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REVIEW

Epidemiology of Cerebellar Diseases and Therapeutic Approaches

Michael S. Salman [1,2]

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Abstract Diseases involving the cerebellum occur relatively commonly in children and adults around the globe. Many factors influence their epidemiology including geography, ethnicity, consanguinity, and the methodology used to ascertain patients. In addition, reliable epidemiological data rely heavily on accurate disease classification. Continuous advances in genetic research and neuroimaging modalities have resulted in improved understanding of cerebellar diseases and have led to several revisions in their classification. Recent global epidemiological studies on ataxia reported an estimated overall prevalence rate of 26/100,000 in children, a prevalence rate of dominant hereditary cerebellar ataxia of 2.7/100,000, and a prevalence rate of recessive hereditary cerebellar ataxia of 3.3/100,000. The management of cerebellar diseases is multidisciplinary and multimodal. General supportive and symptomatic therapies should be initiated. Genetic counseling should be offered, where appropriate. Few drugs, specific motor rehabilitation programs, and noninvasive cerebellar stimulation for the treatment of ataxia have been developed and seem to show early promise, but more studies are needed to replicate and fine-tune their benefits further. Some disease-specific treatments are available. For example, acetazolamide or 4-aminopyridine for patients with episodic ataxia type 2 and vitamin E for patients with ataxia caused by vitamin E deficiency.

✉ Michael S. Salman
msalman@hsc.mb.ca

[1] Section of Pediatric Neurology, Children's Hospital, AE 308, 820 Sherbrook Street, Winnipeg, MB R3A 1R9, Canada

[2] Department of Pediatrics and Child Health, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

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Introduction

Ataxia is derived from the Greek word tassein meaning "arrange" or "put in order." It refers to movements that are poorly organized. Disorders of the cerebellum and its input or output tracts can cause ataxia [1]. However, not all cerebellar abnormalities or lesions cause ataxia, e.g., pontocerebellar hypoplasia type 1. On the other hand, ataxia may be caused by lesions outside the cerebellum. In the following sections, the author discusses the epidemiology and management of ataxia in general and in specific cerebellar disorders in children and adults.

Pitfalls in the Assessment of Ataxia and in the Classification of Cerebellar Diseases

Poor coordination may result from many causes. It is important to exclude mimickers of ataxia, i.e., pseudoataxia caused by subtle seizures, postictal state, nonconvulsive status epilepticus, decreased level of consciousness, extrapyramidal movement disorders, weakness, spasticity, clumsiness, skeletal disorders, and psychogenic disorders.

Reliable epidemiological data depends heavily on the methodology used to ascertain patients and on accurate disease classification. Challenges in classifying cerebellar diseases include complex embryology, partial molecular genetic knowledge, unclear syndromes delineation, variations in the names ascribed to various pathologies, expanding phenotypic spectrum definitions, intrafamilial variability, and developmental disruptions caused by hemorrhage or

ischemia mimicking malformations [2]. Genetic or image-based approaches are used to classify cerebellar disorders. However, brain MRI findings may not be easy to classify and thus pose more challenges. For example, is it cerebellar hypoplasia, atrophy, or both?

Etiology and Epidemiology of Cerebellar Diseases

Ataxia is a relatively common presentation in the pediatric and adult populations. Numerous diseases involve the cerebellum and many are associated with ataxia [1, 3–5]. Broad etiologies include infectious, postinfectious, and other inflammatory etiologies, such as multiple sclerosis, intoxication, e.g., after intravenous phenytoin load, alcohol, illicit drugs, and organic solvent exposure, primary and metastatic neoplastic or paraneoplastic disorders, genetic and neurodegenerative diseases, congenital malformations, metabolic disorders, vascular compromise following ischemia or hemorrhage, and brain trauma.

Factors Influencing Incidence and Prevalence Rates

Many factors can influence the epidemiology of cerebellar diseases (Table 1) including geography, ethnicity, consanguinity, and methodology used to ascertain patients [3, 6, 7].

