Epidemiology of Cerebellar Disorders

S. Shooshtari, B.M. Stoesz, P. Rad, and S. Khoeiniha

Abstract This chapter explains briefly the epidemiology of several cerebellar disorders, many of which are considered rare, and various risk factors associated with their development. For many cerebellar disorders, prevalence and incidence rates are unknown, or the values have been underestimated; this is true both at the global and regional levels. Scant epidemiological information can be attributed to lack of healthcare systems in various parts of the world, inaccurate classification of disorders in published studies, broad inclusion criteria, or simply rarity of the particular disorder. Information about the prevalence, incidence, or number of cases is important for planning and provision of services to address the needs of affected individuals. Epidemiological studies are also necessary to identify factors that contribute to the development of the disorder, which can be used to prevent or reduce the risk of developing the conditions at the population level.

Keywords Cerebellar disorders • Epidemiology • Incidence • Prevalence • Risk factors

Introduction

This chapter is focused on epidemiology of cerebellar disorders, and provides information on global and local prevalence and incidence (where available), and risk factors associated with the development of the disorder. *Prevalence* and *incidence* are the two main measures of disease occurrence in populations. Prevalence refers to the proportion of population with the condition of interest at a certain point in time or within a specific period. Incidence refers to the rate at which new events or cases of the condition of interest occur in a population in a defined period. Prevalence estimates provide useful information for planning and provision of services to address the needs of persons living with the conditions of interest. This information

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can also be used to examine trends in the occurrence of the conditions of interest to determine if the number of cases and rates have increased, decreased, or remained stable over time. Results of incidence studies are of great use for predicting future needs and for investigating causality and identifying factors associated with increased risk of a disorder of interest. Information on factors found to be significantly associated with the risk of the cerebellar disorders could aid in the identification of modifiable risk factors to prevent or reduce the risk of developing the condition at the population level.

Selection of Studies

A search was performed on the MEDLINE, Embase, and Scopus databases. The following search terms were used: [name of condition], AND "epidem*" OR "prevalence" OR "incidence" OR statistic* OR risk*. For the name of the condition, truncation was used to be more inclusive of alternative terms and spellings (e.g., cerebell* was used as appropriate for the cerebellum OR cerebellar). The search was restricted to records published in English. In total, 366 references were located. Initial examination of the records revealed that only 29 references to book, chapters, and sections and 337 references to articles were relevant to epidemiology or risk factors.

We selected studies providing estimates of prevalence and/or incidence for a specified population in a defined geographical region. Because we expected few publications for many of the conditions of interest, we defined broad inclusion criteria: (1) the article must mention estimates of prevalence and/or incidence and/or describe cases of the condition, or (2) the article must identify and describe risk factors for the condition, and (3) only articles published in English. Two authors independently reviewed the titles and abstracts of the publications identified by the initial search strategy. Studies that clearly did not meet the inclusion criteria were excluded, and the remaining studies were examined further. Inclusion was based on agreement between two reviewers; in cases of non-consensus, a third (and sometimes fourth) review was obtained for decision. For selected articles, data were extracted using a predefined data extraction form, which included the following parameters: publication type, geographical area, study population, number of patients identified, research design, study period, data source, condition and subtypes, prevalence and incidence estimates for each condition, and risk factors. Study limitations were noted. For conditions in which prevalence and incidence estimates were not available, the number of cases of a condition was reported. The reference lists of the selected papers were examined for additional studies. The quality of the studies was not assessed.

Results

Many cerebellar disorders are described as rare, very rare, or extremely rare. According to the consortium of European partners [1], "rare" is defined as affecting 1 per 2,000 people. Similarly, the United States Rare Diseases Act of 2002 [2]

defines "rare" as "any disease or condition that affects fewer than 200,000 people in the United States" or about 1 per 1,500 people. In Japan, a "rare" disorder is one that affects fewer than 50,000 people or 1 per 2,500 people.

