Chapter

Childhood-Onset Ataxia

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Abstract

Childhood presentations of ataxia can often be challenging to diagnose. Recognising ataxia is especially difficult in young children, the most frequent reason for consultation is walking instability and loss of balance. Clinical presentations tend to be heterogeneous; key considerations may vary based on the age of onset, time course, and associated manifestations. Ataxias can be acute, intermittent, chronic non-progressive, or chronic progressive conditions. Acute ataxias are mostly acquired conditions (post-infectious or immune-mediated). Intermittent ataxias may be secondary to genetic channelopathies or metabolic diseases. Non-progressive chronic ataxias are mostly related to cerebellar malformations and progressive chronic ataxias are usually secondary to genetic variants, which in children are usually autosomal recessive conditions. A complete medical history and a detailed physical examination are essential for an adequate approach. Treatment of a child with ataxia depends on the aetiology. One of the most important challenges is to identify the treatable causes.

Keywords: gait, ataxia, cerebellar ataxia, paediatrics, childhood

1. Introduction

Diagnosing ataxia in the paediatric age is a challenge since children having difficulty in explaining the symptoms and their temporality and the differential diagnosis can be confusing. Children with ataxia classically present with a difficulty to ambulate often described as a "wide-based gait" [1]. Ataxia is especially incapacitating for children because they are still developing and learning motor abilities [2].

The prevalence of children's ataxia is not widely studied. More reports are focused on single conditions or include adults and paediatric patients. Musselman et al. have estimated the prevalence of ataxia in children is 26/100.000 children [3].

Recognising ataxia is especially difficult in young children, the most frequent reason for consultation is walking instability and loss of balance. History and physical examination represent the basis of the clinical approach [4, 5]. Initially, it is important to determine the temporality of the clinical symptom and elucidate the possible differential diagnosis. Past medical history, including birth history, development, medication, as well a complete family history should be obtained. A history of trauma, medication or toxic ingestion or, recent virus infection should be elicited especially in patients with acute ataxias [5]. In the cases of chronic ataxia, it is important to determine the presence of other neurological symptoms like seizures, sensory abnormalities, or movement disorders.

Physical examination should include skin inspection, looking for telangiectasias, xanthomas or ichthyosis. Neurological assessment must consider the evaluation of the child in a sitting position and during walking. It is important to elucidate if the ataxia is secondary to a cerebellum condition (cerebellar ataxia) or due to other areas of the nervous system (sensory ataxia, vestibular ataxia, etc.) [6]. Abnormal eye movements (abnormalities of saccadic eye movements, nystagmus), dysarthria, dysmetria and dysdiadochokinesis suggest cerebellar ataxia. Paresthesia, impaired position and vibration sense and positive Romberg sign suggest sensory ataxia).

The presence of other neurological signs such as speech disturbances, cognitive impairment, deep tendon reflex abnormalities, or the presence of chorea, dystonia, or myoclonus may be clues to the diagnosis.

Ataxia in children can be in different ways, depending on neuroanatomy (sensory or cerebellar aetiology (primary or secondary), and temporal course [7]. Temporally, ataxia can be divided into two other groups: acute and chronic. Acute ataxias are usually secondary ataxias, whereas chronic ataxia may be either primary or secondary. Chronic ataxias are divided into intermitted or persistent ataxias. Persistent ataxias are divided into progressive and non progressive conditions [6].

2. Acute ataxias

Acutely presenting ataxia is a relatively common presentation to paediatric acute services or child neurologists though the cause of acute ataxia is most often benign, it is important during initial evaluation to recognise or exclude serious causes including brain tumour and central nervous system infections [8]. The most common causes are intoxication and acute cerebellar ataxia (ACA) (**Table 1**).

Causes of Acute Ataxias
Intoxications (alcohol, drugs)
Stroke
Trauma
Brain tumour
Brainstem encephalitis
Opsoclonus Mioclonus
Miller Fisher variant of Guillain Barre Syndrome
Multiple Sclerosis
ADEM
Acute cerebellitis
Labyrinthitis
Basilar migraine
Benign paroxysmal vertigo

Table 1.
Causes of acute ataxia.

2.1 Intoxications

Ingestion of a toxin represents approximately 30% of acute children ataxia cases [9]. The accidental ingestion of prescription and nonprescription medications is more frequent in children less than 6 years of age [9]. Benzodiazepines are the most common drug reported, nevertheless other medications such as carbamazepine, phenytoin, phenobarbital, lamotrigine, dextromethorphan (main ingredient of cough suppressant) [10, 11] and antineoplastic or immunosuppressive drugs such as cyclosporine, tacrolimus may cause ataxia [12]. Toxic agents that may be related to ataxia include lithium, ethanol and marijuana [6, 13].

