Clinical Features, Assessment, and Management of Patients with Developmental and Other Cerebellar Disorders

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Abstract The cerebellum is essential for processing, modulating, and controlling movement, behavior, and cognitive functions. Cerebellar disorders cause tremor and incoordination, larger variability, and inaccuracy of movements during eye and limb movements, stance, and speech. Cerebellar dysfunction also results in impaired cognition and behavior. During the clinical assessment, details of the presenting complaints including onset and time course of ataxia, other symptoms, past medical history including developmental milestones, family history, and drug history are elicited. On examination emphasis is placed on examining the motor system especially speech and eye and limb movements. Other aspects include general examination, head size, dysmorphic features, neurocutaneous stigmata, and cognitive function assessment. A thorough exam of the cranial nerves, tone, strength, coordination, reflexes, gait, and sensation should be undertaken. A comprehensive assessment helps to narrow down the diagnostic possibilities and offers clues to specific disorders of the cerebellum. Management is guided by disease etiology.

Keywords Cerebellum • Motor coordination • Eye movements • Speech articulation • Cognitive function

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H. Marzban (ed.), *Development of the Cerebellum from Molecular Aspects to Diseases*, Contemporary Clinical Neuroscience,
DOI 10.1007/978-3-319-59749-2_20

Introduction

Ataxia is a relatively common presentation in the pediatric population with an estimated prevalence rate of 26 per 100,000 children in Europe. The annual crude incidence rate of chronic ataxia is 3.2 per 100,000 children and adolescents residing in Manitoba, Canada. Ataxia is caused by numerous diseases [1–5].

This chapter discusses the clinical features in children with cerebellar disorders including motor abnormalities, cognitive, affect, and behavioral dysfunction. The clinical assessment of patients with developmental and other cerebellar disorders is described, and different aspects are discussed in detail.

Many clinical motor features of cerebellar disease and their interpretation have been described succinctly by Dr. Gordon Holmes in his Croonian lectures in 1922 [6]. New roles for the cerebellum in health and disease continue to emerge with evidence implicating Purkinje cell dysfunction in the latter [7]. More recently, few comprehensive reviews and consensus papers on symptoms and signs of cerebellar dysfunction, roles of the cerebellum in motor control, and nonmotor role of the cerebellum in language and other related disorders have been published [8–11].

Limbs' Motor Control

Smooth and accurate execution of voluntary movements and adaptation to changing demands of motor tasks rely on an intact cerebellum [12]. The cerebellum can learn and store different combinations needed for precise complex movements through trial and error. Patients with cerebellar lesions can perform simple motor tasks. However, incoordination and impaired initiation of movement appear when compound complex movements are performed especially at a fast pace [13]. Cerebellar dysfunction causes greater impairment in predictive movements than in movements requiring feedback, for example, visual or somatosensory feedback [14]. Patients with cerebellar disorders appear to have proprioceptive deficits during active but not passive limb movements [15]. Furthermore, the ability to adapt to novel changes in movements is impaired. Table 1 shows several clinical motor signs in patients with cerebellar disease.

Ocular Motor Control

The cerebellum serves an important part for the normal functioning of all types of eye movements including saccades, smooth ocular pursuit, modulation of the vestibulo-ocular reflex, and also for ensuring visual fixation stability. The cerebellum fine-tunes eye movements and reduces their baseline variability to ensure that the two eyes are stable and working together. This is essential for bringing and maintaining objects of interest on or very close to the fovea. This, in turn, leads to

Table 1 Cerebellar signs causing abnormal control of stance and voluntary movements