A study from Cantabria, Spain, estimated the prevalence of autosomal dominant (AD) cerebellar ataxias to be 1.6/100,000 [8]. In Japan, the prevalence of AD spinocerebellar ataxias was 5/100,000 and autosomal recessive (AR) spinocerebellar ataxias 0.33/100,000 [9]. A prospective study from the Alsace region in France reported a prevalence rate of AR cerebellar ataxias of 5.3/100,000 during 2002–2008 [10]. A study from Portugal reported a prevalence of hereditary progressive cerebellar ataxia of 4.4/100,000 made up of the following: presumed AR of inheritance in 2.4/100,000, AD pattern of inheritance in 0.8/100,000, mitochondrial in 0.8/100,000, and "congenital" in 0.4/100,000 [11].

Friedreich ataxia (FA) remains the "most common" cause of progressive hereditary ataxia with a prevalence of 2–5/100,000 in Caucasians in central Europe [6, 10, 12]. A nationwide study of genetically confirmed FA in Norway showed a prevalence of 0.57/100,000 [12]. FA is reported to be absent in Japan [9].

In a study on the global epidemiology of hereditary cerebellar ataxia (HCA) [7], a systematic review was performed during 1983–2013 on patients with neurodegenerative disorders with progressive gait impairment. Twenty-two studies from 16 countries that included 14,539 patients were analyzed. The rates of dominant HCA prevalence was 2.7/100,000 (95% CI 1.5–4, range 0–5.6). The most common disease was SCA3 in Brazil then SCA2 in Spain, while third most common disease was SCA6. Recessive HCA prevalence was 3.3/100,000 (95% CI 1.8–4.9, range 0–7.2). The most common disease was FA, followed by ataxia-ocular motor apraxia or ataxia telangiectasia. However, it was reported that most families in population-based series as opposed to hospital bases studies had no diagnosis.

Pediatric ataxia has an estimated prevalence rate of 26/100,000 children in Europe [4]. The crude prevalence rate of ataxic cerebral palsy in Sweden was 10.9/100,000 live births (5% of 2.18 patients with cerebral palsy per 1000 live births) [13]. The prevalence of nonprogressive ataxia resulting from prenatal and perinatal events, after excluding patients with spasticity, was 13/100,000 in 6–22-year-old patients during 1971–1986 birth years in Sweden [14].

Geographic Variations in Hereditary Spinocerebellar Ataxia (SCA) and Other Disorders of the Cerebellum

SCA3 and SCA2 are the most common AD hereditary ataxias, while FA is the most common AR hereditary ataxia among Caucasians; however, there are geographic variations in their distribution (Table 2) [6].

The birth prevalence of Angelman syndrome ranges between 1.6 and 10 with an average of about 5/100,000 in prior studies from several countries including Australia, Denmark, Estonia, and the UK [15]. In Manitoba, Canada, the crude 18-year period prevalence was 5.9/100,000 for Angelman syndrome and 2.6/100,000 for FA, similar to the prevalence rates reported in Caucasians [3]. In studies that included children and adult patients, the prevalence of ataxia telangiectasia was 0.4/100,000 in Norway [16], 0.25/100,000 in France [10], and up to 2.5/100,000 in Caucasians. Ataxia telangiectasia was more common in Manitoba with a crude period prevalence of 4.8/100,000 likely reflecting its higher prevalence in the Mennonite population [3, 17]. Table 3 shows the prevalence of disorders associated with ataxia in children.