Toxin ingestion may manifest with ataxia associated with mental status changes such as lethargy, confusion, inappropriate speech, or impaired consciousness level. Toxicology screening tests are commonly performed in the initial evaluation of acute ataxia in children [14].

2.2 Acute cerebellar ataxia

Acute cerebellar ataxia is the most common cause of acute ataxia in children accounting for nearly 30–50% of all cases [9]. It is a benign and self-limiting syndrome, usually a postinfectious phenomenon. It usually occurs in children between the ages of 3 and 5, but it can be seen in older children [9, 15]. The main clinical manifestation is sudden onset of unsteadiness of gait associated with cerebellar signs, nystagmus is reported in nearly 50% of patients [15]. Ataxia usually starts 1–3 weeks following a viral infection. Different viral agents have been linked to its development; the most common virus associated is varicella (25%) and it can occur in association with vaccines [12]. It has a benign prognosis with spontaneous recovery in most cases, the average duration of cerebellar signs is about 8 weeks [15].

2.3 Postinfectious cerebellitis

Postinfectious cerebellitis is a manifestation of one severe end of a continuous clinical spectrum, with acute cerebellar ataxia representing the milder end. Patients with postinfectious cerebellitis have ataxia and other symptoms, such as vomiting, abnormal mental status, or seizures. It is associated with abnormal brain imaging results due to cerebellar oedema]. Unlike acute cerebellar ataxia, the outcomes of postinfectious cerebellitis are not always favourable and may need aggressive management.

2.4 Acute disseminated encephalomyelitis

ADEM is an acute immune-mediated demyelinating encephalopathy with or without myelitis that is usually preceded by a viral infection. ADEM may present with prodromal signs such as fever, vomiting, or headache. Ataxia is a common feature (42%). Other neurological manifestations include long pathway signs (71%), acute hemiparesis (64%), consciousness impairment (58%), cranial nerve palsies (37%), meningeal reaction (36%), seizures (29%), visual loss due to optic neuritis (19%) and spinal cord involvement (20%) [16]. Diagnosis requires the demonstration of characteristic multifocal demyelinating lesions on MRI (**Figure 1**). The approximate incidence of ADEM is 0.2–0.4 per 100,000 children annually [16, 17]. The most common age of presentation is 3 to 7 years [18].

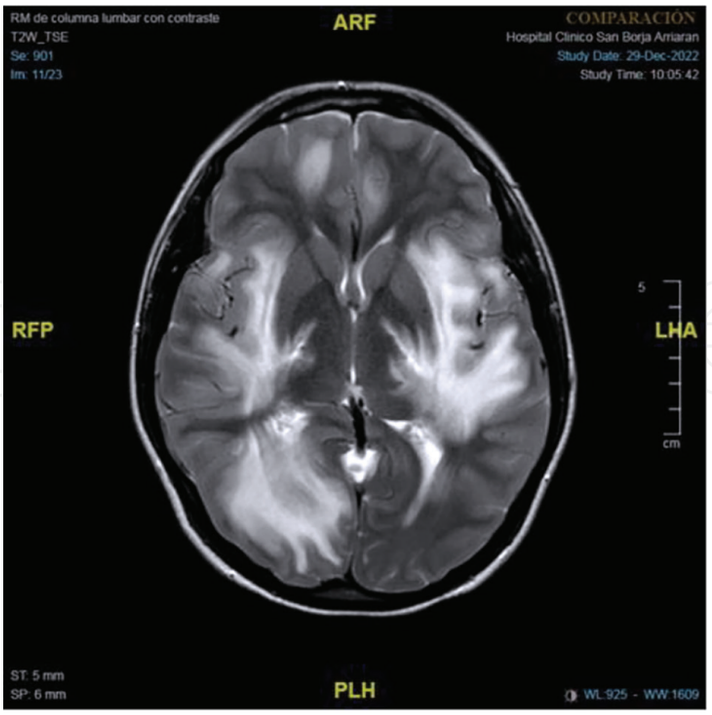

Figure 1.
Multifocal demyelinating lesions on MRI T2 weighted imaging sequence in a patient with ADEM.

Current first-line therapy is methylprednisolone at 20–30 mg/kg IV once a day for 3–5 days, followed by a corticosteroid taper over 4–6 weeks [19]. ADEM typically has a monophasic evolution with a favourable prognosis with complete recovery in almost all the patients usually over 4–6 weeks [20]. There is evidence that a minority of children may have persistent and long-term effects, such as physical or cognitive deficits, including attention difficulties and poor executive functioning [21, 22].

2.5 Opsoclonus-myoclonus syndrome

Opsoclonus-myoclonus syndrome (OMS) is a rare autoimmune neurological disorder that can occur in both children and adults. In childhood OMS, the main age of onset is approximately 18 months [23, 24]. Classic manifestations include an acute or subacute onset of ataxia, opsoclonus and myoclonic jerks associated with irritability and sleep disturbance [25]. All the main features may not be present initially and the diagnosis may be delayed weeks or months from the onset of symptoms.

