sensory ataxia and optic neuropathy with thiamine deficiency. *Nat Rev Neurol*. 2010 May;6(5):288-93. <https://doi.org/10.1038/nrneurol.2010.16>
30. Martinez Estrada KM, Cadabal Rodriguez T, Miguens Blanco I, García Méndez L. [Neurological signs due to isolated vitamin B12 deficiency]. *Semergen*. 2013 Jul-Aug;39(5):e8-11. Spanish. <https://doi.org/10.1016/j.semerg.2012.06.006>
31. Harding AE, Muller DP, Thomas PK, Willison HJ. Spinocerebellar degeneration secondary to chronic intestinal malabsorption: a vitamin E deficiency syndrome. *Ann Neurol*. 1982 Nov;12(5):419-24. <https://doi.org/10.1002/ana.410120503>
32. Datar S, Rabinstein AA. Cerebellar infarction. *Neurol Clin*. 2014 Nov;32(4):979-91. <https://doi.org/10.1016/j.ncl.2014.07.007>
33. Neugebauer H, Witsch J, Zwickberger K, Jüttler E. Space-occupying cerebellar infarction: complications, treatment, and outcome. *Neurosurg Focus*. 2013 May;34(5):E8. <https://doi.org/10.3171/2013.2.FOCUS12363>
34. Datar S, Rabinstein AA. Cerebellar hemorrhage. *Neurol Clin*. 2014 Nov;32(4):993-1007. <https://doi.org/10.1016/j.ncl.2014.07.006>
35. Lyons MK, Kelly PJ. Posterior fossa ependymomas: report of 30 cases and review of the literature. *Neurosurgery*. 1991 May;28(5):659-64. <https://doi.org/10.1227/00006123-199105000-00004>
36. Wu YW, Chin CT, Chan KM, Barkovich AJ, Ferriero DM. Paediatric Chiari I malformations: do clinical and radiologic features correlate. *Neurology*. 1999;53(6):1271-6. <https://doi.org/10.1212/WNL.53.6.1271>
37. Rahman S, Standing S, Dalton RN, Pike MG. Late presentation of biotinidase deficiency with acute visual loss and gait disturbance. *Dev Med Child Neurol*. 1997 Dec;39(12):830-1. <https://doi.org/10.1111/j.1469-8749.1997.tb07552.x>
38. Sitta A, Ribas GS, Mescka CP, Barschak AG, Wajner M, Vargas CR. Neurological damage in MSUD: the role of oxidative stress. *Cell Mol Neurobiol*. 2014 Mar;34(2):157-65. <https://doi.org/10.1007/s10571-013-0002-0>
39. Winchester S, Singh PK, Mikati MA. Ataxia. *Handb Clin Neurol*. 2013;112:1213-7. <https://doi.org/10.1016/B978-0-444-52910-7.00043-X>
40. Choi KD, Choi JH. Episodic ataxias: clinical and genetic features. *J Mov Disord*. 2016 Sep;9(3):129-35. <https://doi.org/10.14802/jmd.16028PMID:27667184>
41. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629-808. <https://doi.org/10.1177/0333102413485658>
42. Hadjipanayis A, Efstathiou E, Neubauer D. Benign paroxysmal torticollis of infancy: an underdiagnosed condition. *J Paediatr Child Health*. 2015 Jul;51(7):674-8. <https://doi.org/10.1111/jpc.12841>
43. Fernández-Alvarez E, Perez-Dueñas B. Paroxysmal movement disorders and episodic ataxias. *Handb Clin Neurol*. 2013;112:847-52. <https://doi.org/10.1016/B978-0-444-52910-7.00004-0>
44. Thenganatt MA, Jankovic J. Psychogenic movement disorders. *Neurol Clin*. 2015 Feb;33(1):205-24. <https://doi.org/10.1016/j.ncl.2014.09.013>
45. Sudarsky L. Psychogenic gait disorders. *Semin Neurol*. 2006 Jul;26(3):351-6. <https://doi.org/10.1055/s-2006-945523>
46. Kaniecki RG. Basilar-type migraine. *Curr Pain Headache Rep*. 2009 Jun;13(3):217-20. <https://doi.org/10.1007/s11916-009-0036-7>
47. Bisdorff A, Von Brevern M, Lempert T, Newman-Toker DE. Classification of vestibular symptoms: towards an international classification of vestibular disorders. *J Vestib Res*. 2009;19(1-2):1-13.