Pediatric Chronic Ataxia in Manitoba, Canada

A hospital-based, multi-source study in children with chronic ataxia up to age 16 years in Manitoba during 1991–2008 was conducted [3]. Chronic ataxia was defined as ataxia lasting more than 2 months or if it was recurrent ataxia. Children with primary brain tumors, isolated disorders of the peripheral nerves and vestibular system were excluded. One hundred seventeen patients of the total cohort of 184 patients (63.6%) developed chronic ataxia by age of 4 years. The annual mean crude incidence rate of chronic ataxia was 3.1/100,000 (95% CI 2.66–3.55, SD 0.89, range 1.5–4.6), while the annual mean crude period prevalence rate was 23/100,000 (95% CI 19.5–

Table 1 Factors influencing incidence and prevalence rates of cerebellar diseases

Factors	Comment
Demographic factors	This includes geography, ethnicity, consanguinity, migration, genetic fitness (age at disease onset, disease duration, which influences survival up to reproductive age, mating capacity, and fertility).
Ascertainment methods	This includes selection bias (multiple sources versus hospital or genetic centers), variation of methods across studies, quality of the data, and the use of heterogeneous inclusion and exclusion criteria.
Disease classification	For example when and how a diagnosis was made and how reclassification and making a diagnosis changed over time
Publication bias and language bias	
Prevalence may change over time	
Generalization of the data	

26.7, SD 7.3, range 9.6–32). The annual mortality rate range for the same period was between 0 and 1.2/100,000. These rates represent the minimum figures.

Recurrent ataxia (episodic and intermittent) occurred in 20 of 184 children with chronic ataxia with one additional new patient identified subsequently. Based on Canada Census for Manitoba for the years 1991, 1996, 2001, and 2006, the crude incidence rate of recurrent ataxia was 6.32/100,000, the crude prevalence rate 7.44/100,000, and the crude mortality rate 0.37/100,000 *during the 18-year study period* in children resident in Manitoba [18]. The etiology was as follows: episodic ataxia (EA) in four (three patients with type 2, one with type 5), EA with first-degree relatives with EA in four (gene testing was negative in three patients, one declined testing), multiple sclerosis in two, and one patient in each of the following diseases: multiphasic acute disseminated encephalomyelitis, carbamoyl phosphate synthetase deficiency, GLUT1 deficiency syndrome, mitochondrial disorder caused by complex 1 deficiency, and

Table 2 Geographic variations in hereditary ataxias

	Countries
(A) Most common autosomal dominant spinocerebellar ataxia:	
SCA3	Brazil, China, France, Germany, Japan, Netherlands, Norway, Portugal, Singapore, Spain, Taiwan, USA
SCA2	Cuba, India, Italy, Korea, Mexico, Spain, UK
SCA1	Serbia, South Africa
SCA6	Australia
SCA7	Finland
(B) Most common autosomal recessive spinocerebellar ataxia:	
Friedreich ataxia	Most common in Caucasians but rare in Finland and is not recorded in Japan
Ataxia-ocular motor apraxia	Next most common
Ataxia-ocular motor apraxia type 1	Most common in the autosomal recessive hereditary ataxias category in Japan where autosomal recessive ataxias are rare
Infantile-onset spinocerebellar ataxia	Most common form of ataxia in children in Finland
(C) Other hereditary ataxias:	
Dentatorubro-pallidoluysian atrophy (DRPLA)	Japan (3rd most common after SCA3 and SCA6)
SCA10	Latin America
Fragile X tremor-ataxia syndrome	1/3000 in males > 50 years old in California
Vitamin E deficiency	North Africa
Ataxia telangiectasia	Iberia, Poland, Russia
Autosomal recessive spastic-ataxia of Charlevoix-Saguenay	1st reported in French Canadians but is now described in several other populations