Sign	Comment
Asthenia	Delay in initiating muscle contraction and slow attainment of full force. It can be elicited by asking the patient to grasp the examiner's hand firmly
Adventitiousness (inappropriate accessary movements)	Failure to fix the proximal muscles to preserve the correct posture in relation to the moving part of a limb. This represents exaggerated activation of muscles that should be paused
Dysdiadochokinesia	Slowness and irregularity of the frequency and amplitude of rapid alternating movements. It can be observed during successive pronation and supination of the forearm at the elbow joint. It also manifests with difficulty on repeating the syllables pa-ta-ka
Rebound	Abnormally large displacement of an outstretched arm following a tap on the wrist with overshooting followed by few oscillations around the primary position
Dysmetria	Inaccurate movement trajectory with under- or overshooting a target. It can be observed during finger-nose exam or heel-to-shin exam. It is speed and inertia sensitive
Intention tremor	Oscillation of a limb especially when approaching a target during goal-directed voluntary movements. It can be observed during finger-nose exam or heel-to-shin exam
Kinetic tremor	Oscillation of a limb at the commencement of voluntary movements
Postural tremor	Oscillations observed during postural tasks, e.g., maintaining the heel of one foot over the contralateral knee for a few seconds or maintaining the outstretched arms parallel to the ground. It affects proximal > distal muscles
Palatal tremor	Rhythmic oscillations of the palate
Titubation	Involuntary rhythmic oscillations of a body part, e.g., the head or trunk
Head tilt	Lateral displacement of the head
Truncal ataxia	Swaying of an unsupported sitting or standing trunk
Ataxia of stance	Swaying of the body while standing up
Ataxia of gait	Wide-based gait with staggering and swaying. Tandem gait and running unmask more subtle gait ataxia
Inability to perform the Romberg maneuver with the eyes open	Inability to stand with the legs and feet touching each other while the eyes are open
Dysrhythmokinesia	Abnormal rhythm observed during tapping of a limb
Abnormal handwriting or drawing	A written sentence will appear irregular, large, and tremulous. An Archimedes' spiral will appear tremulous and dysmetric
Hypotonia	Decreased resistance to passive stretch
Pendular reflexes	Excessive oscillations of a limb (like the swing of a pendulum) observed after eliciting a deep tendon jerk
Motor delay	Slow acquisition of motor milestones

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the best visual acuity whether the person is moving or not [8]. Three cerebellar regions are important for ocular motor control: the flocculus/paraflocculus, the nodulus-ventral uvula, and the dorsal oculomotor vermis/fastigial oculomotor region [8, 16].

Various types of nonphysiological nystagmus (i.e., pathological ocular oscillations), for example, gaze-evoked nystagmus and saccadic intrusions (abnormal fast eye movements that take the fovea off the target), occur following cerebellar damage and result in fixation instability [9, 16]. Saccadic (jerky) smooth ocular pursuit and saccadic dysmetria (hypo- or hypermetria) are other well-recognized ocular motor signs of cerebellar dysfunction [16]. Table 2 shows several ocular motor signs in patients with cerebellar disease.

Speech Control

The production of speech is a complex process that involves several neural networks located in the cerebrum and cerebellum [10]. The production of speech involves the coordination of a large number of muscles, in particular the tongue and orofacial muscles [17]. The cerebellum plays an important role in speech articulation, prosody (i.e., characteristics of speech style including speed, rhythm, pitch, and emphasis), and planning and processing of speech and language [18].

Cerebellar impairment can cause ataxic dysarthria [10]. Abnormalities in speech motor programming through impaired timing and deficits in speech execution are both implicated in ataxic dysarthria [18]. Table 3 shows key features of speech abnormalities in patients with cerebellar disorders.

Nonmotor Impairments in Cerebellar Disorders

A multitude of studies support nonmotor roles for the cerebellum in cognition and behavior control. Cerebellar abnormalities have been identified in patients with cognitive and neuropsychiatric disorders. In addition, developmental delay, learning difficulties, and behavioral problems have been commonly reported in children with developmental cerebellar disorders [11].

Language

The cerebellum modulates several aspects of language production and perception [8]. In addition, the cerebellum is involved in reading and writing [10]. Cerebellar impairment results in disturbances in syntax processing, prosody, and grammar [19], with anomia, perseveration, and reduced speech output and speed [20, 21].