OMS can be idiopathic, parainfectious or occur as a paraneoplastic syndrome. The most frequent neoplasia associated with childhood OMS in neuroblastoma. Neuroblastoma is present in at least 50% of affected children, and OMS presents as a paraneoplastic syndrome in 2–3% of all children with neuroblastomas [26]. Children with neuroblastoma and OMS have a better prognosis for their oncologic disease since they are usually diagnosed at earlier tumour stages and neuroblastoma is better differentiated [25].

The management and outcome depend on the aetiology and the spread of the disease. A regular response of neurological symptoms to immunosuppressive treatment is described. However, although the main neurological symptoms may show a good response, most children remain severe neuropsychological alterations [23].

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2.6 Central nervous system tumours

Central nervous system tumours are the most frequent neoplasia among those aged 0–19 years with an incidence rate of 6.14 per 100,000 population, representing the second cause of death from cancer in childhood [27]. Posterior fossa tumours account for 45–60% of all paediatric brain tumours [28]. Most posterior brain tumours are discovered between 3 and 11 years old [27].

Ataxia associated with posterior fossa brain tumours, in the absence of haemorrhage or acute CSF obstruction, tends to be subacute and is associated with symptoms of increased intracranial pressure (headache, vomiting). Treatment of brain tumours includes surgery, chemotherapy, radiotherapy, and rehabilitation. The prognosis is variable and depends on the type of tumour and localization (**Figure 2A** and **B**).

2.7 Anti: N-methyl-D-aspartate (NMDA) receptor encephalitis

Anti–Nmethyl-D-aspartate (NMDA) receptor encephalitis is a common, autoimmune cause of encephalitis in children. Clinical manifestations usually include abnormal behaviour, change in mental status, speech difficulties, seizures, movement disorders and autonomic dysfunction [29]. Cerebellar ataxia has been described as the initial symptom [30] and during the first months of the disease associated with the other clinical manifestations [31, 32].

2.8 Others

Other causes of acute ataxia in children are Guillain-Barré syndrome, Miller-Fisher syndrome, Bickerstaff brainstem encephalitis, transverse myelitis, stroke, venous sinus thrombosis, meningitis, rhombencephalitis, labyrinthitis, basilar migraine, benign paroxysmal vertigo, cerebellar abscess and celiac disease, among others [8, 33, 34].

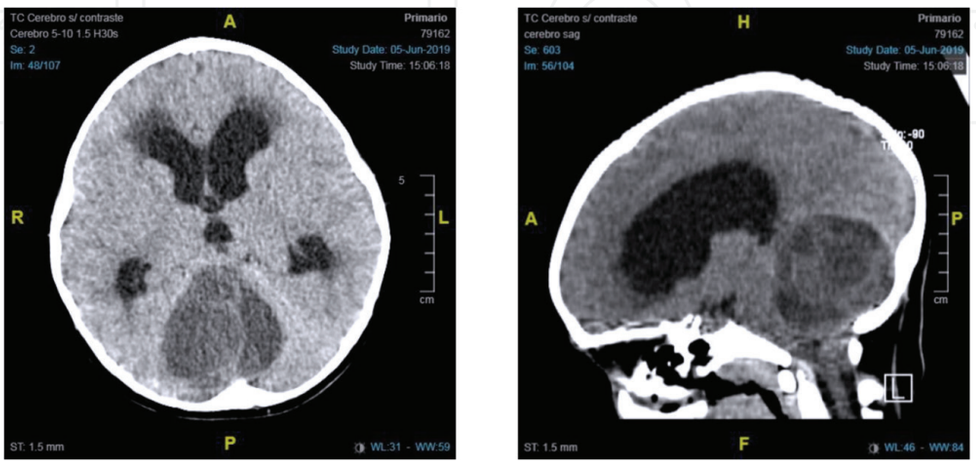

Figure 2.
Head CT scan examination (A) axial section and (B) sagittal section demonstrated an inhomogeneous hyperdense lesion in the posterior fossa.

3. Intermittent ataxias

Intermittent ataxias occur infrequently in paediatrics and are defined as ataxia that recurs after complete or almost complete resolution of an acute or subacute episode of ataxia [35]. The main causes of recurrent ataxia are genetic episodic ataxias; other causes are inflammatory and metabolic diseases (**Table 2**).

3.1 Episodic ataxias

Episodic ataxias (EAs) are a clinically and genetically heterogeneous group of autosomal dominant inherited channelopathies characterised by recurrent episodes of cerebellar ataxia [36]. EAs usually start during childhood or adolescence. Ataxia episodes can vary from seconds to hours or days and are often triggered by different specific stimuli [37]. Eight different forms of autosomal dominant or familial AD are currently identified [38]. EA1 and EA2, represent the most prevalent group of EAs patients and have recognisable ictal and interictal phenotypes [37].