Autism Spectrum Disorder and the Cerebellum

Autism spectrum disorders (ASD) are neurodevelopmental conditions that are characterized by deficits in social communication and social interaction, restricted and repetitive patterns of behavior, interests, or activities [3]. The comorbidity of ASD and intellectual disability (ID) is relatively low, with approximately 31% of US children with ASD being identified as having intellectual disability (i.e., IQ≤70 [4]). The cerebellum is reported to be one of the key brain regions affected in autism [5].

ASD are responsible for 0.3% of the global burden of disease and more than 7.6 million disability-adjusted life years. The global prevalence of ASD is estimated to be one person in 160 [6]. A large number of epidemiological studies from developed countries have investigated ASD prevalence, and less is known about prevalence of ASD in developing countries. Variable estimates of ASD prevalence are reported, ranging from 0.4 to 22.4 per 1,000, depending on the age, sex, and race/ethnic composition of the population studied, ASD diagnostic criteria used, changes in diagnostic criteria over time, the methods of data collection, and case ascertainment. While earlier European studies reported ASD prevalence estimates of 1 in 2,500 children across all ages in the population [7], more recent estimates of ASD prevalence based on large survey data suggest that 1–2% of all children are affected [8, 9]. For example, a UK school-based survey reported 99 per 10,000 [10]. The most recent estimate of ASD prevalence for children aged 3–17 years in the United States was reported at 2.24% based on data from the 2014 National Health Interview Survey (NHIS) [11]. The estimated prevalence was significantly higher than the estimated prevalence of 1.25% based on earlier years of data from the same survey (2011–2013). The observed difference was attributed to the change in wording of the survey questions that allowed parents to better differentiate ASD from other types of developmental disabilities [11]. Other studies from Europe, North America, and Asia also reported prevalence estimates of higher than 2% [4, 12, 13].

The Autism and Developmental Disabilities Monitoring (ADDM) Network is an active surveillance system in the United States, which provides estimates of the ASD prevalence among children aged 8 years living in 11 ADDM sites. According to this source, the overall prevalence of 8-year-olds with ASD in 2010 was 14.7 per 1,000 (1 in 68) [4]. There was variation in the reported prevalence estimates by sex and racial/ethnic background. ASD was four to five times more prevalent in boys (1 in 42 boys) than in girls (1 in 189 girls). Non-Hispanic white children were also 30% more likely than non-Hispanic black children to be identified with ASD. The median age at first ASD diagnosis was 53 months and did not differ by sex or race/ethnicity [4].

The reported estimates of ASD prevalence in Canada are lower due to the different case ascertainment method used. The National Epidemiologic Database for the Study of Autism in Canada (NEDSAC) has been monitoring the prevalence of ASD in three Canadian provinces including Newfoundland and Labrador, Prince Edward Island, and Southeastern Ontario since 2003. Based on information from this database, the prevalence of ASD was estimated at 1 per 94 children. Based on data collected through 2008 in Newfoundland and Labrador and 2010 in Prince Edward Island and Southeastern Ontario, the estimated average annual percent increases in prevalence among children 2–14 years of age ranged from 9.7 (95% CI: 7.8–11.6) to 14.6% (95% CI: 11.3–18.0) [14]. See Table 1 for a summary of prevalence estimates for ASD.

Epidemiological data over the past few decades suggest an increase in ASD prevalence globally. Several explanations are provided for this apparent increase in ASD prevalence including changes in diagnostic criteria and broadening of the diagnostic spectrum, greater awareness about ASD conditions among parents and clinicians, better diagnostic tools that might have led to a higher rate of diagnosis, and better reporting of cases and surveillance systems. The observed increase in ASD prevalence could also be the result of true increase in incidence. Given the complexity of the issue, however, no conclusions regarding causes of increased prevalence of ASD can be made at this time.

Research suggests that a complex and variable combination of genetic and environmental factors influences early brain development, leading to ASD [15, 16]. For example, a higher concordance between monozygotic and dizygotic twins is consistently shown, suggesting a genetic link for ASD [17]. Other researchers have estimated that approximately10–15% of persons with autism have a specific genetic mutation (see [18]).