Table 2 Cerebellar ocular motor signs

Sign	Comment
Gaze-evoked nystagmus	Ocular oscillations observed while trying to hold gaze eccentrically (i.e., off-center), horizontally, and/or vertically. The fast phase of the nystagmus is toward the direction of gaze
Downbeat nystagmus	Ocular oscillations observed with the eyes in central position (i.e., the eyes are located in the primary mid-orbital position). The fast component beats downward. The nystagmus is exacerbated in downgaze and lateral gaze
Upbeat nystagmus	Ocular oscillations observed with the eyes in central position. The fast component beats upward. The nystagmus is exacerbated in up gaze
Rebound nystagmus	Transient ocular oscillations observed with the eyes in central position after returning from a maintained eccentric gaze
Periodic alternating nystagmus	Horizontal ocular oscillations observed with the eyes in central position that change direction gradually after a silent phase. It occurs in a periodical manner, usually every 1–2 min
Opsoclonus	Conjugate, random, involuntary, and multidirectional back-to-back fast eye movements observed during attempted fixation or movement of the eyes
Ocular flutter	Conjugate, random, involuntary, and horizontal back-to-back fast eye movements observed during attempted fixation or movement of the eyes
Ocular bobbing	Fast downward displacement of the eyes followed by slow return back to the central orbital position
Square wave jerks/ macro-saccadic oscillations	Fast, intruding, unwanted, involuntary, and conjugate eye movements, which take the eyes off fixation. They may occur repetitively
Saccadic dysmetria	Inaccurate fast eye movement that either undershoot (hypometria) or overshoot (hypermetria) a visual target
Saccade initiation delay (previously misnamed as ocular motor apraxia)	Increased latency of fast eye movements that can usually be overcome with a head thrust or a blink
Slowing of smooth pursuit velocity (especially initiation)	Jerky (instead of smooth) eye movements that are observed during visual tracking
Impaired response of the vestibulo-ocular reflex	The vestibulo-ocular reflex normally drives the eyes contralateral to the direction of the head movement. Abnormal amplitude and direction of eye movements during the head impulse test may occur in cerebellar disease. The patient is asked to fixate on the examiner's nose, while the head is actively and briskly rotated about 15° to the right and left
Impaired vestibulo-ocular reflex cancellation (VORc)	The ability to fixate objects moving in the same direction of the head requires cancellation of the vestibulo-ocular reflex. Patients with cerebellar disease may not be able to cancel the vestibulo-ocular reflex

(continued)

Table 2 (continued)

Sign	Comment
Abnormal optokinetic nystagmus	Fast ocular oscillations (jerk nystagmus) are normally observed while tracking a rotating drum with alternating white and black stripes. The nystagmus generated with such a stimulus may be exaggerated with chronic cerebellar disease or dampened with acute cerebellar lesions
Impaired adaptation of eye movements	Motor learning (adaptation) of the ocular motor system usually occur physiologically or following disease to repair and improve the accuracy or velocity of eye movements. Adaptation may be impaired in cerebellar disease
Skew deviation	Non-paralytic vertical misalignment of the eyes (i.e., one eye is higher than the fellow eye) which changes as a function of horizontal gaze position
Esotropia	Non-paralytic horizontal misalignment of the eyes with inward deviation
Abnormalities in the control of torsion	Abnormal rotational control of the eye around an axis perpendicular to the center of the pupil

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Table 3 Speech abnormalities in cerebellar diseases

Scanning speech (e.g., hesitation, accentuation of some syllables, omission of appropriate pauses, addition of inappropriate pauses)
Explosive speech
Slowness of speech
Syllables or words are not understandable with lack in speech clarity
Slurring of speech
Loss of intonation (abnormal rhythm and emphasis)
Voice tremor

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Cognition

Investigations on the cerebellar contribution to cognition are consistent with a role for the lateral cerebellar hemispheres in supporting cognitive processes [22]. In children, significant cognitive disruption is associated with pediatric cerebellar diseases ranging from cerebellar developmental abnormalities to inflammatory disorders, ischemic injury, oncologic, and postsurgical injury [23–32]. These cognitive deficits are associated with executive dysfunction, impairment in working memory, procedural memory, and processing abilities, in addition to a lower intellectual quotient and visuospatial abilities.

Affect and Behavior

The cerebellum is thought to modulate behavior. Schmahmann described the cerebellar cognitive-affective syndrome, which manifests with significant behavioral difficulties in patients with cerebellar disorders. The author and his colleagues described behaviors ranging from affective changes to disinhibited behaviors [19]. Other investigations of cerebellar lesions have supported these initial descriptions with many associated behavioral difficulties including alterations in attention, affective disruption, emotional and social blunting, anxious behaviors, and obsessive and compulsive behaviors [19, 27, 33, 34].

Assessment of Pediatric Patients with Developmental and Other Cerebellar Disorders

History

The assessment of patients with pediatric cerebellar disorders starts with a detailed clinical history, which can lead to the diagnosis in as many as 80% of patients [35]. Details of the presenting illness and complaints should be elicited including the age and date of onset, mode of the ataxia onset (i.e., acute, subacute, or chronic), location including whether the symptoms are unilateral or bilateral, severity, duration, rate of progression, factors that make the symptoms better or worse, possible triggers, and medications used [3–5, 36]. An inquiry should be specifically made about the presence of vertigo, dizziness, imbalance, oscillopsia, and blurred vision [8]. Systematic inquiry into other symptoms should then be pursued [35], including headache, confusion, developmental regression, seizures, numbness, tingling, and weakness.

Age of the parents at conception, previous miscarriages, mother's health and toxin exposure during pregnancy, antenatal screening and problems during pregnancy, birth history, birth weight, length, and head circumference, early feeding or respiratory difficulties, neonatal course, the number of days spent in hospital after birth, and past medical history are important part of the assessment.