EA1 is associated with mutations in a voltage-gated K channel gene (KCNA1) [36]. EA1 begins usually in childhood and ataxic episodes are associated with vertigo [38]. In EA1 the episodes are frequent, brief (seconds to minutes) and are triggered by abrupt exercise, stress, startle, fever, caffeine or alcohol [38, 39]. Dysarthria, tremors, diplopia, blurred vision, vertigo, nausea, migraine, or diaphoresis may also be present during the ataxia episodes. Between attacks, EA 1 is associated with myokymia [38]. Approximately 20% of EA1 individuals evolve with persistent cerebellar symptoms [37]. Different medications have been reported to be effective in EA1, including acetazolamide (AZT), carbamazepine and valproic acid [37, 38].

EA2 is caused by heterozygous variants in the calcium channel, voltage-dependent, P/Q type, and α1A subunit (CACNA1A) gene [38]. EA 2 usually presents with recurrent episodes of ataxia that last up to several hours or days and the frequency of the attacks ranges from four times per week to once per year [37]. During the attack, patients can

Causes of Intermittent Ataxias
Autosomal Dominant Episodic Ataxias
Basilar Migraine
Benign paroxysmal vertigo
Multiple Sclerosis
Metabolic Disorders
Urea cycle defects
• Aminoacidopathies (e.g., Maple syrup disease)
• Pyruvate dehydrogenase deficiency
• Pyruvate decarboxylase deficiency
• Glut 1 deficiency
• CAPOS syndrome
Relapsing opsoclonus-myoclonus syndrome

Table 2.
Causes of intermittent ataxia.

also manifest Vertigo and dizziness, dysarthria, migraine, nausea and vomiting, diplopia, tinnitus, and generalised muscle weakness. Ataxic episodes are triggered by emotional stress, exercise, phenytoin, and caffeine but not by startle [36]. Clinical onset is usually in the first two decades of life, although late-onset cases have been reported [38]. In EA2 often an interictal downbeat nystagmus with other cerebellar dysfunctions is present [38]. Acetazolamide is the first line treatment for EA2, patients unresponsive to or unable to tolerate acetazolamide may respond to 4-aminopyridine [39].

3.2 Glucose transporter type 1 deficiency

Glucose transporter type 1 (Glut1) deficiency syndrome is caused by heterozygous, mostly de novo, mutations in the SLC2A1 gene encoding the glucose transporter GLUT1. This glucose transporter is the most important energy carrier of the brain through the blood–brain barrier [40]. Glut1 deficiency syndrome is classically characterised by the presence of childhood epilepsy, developmental delay, acquired microcephaly, cognitive impairment, spasticity, ataxia, and dystonia.

Paroxysmal manifestations including seizures and nonepileptic paroxysmal episodes are also part of the phenotype [40, 41]. Clinical severity may vary from mild to severe neurological dysfunction. In children with mild phenotypes, paroxysmal manifestations, such as exercise-induced dyskinesia or episodic ataxia, may be the only manifestations of this condition [41]. Low CSF level of glucose is a characteristic finding in Glut1 deficiency syndrome and mutation analysis of the SLC2A1 gene confirms the diagnosis [38].

The ketogenic diet provides an alternative source of energy by switching brain metabolism from glucose to ketone bodies, it is considered the gold standard treatment and can improve or reverse symptoms, especially if started as early as possible.

3.3 CAPOS syndrome

CAPOS syndrome, named after its symptoms (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss) is a rare condition caused by variants in the ATP1A3 gene that encodes the α3 subunit of Na+/K+ -ATPase, an integral membrane protein responsible for the regulation of sodium and potassium concentrations over the cell membrane [42]. Three classic phenotypes (rapid-onset parkinsonian dystonia, alternating infantile hemiplegia, and CAPOS syndrome) were initially described, but recently an increasing number of cases presenting with atypical and overlapping features have been reported [43].

The symptoms usually start in childhood between 1 and 5 years of age, and patients typically present an acute episode of fever-induced ataxia associated with encephalopathic features and weakness [42, 43]. Recovery from the episode is complete in most cases and a recurrent course is characteristic. Afterwards, the patients show a slow progression of the disease [42, 44]. Patients classically experience two to three episodes of acute ataxia during life before transitioning to a slowly progressive evolution [44]. There is no specific treatment for CAPOS syndrome, acetazolamide has been used to prevent relapses of the acute episodes [42].

3.4 Others

Other causes of intermittent ataxia in children include metabolic disorders like pyruvate dehydrogenase deficiency [45, 46], pyruvate decarboxylase deficiency, urea

cycle defects, aminoacidopathies, organic acidopathies, recurrent ADEM, multiple sclerosis, benign paroxysmal vertigo [36], vestibular migraine, between others [35].