Table 3 The prevalence of disorders associated with ataxia in children

(1) "Musselman et al. 2014"	Prevalence per 100,000 in Europe age 0–19 years
Metabolic ataxia	7.25
Rett syndrome	3.25
Friedreich ataxia	1.8
AD cerebellar ataxia	0.45
Dandy-Walker syndrome	0.34 (10 in eastern Mediterranean region)
Ataxia telangiectasia	0.21
"Cerebellar hypoplasia"	0.17
Joubert syndrome and related disorders	0.17 (estimate: 1 in the USA)
(A) All genetic	14.61
(B) Acquired (Varicella, acute disseminated encephalomyelitis)	0.26
(C)	
(i) Ataxic cerebral palsy	10.65 (range 2.1–25.96)
(ii) Pediatric multiple sclerosis	0.67
Overall in Europe (A + B + C)	26
(2) "Salman et al. 2013"	Crude prevalence rate per 100,000 in Manitoba, Canada, for 0–16 years (1991–2008)
Nonprogressive ataxia of unknown etiology	14.8
Angelman syndrome	5.95
Ataxia telangiectasia	4.83
Mitochondrial disorders (associated with ataxia)	3.34
All ischemic strokes (associated with ataxia)	3.34
Friedreich ataxia	2.6
Neuronal ceroid lipofuscinosis	2.23
Joubert syndrome and related disorders	1.85
Neuronal migration disorders (associated with ataxia)	1.48
Hypoxic ischemic encephalopathy at birth (associated with ataxia)	1.48
Rett syndrome	1.48
Leukodystrophy	1.48
Salla disease	1.48
Dandy-Walker syndrome	0.74

polyarteritis nodosa. The etiology was unknown in six patients. The author found only estimates of the incidence and prevalence of EA in the medical literature. In the Manitoba study, the annual crude incidence rate of EA was 0.13/100,000 and the crude annual prevalence rate was 0.16/100,000 in children.

Management of Cerebellar Disorders

Management of patients with cerebellar disorders starts with patient education. The discussion needs to take the age of the patient and their level of education into account. Family members/guardians are also involved if the patient is a child. Diagnostic limitations should be disclosed. Prognosis should be mentioned. Encouraging contact with support groups (disease-specific or National Ataxia Foundation) is usually beneficial. Referral to a geneticist for counseling, further investigations, and antenatal diagnosis, if relevant, should be made.

Treatment of the underlying disease etiology in acquired ataxias is possible in some disorders, for example, tumors, stroke, avoidance of toxins/certain medications, and inflammatory disorders (Table 4) [1]. General supportive management options for the symptomatic treatment of ataxia include physiotherapy, occupational therapy, speech and language therapy, and referral to other rehabilitation specialists for their expert care and for equipment, e.g., walkers, orthotics, and wheelchairs. Social workers can provide invaluable help to

Table 4 Summary of management approaches

(A) Family education/support groups	Disease-specific or National Ataxia Foundation
(B) General:	
(1) Supportive	Physiotherapy, occupational therapy, speech and language therapy, rehabilitation
(2) Medical	Drugs, e.g., riluzole, individualized motor rehabilitation program, noninvasive cerebellar stimulation
(3) Surgical	Deep brain stimulation for tremor, correct deformity
(4) Treatment of associated noncerebellar symptoms	
(C) Disease specific:	
(1) Genetic counseling	
(2) Treatment of the cerebellar symptoms:	
Medication	Disease
(a) Acetazolamide, aminopyridines	Episodic ataxia especially type 2
(b) Aminopyridines	Downbeat nystagmus, ? other ataxic disorders
(c) Vitamin B1	Ataxia caused by Wernicke encephalopathy
(d) Vitamin B2	Hartnup disease
(e) Vitamin B12	Sensory ataxia caused by vitamin B12 deficiency
(f) Vitamin E	Ataxia caused by vitamin E deficiency
(g) Vitamin E and a complex diet	Abetalipoproteinemia
(h) Remove alcohol/toxins/drugs including antiseizure medications	
(i) Coenzyme Q10	Coenzyme Q10 deficiency
(j) Betamethasone	Ataxia telangiectasia
(k) Biotin	Biotinidase deficiency
(l) Plasma exchange, dietary change	Refsum disease
(m) Oral deoxycholic acid	Cerebrotendinous xanthomatosis
(n) Ketogenic diet	Glut1 deficiency syndrome, pyruvate dehydrogenase deficiency
(o) Specific dietary modifications/supplementations in metabolic diseases	Maple syrup urine disease, isovaleric acidemia, urea cycle defects, some mitochondrial diseases
(p) Gluten-free diet	Ataxia caused by celiac disease
(q) Thyroid hormone	Ataxia caused thyroid hormone deficiency
(r) Acetazolamide, branched chain amino acid therapy, D-cycloserine	SCA6
(s) Copper chelating agents	Wilson disease
(t) Miglustat	Niemann-Pick type C
(u) Immune modulation	Acute disseminated encephalomyelitis, multiple sclerosis, opsoclonus-myoclonus-ataxia syndrome, anti-GAD ataxia
(v) Surgery	Posterior fossa tumors, neuroblastoma