Recent epidemiological studies have shown a positive association between increasing parental age at conception and ASD risk in offspring (see [19] for a review); however, a review of US data concluded that parental age is a very small contributor to the observed increases in the prevalence of ASD [20]. Maternal illness and infection during pregnancy, extreme prematurity, very low birth weight, and complications during birth, particularly those involving periods of oxygen deprivation to the baby's brain, are reported as important risk factors for ASD [19, 21]. Mothers exposed to high levels of pesticides and air pollution may also be at higher risk of having a child with ASD (e.g., [22]), although the evidence for this assertion has been described as limited and of moderate strength (see [23]). Interestingly, maternal smoking is also not associated with increased ASD [24]. A significant positive association has been observed between ASD prevalence and socioeconomic status (SES), suggesting increased risk of ASD with increasing SES. This observed association likely reflects diagnostic biases and/or disparities that exist in accessing services for ASD assessment [25]. Findings from a small number of studies suggest that autism risk is reduced among children whose mothers ingested prenatal vitamins and folic acid, fish and fish oil supplements, and/or fatty acids in the months before and after conception (see [26] for a review). The information available on risk factors associated with ASD clearly suggests that there is no single cause of autism.

Table 1 Prevalence of autism spectrum disorders

	Study details				Population			
Author, date	Publication type/ research design	Country (region)	Study period	Data source	Age	Sex	*N*	Prevalence
World Health Organization, 2013	Report	Global	–	–	–	–	–	6.25/1,000
Baron-Cohen et al., 2009	Cross-sectional	UK	–	Special Educational Needs (SEN) register and survey	5–9 years	M and F	11,700	9.9/1,000
Zablotsky et al., 2015	Cross-sectional	US	2011–2014	Population-based	3–17 years	M and F	43,283	22.4/1,000
Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, 2014	–	US	2010	ADDM Network	8 years	M and F	–	14.7/1,000 (overall) 1/42 (boys) 1/189 (girls)
Ouellette-Kuntz et al., 2014	Retrospective	Three Canadian provinces	2008–2010	The National Epidemiologic Database for the Study of Autism in Canada (NEDSAC)	2–14 years	M and F	–	10.6/1,000

ADDM Autism and Developmental Disabilities Monitoring

Ataxia

The word ataxia is derived from the Greek word "a taxis" meaning "without order." Patients with ataxia suffer from lack or loss of movement coordination resulting in poor coordination of gait or hands and disturbances in speech and oculomotor control [27]. Ataxia can negatively influence a person's ability to walk, sit, and stand [28]. The prevalence of ataxia in children has been estimated to be 26 per 100,000 [27], and the lifetime prevalence rate is reported to be 50 per 100,000 (see [29]), but these estimates vary depending on the type of ataxia or region. The most common types of ataxia are cerebellar, sensory, and vestibular. Cerebellar ataxia can also be divided into hereditary and nonhereditary ataxias.

Hereditary Ataxias

Hereditary cerebellar ataxias (HCA) can be inherited in an autosomal recessive, autosomal dominant, X-linked, and mitochondrial manner.

Autosomal Recessive Ataxias

In their systematic review and meta-analysis of prevalence in 22 studies, reporting on 14,539 patients from 16 countries, published between 1983 and 2013, Ruano, Melo, Silva, and Coutinho [30] reported that the prevalence rates for autosomal recessive hereditary cerebellar ataxia (AR-HCA) ranged from 0.0 to 7.2 per 100,000. Studies from this review are briefly described here. Two hospital-based studies from Cantabria region in Spain and Alsace region in France reported the highest prevalence rates at 7.2 per 100,000 [31] and 5.3 per 100,000 [32]. Prevalence estimates from multisource studies (i.e., cases from community settings, hospitals, and probands' families included in the estimates) tended to be lower (e.g., 2.3–4.8 per 100,000). For example, in a cross-sectional study conducted in southeast Norway between January 2002 and February 2008, Erichsen, Koht, Stray-Pedersen, Abdelnoor, and Tallaksen [33] found that the prevalence of AR-HCA was 2.3 per 100,000; patients were on average 32 years (range, 4–71 years) and were diagnosed at 9 years of age (range, 1–55 years). Gender differences in prevalence have not been observed. Globally, the incidence rate for AR-HCA is 4 per 100,000 (see [34]). See Table 2 for a summary of statistics found in studies examining the epidemiology of ataxia.