4. Chronic non-progressive ataxias

Chronic non-progressive ataxias are conditions that manifest with chronic ataxia with a stable (non-progressive) evolution. In this group are included congenital ataxias and their four subgroups recently proposed: cerebellar malformation, syndromic congenital ataxias, congenital cerebellar hypoplasia, and pontocerebellar hypoplasia [47]. Cerebellar structural disruption related to congenital infectious, tumours and stroke are also chronic non-progressive ataxias (**Table 3**).

4.1 Congenital ataxia

Congenital ataxias (CA) are a genetically heterogeneous group of disorders characterised by the presence of varying degrees of motor and language developmental delay, very early-onset cerebellar ataxia, cognitive impairment, and hypotonia [48]. Other common features include seizures, ocular signs (nystagmus, strabismus), behaviour changes, and microcephaly. Most cases have a non-progressive course, and patients report improvement in their motor and cognitive skills over time [47]. Recently, Raslan et al. [47] have proposed to classify CA into four categories:

- Cerebellar Malformations: patients with structural changes of the cerebellum. Neuroimaging is mandatory for the diagnosis. Cerebellar Malformations include Dandy-Walker malformation (hypoplasia of the cerebellar vermis, cystic dilation of the fourth ventricle, and an enlarged posterior fossa with upward displacement of the lateral sinuses, tentorium, and torcular) [49], rombencephalosynapsis, macrocerebellum, pontine tegmental cap dysplasia and cerebella dysplasia.

- Syndromic Congenital Ataxias: a group of conditions that associate specific dysmorphic characteristics, cerebellar hypoplasia, and early ataxia as the main feature. Syndromic congenital ataxias include Joubert Syndrome (characterised clinically by hypotonia progressing to ataxia, global developmental delay, ocular motor apraxia, and breathing dysregulation associated with the presence of the molar tooth sign on brain imaging consisting of elongated and thickened of the superior cerebellar peduncles) [50], Gillespie syndrome (iris hypoplasia, cognitive impairment and

Causes of Chronic Non-Progressive Ataxias
Congenital Ataxia (CA)
• Cerebellar Malformations
• Syndromic Congenital Ataxias (e.g., Joubert Syndrome)
• Congenital Cerebellar Hypoplasia
• Pontocerebellar Hypoplasia
Cerebellar structural disruption secondary to congenital infectious, tumours and stroke

Table 3.
Causes of chronic non-progressive ataxias.

cerebella hypoplasia), Dekaban-Arima syndrome (agenesis or hypoplasia of vermis, congenital polycystic kidneys, and hepatic disease), among others [47].

- Congenital Cerebellar Hypoplasia: In children with cerebellar hypoplasia as a main feature in neuroimaging, ataxia is frequently associated with cognitive impairment. Some genes have been linked with specific phenotypes and structural disorders of the cerebellum, including CACNA1A, CAMTA1, TUBA1A, TUBA8, RELN, OPHN1 genes [47].
- Pontocerebellar Hypoplasia: a group of heterogeneous conditions characterised by cerebellar and brainstem hypoplasia. Clinical manifestations include severe global development delay associated with dysmorphic features, microcephaly, optic atrophy, spasticity, epilepsy, and movement disorders [51]. Thirteen different types are described (from PCH1 to PCH 13) [47].

5. Chronic progressive ataxias

Chronic progressive ataxias are usually inherited ataxias that include a heterogeneous group of clinically and genetically distinguished neurodegenerative disorders. Depending on its inherence chronic ataxias are classified in autosomal dominant, autosomal recessive, and X-linked ataxias (**Table 4**).

Principal Causes of Chronic Progressive Ataxias
Primary Autosomal Recessive Ataxias
Friedreich Ataxia
Ataxia Telangiectasia
Ataxia with vitamin E deficiency
Ataxia with oculomotor apraxia 1 and 2
Ataxia with coenzyme Q deficiency
Abetalipoproteinemia
Cerebrotendinous xanthomatosis
Autosomal recessive ataxia of Charlevoix-Saguenay (ARSACS)
Other metabolic or complex autosomal recessive disorders that have ataxia as an associated feature
Niemann Pick C
Refsum Disease
Vanishing white matter disease
Wilson disease
Biotinidase Deficiency
Lafora Disease
Tay-Sachs disease
Sandhoff disease
Glut 1 deficiency
Hartnup disease
GM1 gangliosidosis type II

Table 4.
Causes of chronic progressive ataxias.

5.1 Autosomal dominant ataxias

Autosomal dominant ataxias usually presenting as spinocerebellar ataxia (SCAs). SCAs are rare in children and the clinical clue for the diagnosis is the identification of family history [7]. Most common SCAs are caused by an expansion of a CAG trinucleotide repeat in the respective gene, therefore an anticipation phenomenon can occur in some families.