Observing videos of children at different ages can be very valuable [36]. Developmental milestones may give further clues. For example, many patients with nonprogressive ataxia without brain malformations or with developmental cerebellar disorders manifest with motor delay and hypotonia before the ataxia becomes apparent [37–40].

Drug history and possible exposure to toxins or drugs should be obtained [4, 35]. Ethnicity, family history of consanguinity, ataxia, or other symptoms and disorders may all offer useful diagnostic clues [5]. However, it is important to be aware of challenges when obtaining the family history [41]:

1. Young parents or grandparents in autosomal dominant disorders (age-dependent penetrance). In such situation, the disease may not have manifested in family members yet.
2. Incomplete penetrance. The disease is not apparent in affected family members.
3. Early death in carriers from an unrelated cause.
4. New (de novo) mutations.
5. Lack of awareness of disease in family members especially further than one or two generations (i.e., the disorder is not known in the past or is unrecognized, or if the individual affected has not sought an assessment, or information on deceased relatives is not passed on).
6. Hidden or concealed symptoms from family members.
7. Family members may be divorced or scattered or had symptoms after they are out of touch.
8. Nonpaternity, infertility, adoption, or egg/sperm donation.
9. Small family with no affected members.
10. Negative prior genetic testing. It is important to inquire about what test was done, when, and how. New advances in techniques may have occurred since the test was done, pathogenicity of variants of unknown significance has been found, a previously unknown abnormality has been reported, or a newly described disease has been published.

Physical Examination

Careful general and then more focused examination should then be undertaken to look for cerebellar (Tables 1, 2, and 3) and non-cerebellar signs [4, 5, 35, 39, 40], for example, head size; weight; height; dysmorphic features; neurocutaneous stigmata (i.e., skin abnormalities that may be indicative of an underlying brain malformation); other skin lesions, e.g., telangiectasia; respiratory, cardiac, and abdominal examination for enlarged liver and spleen; scoliosis; pes cavus; contractures; and wasting.

Visual acuity, visual fields, pupillary reaction to light and near objects, and funduscopy exam in each eye should be done. A careful assessment of the different classes of eye movements in patients with ataxia can be quite helpful and may offer clues to the diagnosis [42]. A practical and comprehensive guide on the examination and interpretation of eye movements in children is available for the interested reader [43]. Ocular alignment, fixation stability, slow and fast eye movements (including smooth ocular pursuit, convergence, vestibulo-ocular reflex and its cancellation, and saccades) (Table 2) should be ascertained. In addition, facial and tongue movements, bulbar (ability to swallow liquid and solid food safely and without choking), speech (voice quality, clarity, prosody) (Table 3), tone (resistance to passive stretch), strength, coordination of the upper and lower limbs, reflexes, plantar response, various sensation modalities including proprioception, and gait should then be assessed (Table 1) [16].

Table 4 Cognitive and behavioral abnormalities in cerebellar diseases

Language (nonmotor speech, reading, writing)
Executive function and working memory
Autistic behavior (repetitive/restricted, social impairment)
Attention deficit hyperactivity disorder
Schizophrenia
Anxiety behavior
Mood disorders

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In young infants and toddlers, an opportunistic approach is recommended, at least initially, as the child may not be fully cooperative. A lot of information can be gleaned by hearing the child talk and watching the child interact with the parents, other siblings, or the physician during history taking. In addition, watching the child play, use an iPad, or move around the clinic room can be invaluable. It is worth paying attention to the child's affect, behavior, language use, and cognitive abilities. Are there any features suggestive of the cerebellar cognitive-affective syndrome (some of these features are shown in Table 4)?

Extracerebellar features should be looked for to identify red flags [4, 35]. For example, swollen optic disks suggest an expanding mass; decreased visual acuity from optic neuritis suggests acute disseminated encephalomyelitis or multiple sclerosis; altered level of consciousness suggests acute disseminated encephalomyelitis, stroke, or intoxication; facial nerve palsy, hearing loss, tinnitus, nausea, and vomiting may indicate brainstem compression from a tumor; apraxia of gait may be caused by hydrocephalus or Rett syndrome; and head size, if large then hydrocephalus should be excluded, and if small then genetic, viral, or metabolic diseases that affect the cerebrum should be pursued. Pyramidal tract signs (spasticity, hyperreflexia, Babinski's sign, or clonus), seizures, and dyskinesia imply involvement of the cerebrum.