AR-HCA can be grouped into four classes based on the age of onset and key phenotypic features: Friedreich ataxia and early-, adolescent-, and adult-onset ataxias [34]. Friedreich ataxia is the most common form of AR-HCA in the world ([30]; see [35]). Some reports indicate that nearly 50% of all AR-HCA cases comprise Friedreich ataxia; therefore, screening all patients suspected of having AR-HCA for Friedreich ataxia prior to other genetic testing has been recommended [34]. In a retrospective cross-sectional study conducted in Iran, Friedreich ataxia and spinocerebellar ataxia (a type of adolescent-onset ataxia) were the most common types of

Table 2 Prevalence, incidence, and/or number of cases reported in studies examining the epidemiology of ataxia

	Study details				Population					
Author, date	Publication type/research design	Country (region)	Study period	Data source	Age	Sex	*N*	Prevalence	Incidence	Number or % of cases
Anheim et al., 2010	Retrospective	France (Alsace)	2002–2008	Hospitals	–	M and F	95	AR = 5.3/100,000	–	–
Erichsen et al., 2009	Cross-sectional	Norway (Southeast)	2002–2008	Population-based	0–80 years	M and F	171	AR = 2.3/100,000 AD = 4.2/100,000	–	–
Farghaly et al., 2011	Community-based	Egypt	–	Door-to-door survey	4–72 years	M and F	62,583	Acquired ataxia = 27.16/100,000	–	17 cases (7F; 10 M)
Polo et al., 1991	Retrospective	Spain (Northern)	1974–1986	Hospitals, families	M and F	54	AR = 7.2/100.000	–	–	
Nafissi et al., 2009	Retrospective cross-sectional	Iran	1993–1999	Dr. Shariati Hospital, University of Tehran	6–73 years	M and F	135	–	–	15 cases of HCA
Salman et al., 2013	Retrospective	Canada (Manitoba)	1991–2008	Children's hospital	0–16 years	M = F	184	Chronic ataxia = 2.4/10,000	Chronic ataxia = 3.2/100,000	9 cases of mitochondrial disease

AD autosomal dominant, *AR* autosomal recessive, *HCA* hereditary chronic ataxia

HCA identified among 135 patients with cerebellar ataxia from March 1993 to March 1999 in Dr. Shariati Hospital, University of Tehran [36]; however, the percentage of cases of the 15 patients with HCA was not reported. Other reports have estimated lower prevalence of Friedreich ataxia at 0.15 per 100,000, but higher rates for early-onset ataxias (i.e., 0.4 per 100.000 for ataxia telangiectasia) [33].

Autosomal Dominant Ataxias

In their review, Ruana and colleagues [30] found significant variation in the reported prevalence estimates for autosomal dominant HCA (AD-HCA) across 15 studies. Overall, prevalence of AD-HCA was 2.7 per 100,000 (range, 0–5.6 per 100,000). No cases of AD-HCA were found among 16 Italian patients with hereditary ataxia [37], whereas other work conducted in Portugal suggests a prevalence rate of 5.6 per 100,000 population [38]. Prevalence rates in multisource population-based surveys (e.g., [38]) or in the registry studies (e.g., [39]) were higher than genetic center-based studies ranging from 1.6 to 2.5 per 100,000. In the Netherlands, the prevalence of the AD-HCA is at least 3 per 100,000 [40]. In a cross-sectional study conducted in southeast Norway between January 2002 and February 2008, the prevalence rate of AD-HCA was estimated at 4.2 per 100,000, and only 8% of cases had a genetic diagnosis [33]. The mean age of the cases of AD-HCA was 57 years (13–94 years) without any gender difference after adjustment for age [33]. Among patients with AD-HCA, spinocerebellar ataxia type 3 (SCA3)/Machado-Joseph disease may be the most common, followed by SCA2 and SCA6 (see [30]). See Table 2.