Infantile and childhood onset has been described in SCA2, SCA7, SCA10, SCA13, SCA14, SCA21, SCA25, SCA28, SCA42, SCA44, and DRPLA (dentatorubral-pallidoluysian atrophy) [52].

5.2 Autosomal recessive ataxias

Autosomal recessive ataxias are a group of complex genetic ataxia disorders associated with variable central and peripheral involvement and systemic manifestations. A new clinical and pathophysiological classification of autosomal recessive cerebellar ataxia has recently become available [53] and is a very useful tool for the initial clinical approach to a patient presenting with ataxia. There is a long list of disorders associated with autosomal recessive ataxias, some of which are described below.

Autosomal recessive ataxias are a group of complex genetic ataxia disorders associated with variable central and peripheral involvement and systemic manifestations. A new clinical and pathophysiological classification of autosomal recessive cerebellar ataxia has recently become available [53]. This classification separates autosomal recessive ataxias in two groups: primary autosomal recessive cerebellar ataxias and complex multisystem disorders that are associated with ataxia. There is a long list of disorders associated with autosomal recessive ataxias, some of which are described below.

5.3 Primary autosomal recessive cerebellar ataxias

5.3.1 Friedreich ataxia

Friedreich Ataxia (FA) is caused by mutations in the FXN gene (9q21.11), which encodes the synthesis of frataxin, a protein that is involved in mitochondrial function. Its deficiency leads to mitochondrial iron overload, defective energy supply and generation of reactive oxygen species. Most patients carry homozygous GAA expansions in the first intron of the frataxin gene on chromosome 9 [54].

FA age of onset has a wide range, which can go from 5 to 25 years of age, although cases of late-onset (after 25 years of age) and very late onset (after 40 years of age) have been described [55]. Usually, the onset of symptoms is between the ages of 10 and 16 with gait instability [54]. The classical phenotype of FA is associated with progressive sensory and cerebellar ataxia, with areflexia, loss of position or vibration sensation, pes cavus, Babinski sign, and scoliosis. Patients usually become wheelchair-bound after a mean disease duration of 10–15 years [56]. Other neurological manifestations include dysmetria, dysarthria, and auditory and optic neuropathy. FA patients also have systemic complications, including cardiomyopathy and diabetes [57]. MRI usually shows spinal atrophy [54]. Currently, there is no effective treatment to delay neurodegeneration in Friedreich's ataxia, but different newer treatments are now being studied.

5.3.2 Ataxia telangiectasia

Ataxia-telangiectasia (AT) is the second most common autosomal recessive hereditary ataxia in children [7]. AT is caused by a mutation in the AMT gene, which encodes a kinase protein involved in DNA repair [58]. The onset of symptoms is usually in early childhood, classical neurological signs include progressive cerebellar ataxia, oculomotor apraxia, chorea and cognitive dysfunction [59]. Scleral and cutaneous telangiectasias are characteristic of AT, although they may be absent initially. Other systemic manifestations include variable immunodeficiency with recurrent infections, radiosensitivity, susceptibility to malignancies, poor growth and insulin-resistant diabetes [60]. Serum elevation of carcinoembryonic antigen and alpha-fetoprotein are constant markers. Immunoglobulins are typically decreased and MRI classically shows marked atrophy of the cerebellum [61]. AT patients have a poor prognosis, and average life expectancy was reported to be approximately 25 years [60]. No curative therapy is available for ataxia-telangiectasia.

5.3.3 Ataxia with oculomotor apraxia type 1 (AOA1) and type 2 (AOA2)

Both recessive conditions manifest as the main clinical features of ataxia and oculomotor apraxia. AOA1 is caused by mutations in the APTX gene which encodes a nuclear protein called aprataxin that is involved in DNA repair [62]. Ataxia usually begins during the first decade of life and is often associated with neuropathy, chorea, nystagmus, and oculomotor apraxia [62]. AOA1 patients do not have extra neurological manifestations. Most AOA1 patients lose the ability to walk independently approximately 7–10 years after the first symptoms [7]. Hypoalbuminemia and hypercholesterolemia are frequent [63].

AOA2 is caused by mutations in the SETX gene which encodes the synthesis of senataxin, a helicase considered to be involved in the defence against DNA damage [64]. Usually, the onset of the disease occurs between 12 and 22 years of age (later than AOA1) [65]. The most frequent presenting manifestation is cerebellar ataxia, which is slowly progressive. Oculomotor apraxia may be absent. Other clinical manifestations include strabismus, sensorimotor peripheral neuropathy and different movement disorders (specially chorea and dystonia) [64, 65]. Elevated serum AFP levels are characteristic, and creatine kinase (CK) levels are occasionally elevated. Cerebellar atrophy appears to be an early sign of AOA2, which stabilises after several years after disease onset [64].