Pitfalls in the Assessment of Ataxia

Although disorders of the cerebellum and its input or output tracts can cause incoordination, which we refer to as ataxia, it is important to exclude mimickers of ataxia, i.e., pseudoataxia. Poor coordination may result from many causes including decreased level of consciousness; subtle seizures; postictal state; nonconvulsive status epilepticus; extrapyramidal movement disorder; spasticity; weakness, e.g., from peripheral neuropathy; clumsiness only (i.e., developmental coordination disorder); muscular or skeletal disorders, for example, irritable hip; and psychogenic disorders [35, 44].

Formulating a Clinical Impression and a Plan of Investigations

After the history and physical examination are completed, the pattern of abnormalities is summarized. Variations in the clinical phenotype in relation to several disease etiologies in 184 children with chronic ataxia have been recently explored using latent class analysis. Few specific clinical patterns emerged that were highly associated with certain disease etiologies [45]. For example, if a child presents with global developmental delay, hypotonia, and seizures (which may occur before the ataxia becomes manifest), then Angelman syndrome, disorders of neuronal migration, and Joubert syndrome and related disorders should be suspected. A brain MRI with thin cuts will likely show the neuronal migration abnormalities, while genetic testing is needed for the diagnosis of Angelman syndrome where brain MRI is typically normal. In addition Joubert syndrome and related disorders have diagnostic MRI features known as the molar tooth sign. Another example is the child that has no history of seizures and has symptoms onset including ataxia at greater than 10 years of age with otherwise normal development but has slurred or scanning speech. In such a clinical scenario, episodic ataxia and Friedreich ataxia should be considered. If the ataxia is progressive, then Friedreich ataxia should be suspected first, but if the symptoms are intermittent, then episodic ataxia should be considered first. This clinical approach may aid the diagnostic process by making it more efficient. In general, one should ascertain the following:

1. What regions/networks are affected by the incoordination? Specifically, head, eye movements, speech, swallowing, arms, and gait involvement should be documented. There is a rough map for localizing cerebellar symptoms and signs. For example, symptoms of damage of the lateral cerebellar hemisphere include hypotonia, asthenia, intention tremor, and dysmetria, while vermal and paravermal lesions are associated with ataxia of gait and stance. Similarly, damage to the dorsal vermis and fastigial nuclei is associated with saccadic dysmetria and impaired saccadic adaptation, while damage to the vestibulocerebellum is associated with impaired smooth ocular pursuit and various types of nystagmus [8, 16, 46].
2. What is the mode of ataxia onset? Acute onset is suggestive of toxic, metabolic, vascular, or traumatic etiologies. Subacute onset may indicate infectious, inflammatory, or paraneoplastic etiologies, while chronic ataxia is more likely to be caused by genetic or neurodegenerative disorders [41]. There is however an overlap in the mode of onset among the different etiologies.
3. How does the ataxia change over time? Is the ataxia improving thus suggesting a postinfectious etiology, nonprogressive suggesting a cerebellar malformation, recurrent (i.e., episodic or intermittent with resolution between the episodes) suggesting an episodic ataxia or a metabolic disorder, or is the ataxia progressive suggesting a tumor or a neurodegenerative disorder? This information will help focus the investigations on more likely etiologies [3–5, 35, 36, 41].
4. Is it pure ataxia? Some diseases only affect the cerebellum, thus narrowing the list of diagnostic possibilities.

5. Are there any clues in the family history?
6. Are there non-ataxia central nervous system features? For example, spasticity, dyskinesia, seizures, or optic atrophy implies widespread central nervous system involvement beyond posterior fossa structures [41].
7. Are other organs affected? For example, heart, liver, and kidney involvement raises suspicion of a metabolic disorder.

Based on the clinical impression, a plan of investigation is carried out [3, 35, 41, 45]. Neuroimaging is usually very helpful, even when it is normal [44]. A brain magnetic resonance imaging (MRI), with magnetic resonance angiography and spectroscopy if indicated, offers the best spatial resolution of cerebellar and extracerebellar brain structures [44, 47]. A spinal MRI is occasionally helpful. For example, it may reveal spinal cord atrophy in patients with Friedreich ataxia [44]. In selected patients repeating a brain MRI several months or few years after the first brain MRI may offer further diagnostic clues in patients, who remain without a diagnosis despite extensive investigations [44].