X-Linked Ataxias and Ataxias Due to Mitochondrial Mutations

Little information is available on the epidemiology of X-linked and mitochondrial HCA. This may be due to the fact that the required genetic testing for the diagnosis of these conditions is not performed. The few studies that describe X-linked ataxias or ataxias linked to mitochondrial mutations have only found few cases. For example, in a retrospective study using multiple sources of data of children examined at a children's hospital in Manitoba, Canada, Salman, Lee, Tjahjadi, and Chodirker [41] reported nine cases of intermittent or chronic ataxias in children linked to mitochondrial disorder. Therefore, further epidemiological studies are required to determine the extent to which X-linked and mitochondrial HCA occur. See Table 2.

Acquired Ataxias

Acquired ataxias are a group of nonhereditary ataxias associated with exposure to alcohol or other toxins or infections or can be due to vitamin deficiency or metabolic disorders [42]. Acquired ataxias are typically divided into two main groups: acute (in a period of minutes to hours it occurs) and subacute (onset is from days to weeks).

Our literature search revealed only one original research study describing the epidemiology of acquired ataxia. In a population-based study, Farghaly and colleagues [29] estimated the crude prevalence rate of acquired ataxia to be 27.16 per 100,000 in Al-Kharga district, New Valley, Egypt. Using a door-to-door survey method, 17 cases of acquired ataxia were identified; on average, individuals were 31.8 years of age (range, 4–72 years) and the male to female ratio was 2.1:1 [29]. See Table 2.

Describing the prevalence rates of acquired ataxia by age group is important because risk factors for the condition often differ across age. In a retrospective study conducted at a children's hospital in Pittsburgh, USA, Thakkar and colleagues [43] reported that post-infectious cerebellar ataxia was a common cause of acute cerebellar ataxia (ACA) affecting 59% of patients with ACA. The authors reported no cases of ACA related to varicella infections; however, other research has indicated that varicella and other infections are strongly associated with ACA [44]. Post-infectious cerebellar ataxia accounts for up to 40% of ACA in preschool children (age 1–4 years), which is followed by toxic ingestion (i.e., 30% of ACA cases) [28]. Strokes (ischemic or hemorrhagic) and medications are other potential causes of ACA, particularly in elderly individuals [29]. Subacute ACA can be observed in various situations, including nutritional deficiencies (vitamin B12, vitamin E, folate, copper), autoimmune or inflammatory diseases, and infectious, primary, and metastatic tumors [34].

Cerebellar Tumors

Primary brain tumors are the most common type of neoplasms of childhood, comprising approximately 20% of all pediatric tumors. Globally, about 30,000–40,000 children develop central nervous system tumors each year (see [45]). In the United States, over 3,000 children under the age of 20 years are diagnosed with a brain or spinal cord tumor annually [46]. The incidence of brain tumors in children is estimated between 2.76 and 4.28 per 100,000 children per year [47]. Although significant progress has been made in the diagnosis and treatment of brain tumors in children, they are still the primary cause of cancer-related deaths in children. Tumor type and location are important prognostic factors. Tumors of the cerebellum are associated with symptoms such as ataxia, horizontal nystagmus, dysmetria, headache, vomiting, and lethargy [47, 48].

Medulloblastoma

Medulloblastomas, which typically arise in the cerebellum, are the most common malignant central nervous system tumor in children and the second most common pediatric brain neoplasm. Medulloblastoma accounts for 12–25% of all central nervous system tumors in children [46]. Medulloblastomas present at approximately

5–7 years of age on average and occur more frequently in boys than in girls [49–51]. Moreover, 25% of newly diagnosed cases of medulloblastoma occur in individuals aged 19 years and older [52]. The earlier incidence estimates of medulloblastoma brain tumor were 9.6 per million in children and 0.54 per million in adults [53, 54]. The European annual incidence rate for primitive neuroectodermal tumors (PNET, morphologically similar tumors arising in other areas of the central nervous system) was reported to be 6.5 per million children (age 0–14 years) for the period 1988–1997 [55]. The incidence rates of medulloblastoma and PNET are fairly stable from birth through 3 years of age and decline gradually thereafter. See Table 3 for a summary of statistics.