the patients and their families [19]. For multisystem diseases, patients should be referred to other specialists. For example, in FA, an endocrinologist may be needed to treat glucose intolerance and diabetes, while a cardiologist can help manage the cardiomyopathy [19].

Treatment of associated symptoms in some disorders should be offered including cramps, spasticity, parkinsonism, seizures, myokymia, hearing loss, sleep disturbance, depression, anxiety, and infections. Surgical options include deep brain stimulation for tremor (currently in research stage) and surgical correction of deformity.

There are limited treatment options available for treating ataxia. Treatments for developmental cerebellar disorders and most hereditary ataxias are generally not available with rare exceptions [20]. A Cochrane review on the management of FA neither supports nor refutes a beneficial effect from antioxidants [21]. Idebenone was found to have favorable effects on the cardiomyopathy and neurological dysfunction, but this is controversial since the benefits have not been replicated. In addition, several study designs were used for variable durations and mixed outcomes. Coenzyme Q10 and vitamin E were found to have no benefit in a randomized

controlled trial. Others treatments used include EPI A0001 (an α-tocopheryl quinone), L-carnitine, deferiprone, and erythropoietin. None showed proven benefits [21].

Drugs with Possible Benefit on Cerebellar Symptoms

Riluzole has shown early promise for the treatment of ataxia. It opens small conductance potassium channels, which regulate the firing rate of neurons in the cerebellar nuclei. The International Cooperative Ataxia Rating Scale (ICARS) scores decreased by ≥ 5 points at 8 weeks in a randomized controlled trial in 40 patients with ataxia of various etiologies [22]. In addition, the scale for the assessment and rating of ataxia (SARA) score decreased by ≥ 1 point at 1 year in a randomized controlled trial in 55 patients with SCA (mostly 1 and 2) and FA [23]. Varenicline has been used in patients with SCA3, but its use was associated with a 40% dropout rate due to side effects. Other drugs include acetyl-DL-leucine (open label in patients with mixed ataxia etiologies), amantidine (randomized controlled trial in 30 patients with "olivo-ponto-cerebellar atrophy" in 1996), zinc sulfate (randomized controlled trial in 36 Cubans with SCA2), lithium carbonate, IV immunoglobulins, and stem cell in SCA. Further studies are needed to replicate the benefits reported in these studies [20].

A Cochrane review on the treatment of dysarthria in patients with FA and other hereditary ataxia syndromes stated that "there is insufficient and low or very low quality evidence from randomized controlled trials or observational studies to determine the effectiveness of any treatment for the speech disorder" [24].

Motor Rehabilitation

The recovery potential of ataxia depends on the site and cause of the cerebellar lesion (i.e., static versus degenerative). In addition, the cerebellum is important for motor learning and damage can impair relearning of motor skills. Despite these potential challenges, continuous intensive motor training is beneficial [20].