Biochemical tests, drugs and toxins screen, and metabolic investigations on blood, urine, or where appropriate cerebrospinal fluid are then performed in a stepwise manner [3, 5, 41]. These include but are not limited to the following: full blood count, ESR, CRP, glucose, electrolytes, calcium, magnesium, phosphorus, albumin, creatinine kinase, liver and thyroid function tests, cholesterol, alpha fetoprotein, immunoglobulins, autoimmune antibodies (including ANA, ANCA, antigliadin antibodies), and metabolic tests (including ammonia, lactate, amino acids, ceruloplasmin, transferrin isoelectric focussing, uric acid, total and free carnitine, acylcarnitine, very long chain fatty acids, lysosomal enzymes, vitamins E, B1, and B12, phytanic acid, urine organic acids and amino acids, and CSF neurotransmitters).

Many genetic tests are available [36, 47], and are usually also requested in a stepwise manner guided by findings from the clinical assessment and neuroimaging findings. The tests include microarray, karyotype, FISH, calcium channel mutations, and mutations in selected spinocerebellar ataxia genes. Gene panel testing is another option for diseases with similar phenotypes. Whole-exome sequencing is not widely available in routine clinical practice but is proving to be a useful investigation in patients with undiagnosed ataxia.

Nerve conduction studies, electromyogram, electroencephalogram, and skin and muscle biopsies may also be indicated in some patients with ataxia.

Management

Management of the patients starts with discussing the findings of the clinical assessment with the patient and their parents. The discussion needs to be done honestly and in a sensitive manner. Every effort should be made to avoid using technical and medical jargons, taking the age of the patient and level of parental education into account. Diagnostic uncertainties and limitations should be disclosed. A plausible

list of diagnostic possibilities or details on a specific disorder when a diagnosis is made should then be discussed. Prognosis and availability of antenatal diagnosis for families that are interested in having more children should be mentioned. Referral to a geneticist for further investigations and counseling should be made, if indicated.

Treatment of the underlying disease etiology in acquired ataxias is possible in some disorders, for example, tumors, strokes, avoidance of toxins and certain medications, and inflammatory disorders [3].

General nonspecific management options for the symptomatic treatment of ataxia include physiotherapy, occupational therapy, and referral to other rehabilitation specialists. Continuous intensive motor training is beneficial [48]. Drugs and noninvasive cerebellar stimulation techniques such as transcranial magnetic stimulation or transcranial direct current stimulation are being explored, and preliminary studies show possible therapeutic benefit [48]. Referral to a speech and language pathologist in patients with dysarthria and speech or language delay should be made. Social workers and referral to support organizations such as the National Ataxia Foundation can be invaluable to the patients and their families [41].

There are limited treatment options available for the ataxic patients. Treatments for developmental cerebellar disorders and most hereditary ataxias are generally not available, and specific treatments are only available for a handful of diseases that are usually caused by metabolic dysfunction [3, 5, 48]. For example, vitamin E is given to patients with abetalipoproteinemia or ataxia with vitamin E deficiency, biotin to patients with biotinidase deficiency, coenzyme Q to patients with coenzyme Q deficiency, acetazolamide or 4-aminopyridine to patients with episodic ataxia type 2, nicotinamide for Hartnup disease, dietary modification and thiamine to patients with maple syrup urine disease, dietary modification and sodium benzoate to patients with urea cycle defects, and the ketogenic diet to patients with pyruvate dehydrogenase deficiency.

Other symptoms associated with ataxia should also be addressed and treated, for example, epilepsy, spasticity, sleep disturbance, behavioral difficulties, and anxiety.

Patients with multisystem disease should be referred to other specialists [41]. For example, patients with Friedreich ataxia should be referred to an endocrinologist, as they are at risk of developing glucose intolerance and diabetes, and a cardiologist since a life-threatening cardiomyopathy can occur in this disorder where possible treatments are available including idebenone, vitamin E, and coenzyme Q.

Conclusions

The cerebellum functions beyond motor coordination (Table 4). Roles for the cerebellum in children are identified in motor functions, cognition, and behavior in both normal development and also in disease. Since a significant part of cerebellar development stretches from the third trimester of pregnancy to the early postnatal years, diverse causes of cerebellar disruption contribute to the pathogenesis of

neurodevelopmental disorders. A comprehensive detailed history and physical examination are essential components of the clinical assessment in patients with cerebellar diseases and usually guide clinical investigations. Based on the list of differential diagnosis (i.e., plausible diagnostic possibilities), neuroimaging, usually a brain MRI, and various investigations including genetic testing are usually performed as part of the evaluation of these patients to reach a specific diagnosis. General physical rehabilitation therapy and disease-specific treatments are available. Novel drugs and noninvasive cerebellar stimulation techniques are showing an early therapeutic promise for the symptomatic treatment of some of the cerebellar symptoms.