5.3.4 Ataxia with vitamin E deficiency

Ataxia with vitamin E deficiency (AVED) is caused by variants in the APTT gene, which encodes the synthesis of the alpha-tocopherol transfer protein, responsible for incorporating vitamin E into very low-density proteins in the liver, which will transport it to the brain. The first manifestations are observed between 4 and 18 years of age in individuals with or without a history of malabsorption disorders [66]. Subjects with AVED develop a neurological phenotype very similar to Friedreich's ataxia [67]. AVED is characterised by progressive ataxia, areflexia, head tremor, loss of proprioception and retinitis pigmentosa [68]. Supplementation improves symptoms and prevents the progression of the disease [68].

5.3.5 Autosomal-recessive spastic ataxia of Charlevoix: Saguenay

Autosomal-recessive spastics ataxia of Charlevoix Saguenay (ARSACS) is caused by mutations in the SACS gene which is located on chromosome 13q12.12 [69]. SACS gene encodes sacsin, a protein that has chaperone activity and interacts with the proteasome, but is also involved in mitochondrial function and affects axonal and dendritic transport [70]. The mean age at onset is approximately 6 years (range: 0–40 years) [71]. ARSACS is clinically characterised by early-onset progressive cerebellar ataxia, spasticity and peripheral neuropathy. Oculomotor disturbances and dysarthria are also common manifestations. A characteristic finding is the presence of yellow streaks of hypermyelinated fibres radiating from the edges of the optic disc seen on ophthalmologic examination. In the optical coherence tomography study, an increase in the thickness of the retinal fibre layer can be observed [72]. MRI imaging shows atrophy of the cerebellar vermis, atrophy of the posterior part of the corpus callosum, and linear hypointensities in the pons on T2 and T2-FLAIR [73].

5.4 Other metabolic or complex autosomal recessive disorders that have ataxia as an associated feature

5.4.1 Niemann-pick disease type C

Niemann-Pick disease (PC) is caused by autosomal recessive mutations in either the NPC1 or NPC2 gene. NP1 encodes a transmembrane protein and NP2 an intralysosomal protein, the deficiency of which results in the intracellular accumulation of cholesterol and complex lipids, such as sphingolipids and phospholipids, within the endosomal/lysosomal system [74]. NPC has a heterogeneous spectrum of signs and symptoms in visceral, neurologic, and psychiatric domains, with characteristic symptomatology depending on the age of onset. Ataxia is a frequent manifestation in late infantile, juvenile and adult forms and can be associated with vertical gaze palsy, epilepsy, dystonia and cataplexy [75]. The prognosis is correlated with the age at onset of the neurological manifestations, with early-onset forms progressing more rapidly than late-onset forms [74]. MRI and CT may be normal or show cerebellar or cortical atrophy [76].

5.4.2 Wilson disease (WD)

Wilson Disease (WD) is caused by mutations in the ATP7B gene, which encodes the synthesis of an ATPase that participates in the copper transport, located preferentially in the liver but also in the brain [77]. WD generally presents in childhood and young adulthood. The most common age of presentation is 10 to 20 years [78]. WD have different forms of presentation, including fulminant hepatitis, psychosis, or neurological disorder (tremor, dystonia, akinetic-rigid syndrome, and ataxia). A characteristic ophthalmological manifestation includes the Kayser-Fleischer ring [79]. MRI imaging findings are variable, with neurological patients classically presenting with bilateral high signal intensities on T2 and Flair-weighted images in the basal ganglia, the mesencephalon and the cerebellum [77]. Low levels of ceruloplasmin and copper are detected in the blood, the excretion of which is increased in urine [78]. D-penicillamine and trientine as chelators, and tetrathiomolybdate and zinc sulfate are the usual treatment [79].

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5.4.3 Vanishing white matter disease

Vanishing White Matter Disease (VWM) is an autosomal recessive leukoencephalopathy, most often with onset in childhood. The classic phenotype is characterised by chronic progressive neurological deterioration, especially cerebellar ataxia, with additional episodes of rapid deterioration after minor head trauma and febrile infections possibly leading to coma or death [80]. MRI shows a diffuse cerebral white matter abnormality, beginning in the presymptomatic stage. Subsequently, the affected white matter disappears and is replaced by fluid (**Figure 3**) [80].

6. Ataxias scales in children

Ataxia scales are used especially in clinical trials evaluating the potential effect of therapeutic agents. Different ataxia rating scales have been used in the paediatric age, the most commonly applied in children include the International Cooperative Ataxia Rating Scale (ICARS) and the Scale for Ataxia Assessment and Rating (SARA) [81].