Studies on Adults An intensive whole-body coordinative training on balance and mobility using case control with intraindividual design was completed in 16 patients with degenerative ataxia. SARA scale improved after 4 weeks. The improvement was also seen on quantitative movement analysis. The improvement was notable in the cerebellar ataxia but not the afferent ataxia group. The benefits lasted for 1 year with continuous training despite progression of the disease [25, 26]. In another study, a physiotherapy and occupational therapy program for 12 hours per week for 4 weeks in 42 patients with degenerative ataxia was completed. There was improved motor coordination, especially of the trunk more than limb ataxia, and also in activities of daily living. The sustained improvement seen in ataxia was mild but gains were maintained in more than half the patients at 24 weeks despite functional decline to baseline level [27]. Furthermore, a home balance exercise program for 6 weeks that was individualized in 14 ambulatory patients with severe mixed ataxias (sporadic, SCA's), revealed improved locomotor performance on clinical and laboratory assessment of balance and walking but not on ICARS scores. The level of challenge was noted to be a very important determinant of improvement [28]. The above studies focused on ambulatory patients with or without walking aids.

In addition, treadmill training and orthotics may still be helpful in patients with ataxia.

Is Relearning Occurring In or Outside the Cerebellum?

Imaging data have shown that patients with cerebellar degeneration rely more on extracerebellar areas during motor performance and training. The site of learning may depend on the task, i.e., whether cortico-basal (ganglia) nuclei loop is recruited, or parts of the cortico-cerebellar loop unaffected by the disease. Additional use of prefrontal areas may reflect increased reliance on strategic learning. The contralesional cerebro-cerebellar loop plays an important role in recovery of motor function of patients with cerebellar stroke [20].

Studies in Children and Adolescents There are only few small case reports in the pediatric age group. Lack of motivation to continue a rigorous training module as part of a treatment program is often cited; however, new technologies have been developed aiming to make the training program more exciting. A whole-body controlled video game technology for intensive coordinative training was used in one study [29]. Ten children with progressive spinocerebellar ataxia were trained for 8 weeks. The task demanded dynamic balance, goal-directed movements, and cognitive interaction. Raters were blinded. SARA score decreased by about two points at 8 weeks or better with more intense training. Biomechanical measures also improved and children were motivated.

Noninvasive Cerebellar Stimulation

Transcranial magnetic stimulation (TMS) utilizes a rapid electric current to induce a magnetic field that results in a rapidly changing electric field, which in turn depolarizes neurons.

TMS decreased truncal ataxia in patients with spinocerebellar degeneration [30].

Transcranial direct current stimulation (tDCS) utilizes direct current and has a neuromodulatory effect on cerebellar excitability. Anodal stimulation is excitatory. It is noninvasive, easily delivered, well tolerated, and has not shown serious side effects [20, 30]. Through direct electrical and nonelectrical effects (e.g., vascular or metabolic), cerebellar activity is modified and output of the cerebellar nuclei are altered. Cerebellar-motor connectivity is modified likely through the cerebellar-thalamocortical pathways. Cerebellar lobules VI–VIII seem most susceptible to modulation. Cerebellar tDCS can modulate motor learning and influence cognitive and emotional processes [31, 32]. In a double-blinded, randomized, sham controlled trial, 2-week treatment with cerebellar anodal tDCS was given to 20 patients with ataxias of mixed etiologies (e.g., SCAs, FA, ataxia-ocular motor apraxia type 2, multiple system atrophy-cerebellar subtype). Outcomes were determined using SARA score, ICARS score, nine-hole peg test, and 8-m walking time. Cerebellar brain inhibition (CBI) using TMS was also measured. Follow-up was up to 3 months. Significant improvements on all performance scores and CBI in the tDCS group (N = 12, mean age 55.2 years) was seen in comparison to the sham group (N = 8, mean age 49.9 years). tDCS is a potentially promising approach in patients with degenerative ataxia [33].

Treatment of Specific Disorders Associated with Ataxia

Specific treatments are available for some disorders associated with ataxia (Table 4) [1, 5, 19, 20, 34–38]. For example, acetazolamide or 4-aminopyridine for patients with EA type 2 [39] and vitamin E for patients with vitamin E deficiency.

Experimental treatments at the animal research stage include RNA interference therapy and mesenchymal and cerebellar neural stem-cell transplantation [20].

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Compliance with Ethical Standards

Disclosure None.

Conflict of Interest The author declares that he has no conflict of interest.

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