References

1. Salman MS, Lee EJ, Tjahjadi A, Chodirker BN. The epidemiology of intermittent and chronic ataxia in children in Manitoba, Canada. Dev Med Child Neurol. 2013;55(4):341–7.
2. Musselman KE, Stoyanov CT, Marasigan R, Jenkins ME, Konczak J, Morton SM, et al. Prevalence of ataxia in children: a systematic review. Neurology. 2014;82(1):80–9.
3. Pandolfo M, Manto M. Cerebellar and afferent ataxias. Continuum (Minneap Minn). 2013;19(5):1312–43.
4. Prasad M, Ong MT, Setty G, Whitehouse WP. Fifteen-minute consultation: the child with acute ataxia. Arch Dis Child Educ Pract Ed. 2013;98(6):217–23.
5. Bernard G, Shevell M. The wobbly child: an approach to inherited ataxias. Semin Pediatr Neurol. 2008;15(4):194–208.
6. Holmes G. The Croonian lectures on the clinical symptoms of cerebellar disease and their interpretation. Lecture III. Lancet. 1922;200:59–65.
7. Reeber SL, Otis TS, Sillitoe RV. New roles for the cerebellum in health and disease. Front Syst Neurosci. 2013;7:83.
8. Bodranghien F, Bastian A, Casali C, Hallett M, Louis ED, Manto M, et al. Consensus paper: revisiting the symptoms and signs of cerebellar syndrome. Cerebellum. 2016;15(3):369–91.
9. Manto M, Bower JM, Conforto AB, Delgado-García JM, da Guarda SN, Gerwig M, et al. Consensus paper: roles of the cerebellum in motor control – the diversity of ideas on cerebellar involvement in movement. Cerebellum. 2012;11(2):457–87.
10. Marien P, Ackermann H, Adamaszek M, Barwood CH, Beaton A, Desmond J, et al. Consensus paper: language and the cerebellum: an ongoing enigma. Cerebellum. 2014;13(3):386–410.
11. Salman MS, Tsai P. The role of the pediatric cerebellum in motor functions, cognition and behavior: a clinical perspective. Neuroimaging Clin N Am. 2016;26(3):317–29.
12. Morton SM, Bastian AJ. Mechanisms of cerebellar gait ataxia. Cerebellum. 2007;6(1):79–86.
13. Thach WT. Does the cerebellum initiate movement? Cerebellum. 2014;13(1):139–50.
14. Bastian AJ. Learning to predict the future: the cerebellum adapts feedforward movement control. Curr Opin Neurobiol. 2006;16(6):645–9.
15. Bhanpuri NH, Okamura AM, Bastian AJ. Predictive modeling by the cerebellum improves proprioception. J Neurosci. 2013;33(36):14301–6.
16. Kheradmand A, Zee DS. Cerebellum and ocular motor control. Front Neurol. 2011;2:53.
17. Urban PP, Marx J, Hunsche S, Gawehn J, Vucurevic G, Wicht S, et al. Cerebellar speech representation: lesion topography in dysarthria as derived from cerebellar ischemia and functional magnetic resonance imaging. Arch Neurol. 2003;60(7):965–72.
18. Spencer KA, Slocomb DL. The neural basis of ataxic dysarthria. Cerebellum. 2007;6(1):58–65.
19. Schmahmann JD, Sherman JC. Cerebellar cognitive affective syndrome. Int Rev Neurobiol. 1997;41:433–40.