ICARS was initially developed to evaluate treatment efficacy in randomised clinical trials. ICARS is constituted by four clinical subscales domains including posture and gait, limb coordination, speech and oculomotor function [81]. ICARS ranges from 0 (optimal outcome) to 100 (most severely affected outcome). In children, some reports are suggesting an age-dependent ICARS score, with performance improving with age [82].

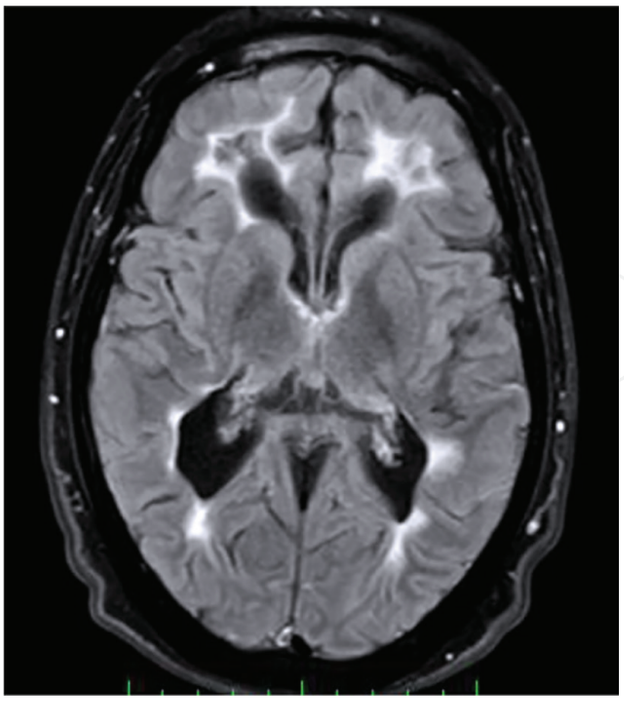

Figure 3.
MRI FLAIR sequence revealed diffuse white matter hyperintensity and interspersed areas of low signal intensities findings in classic vanishing white matter (VWM) disease.

SARA includes eight items that range a total score from 0 (no ataxia) to 40 (most severe ataxia), assessing gait, stance, sitting, speech disturbance, finger chase, nose-to-finger test, fast alternating hand movements, and heel-shin slide. Studies also indicate an exponential decline of SARA scores [83] with age, and some authors do not recommend its use in children under 12 years of age [84].

In both mentioned scales, the presence of different types of movement disorders can influence scores, so its application in uniform phenotypes of movement disorders is suggested for an adequate interpretation [85].

7. Treatment of childhood ataxias

Treatment of a child with ataxia depends on the aetiology. One of the most important challenges is to identify the treatable causes. For example, ataxia with vitamin E deficiency (AVED), abetalipoproteinemia, and hypobetalipoproteinemia are treated with vitamin E. Wilson's disease is treated with D-penicillamine and trientine as copper chelators. Some metabolic disorders are treated with dietary modifications, such as glutamate 1 deficiency and pyruvate dehydrogenase deficiency, which are treated with the ketogenic diet. Specific enzymatic treatments have recently been developed for some metabolic disorders, especially focused on slowing down their progression. An example is Miglustat for NPC patients [74].

Physical therapy is an important part of treatment to help maintain mobility as long as possible. Occupational therapy, and speech or language therapy are also part of the symptomatic therapy [86].

There are also reports of some benefits in adults with cerebellar ataxia with transcranial magnetic stimulation [87] and transcranial direct current stimulation [88], but the evidence is still lacking, especially in children.

8. Conclusions and final remarks

Ataxia can be difficult to diagnose in children. It may be undetected mainly in very young children and incorrectly related to a delay of coordination. The differential diagnosis of ataxia remains challenging. An increasing number of diseases are described, and the phenotypes are not always typical. A complete medical history and a detailed physical examination are keys to an adequate approach. It is important to always identify the time course of onset and associated manifestations. The causes of ataxia are various and have different prognoses that can range from transient and benign to particularly severe conditions. Ataxias manifest in various forms: acute, intermittent, chronic non-progressive, and chronic progressive. Acute ataxias predominantly arise from acquired causes such as post-infectious or immune-mediated conditions. Intermittent ataxias may stem from genetic channelopathies or metabolic disorders. Non-progressive chronic ataxias primarily result from cerebellar malformations, whereas progressive chronic ataxias commonly arise from genetic variants, which in children tend to be autosomal recessive conditions. It is imperative to consider treatable disorders. New genetic diagnostic techniques have emerged, enabling the identification of specific pathologies. However, a comprehensive description of the clinical and laboratory phenotypes of each patient is necessary to guide the genetic study and interpret the results. While there are currently limited treatable conditions, ongoing studies are proposing promising treatments for

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certain pathologies soon, thereby increasing the importance of accurate diagnostic approaches. Physical therapy is an important part of treatment. Occupational therapy, and speech or language therapy are also part of the symptomatic therapy.

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