20. Marien P, Engelborghs S, Fabbro F, De Deyn PP. The lateralized linguistic cerebellum: a review and a new hypothesis. Brain Lang. 2001;79(3):580–600.
21. Murdoch BE, Whelan BM. Language disorders subsequent to left cerebellar lesions: a case for bilateral cerebellar involvement in language? Folia Phoniatr Logop. 2007;59(4):184–9.
22. Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. NeuroImage. 2009;44(2):489–501.
23. De Smet HJ, Baillieux H, Wackenier P, De Praeter M, Engelborghs S, Paquier PF, et al. Long-term cognitive deficits following posterior fossa tumor resection: a neuropsychological and functional neuroimaging follow-up study. Neuropsychology. 2009;23(6):694–704.
24. McAndrew S, Listernick R, Kuntz N. Cerebellar mutism in acute disseminating encephalomyelitis. Pediatr Neurol. 2014;50(5):511–4.
25. Parrish JB, Weinstock-Guttman B, Yeh EA. Cerebellar mutism in pediatric acute disseminated encephalomyelitis. Pediatr Neurol. 2010;42(4):259–66.
26. Weier K, Till C, Fonov V, Yeh EA, Arnold DL, Banwell B, et al. Contribution of the cerebellum to cognitive performance in children and adolescents with multiple sclerosis. Mult Scler. 2015;22(5):599–607.
27. Bolduc ME, Du Plessis AJ, Sullivan N, Khwaja OS, Zhang X, Barnes K, et al. Spectrum of neurodevelopmental disabilities in children with cerebellar malformations. Dev Med Child Neurol. 2011;53(5):409–16.
28. Bolduc ME, Limperopoulos C. Neurodevelopmental outcomes in children with cerebellar malformations: a systematic review. Dev Med Child Neurol. 2009;51(4):256–67.
29. Hennes E, Zotter S, Dorninger L, Hartmann H, Häusler M, Huppke P, et al. Long-term outcome of children with acute cerebellitis. Neuropediatrics. 2012;43(5):240–8.
30. Hoang DH, Pagnier A, Guichardet K, Dubois-Teklali F, Schiff I, Lyard G, et al. Cognitive disorders in pediatric medulloblastoma: what neuroimaging has to offer. J Neurosurg Pediatr. 2014;14(2):136–44.
31. Hoche F, Frankenberg E, Rambow J, Theis M, Harding JA, Qirshi M, et al. Cognitive phenotype in ataxia-telangiectasia. Pediatr Neurol. 2014;51(3):297–310.
32. Riva D, Cazzaniga F, Esposito S, Bulgheroni S. Executive functions and cerebellar development in children. Appl Neuropsychol Child. 2013;2(2):97–103.
33. Catsman-Berrevoets CE, Aarsen FK. The spectrum of neurobehavioural deficits in the posterior fossa syndrome in children after cerebellar tumour surgery. Cortex. 2010;46(7):933–46.
34. Tavano A, Grasso R, Gagliardi C, Triulzi F, Bresolin N, Fabbro F, et al. Disorders of cognitive and affective development in cerebellar malformations. Brain. 2007;130(Pt 10):2646–60.
35. Poretti A, Benson JE, Huisman TA, Boltshauser E. Acute ataxia in children: approach to clinical presentation and role of additional investigations. Neuropediatrics. 2013;44(3):127–41.
36. Fogel BL. Childhood cerebellar ataxia. J Child Neurol. 2012;27(9):1138–45.
37. Esscher E, Flodmark O, Hagberg G, Hagberg B. Non-progressive ataxia: origins, brain pathology and impairments in 78 swedish children. Dev Med Child Neurol. 1996;38(4):285–96.
38. Steinlin M, Zangger B, Boltshauser E. Non-progressive congenital ataxia with or without cerebellar hypoplasia: a review of 34 subjects. Dev Med Child Neurol. 1998;40(3):148–54.
39. Wassmer E, Davies P, Whitehouse WP, Green SH. Clinical spectrum associated with cerebellar hypoplasia. Pediatr Neurol. 2003;28(5):347–51.
40. Shevell MI, Majnemer A. Clinical features of developmental disability associated with cerebellar hypoplasia. Pediatr Neurol. 1996;15(3):224–9.
41. Fekete R. Ataxia. In: Jankovic J, Greenamyre JT, editors. MedLink neurology. San Diego: MedLink Corporation. Available at www.medlink.com. Last updated: 28th October 2015.
42. Salman MS, Chodirker BN. Neuro-ophthalmological findings in children and adolescents with chronic ataxia. Neuro-Ophthalmology. 2015;39(3):125–31.
43. Cassidy L, Taylor D, Harris C. Abnormal supranuclear eye movements in the child: a practical guide to examination and interpretation. Surv Ophthalmol. 2000;44(6):479–506.
44. Salman MS, Chodirker BN, Bunge M. Neuroimaging findings and repeat neuroimaging value in pediatric chronic ataxia. Can J Neurol Sci. 2016;43(6):824–32.

45. Klassen S, Dufault B, Salman MS. Can latent class analysis be used to improve the diagnostic process in pediatric patients with chronic ataxia? Cerebellum. 2017;16(2):348–57.
46. Dichgans J. Clinical symptoms of cerebellar dysfunction and their topodiagnostical significance. Hum Neurobiol. 1984;2(4):269–79.
47. Doherty D, Millen KJ, Barkovich AJ. Midbrain and hindbrain malformations: advances in clinical diagnosis, imaging, and genetics. Lancet Neurol. 2013;12(4):381–93.
48. Ilg W, Bastian AJ, Boesch S, Burciu RG, Celnik P, Claaßen J, et al. Consensus paper: management of degenerative cerebellar disorders. Cerebellum. 2014;13(2):248–68.