Several studies from Asia have examined the epidemiology of cerebellar tumors. In a retrospective cohort study, Tabatabaei and colleagues [47] reviewed the medical records for all pediatric cases of posterior fossa tumor that were referred to a neurosurgical clinic in Iran for surgery from 1981 to 2011. The authors extracted demographic data including patient's age, gender, and tumor characteristics along with the location and pathological diagnosis for all the cases and assessed the surgical outcomes according to pathological diagnosis. The study cohort consisted of 84 patients (52 males, 32 females). Medulloblastoma was found in 42.8% of cases, followed by cerebellar astrocytoma (28.6%), ependymoma (14.3%), brain stem glioma (7.2%), and miscellaneous pathologies (e.g., dermoid, and tuberculoma) (7.2%).

Ahmed and colleagues [56] examined the epidemiology of brain tumors during infancy and childhood using 10 years of data (1989–1998) at a tertiary care hospital in Karachi, Pakistan. Of the 81 cases that were identified, 71.6% were males and 28.4% were females (i.e., male to female ratio of 2.5:1). When dividing the cases into three age groups (0–4, 5–9, 10–14 years), the largest number of cases was found in children ages 5–9 years. The mean age for all cases was 8.8 years (95% CI: 7.9; 9.6) with a marginal variation for cases occurring in the cerebrum and cerebellum. Of the 81 cases, 33.3% were supratentorial, and 66.7% were infratentorial tumors, and 70.4% of the infratentorial tumors were medulloblastomas. Consistent with other research [50], Ahmed and colleagues [56] concluded that pediatric brain tumors are more prevalent among males than females and that medulloblastoma is the most common type of brain tumors in children. Similarly, Asirvatham and colleagues [49] found that medulloblastomas were the second most common type of brain cancers (11.4% of cases) among 1,403 tumors that were identified in children (aged 0–18 years) diagnosed between 1990 and 2004 at a tertiary care center in South India. The mean age at diagnosis was 10.9 years, and males were more frequently diagnosed than females (i.e., ratio of 1.7:1).

Chan and colleagues [57] conducted a 9-year retrospective study based on data reported to the Singapore Children's Cancer Registry from 1997 to 2005. A total of 39 children aged 15 years and younger were diagnosed with medulloblastoma or PNET arising in the cerebellum. Follow-up data for these children were collected up to 2006. Medulloblastoma/PNET was the most common type of brain tumor in the sample, accounting for 40.7% of all brain tumors.

Table 3 Prevalence, incidence, and/or number of cases reported in studies examining the epidemiology of cerebellar tumors

	Study details				Population					
Author, date	Publication type/research design	Country (region)	Study period	Data source	Age	Sex	*N*	Prevalence	Incidence	Number or % of cases
Ahmed et al., 2007	Cross-sectional	Pakistan	1989–1998	Hospital database	M_{age} = 8.8 years; range: 5–9 years	M = 71.6%; F = 28.4% M/F = 2.5/1	81	–	–	–
Asirvatham et al., 2011	Retrospective cohort	India	1990–2004	Pathology and medical records	M_{age} = 10.9 years; range: 0–18 years	M/F = 1.7/1	1043	–	–	5 most frequent tumors: astrocytoma (47.3%), medulloblastoma (11.4%), craniopharyngioma (9.7%), ependymal tumors (4.8%), nerve sheath tumors (4.1%)
Chan et al., 2007	Retrospective cohort	Singapore	1997–2005	Singapore Children's Cancer Registry	0–15 years	M and F	39	–	–	Medulloblastoma/PNET = 40.7% of tumors
Giordana et al., 1999	Retrospective cohort study	Italy	1976–1995	Hospital charts and operating room books from 5 neurosurgical units	16–69 years	M and F	4.3 million	–	All ages: 0.5/million/year; males (0.82/million/year); females (0.28/million/year); highest incidence for 16–19 years old (2.33/million/year)	45 (32M; 13F) cases of medulloblastoma

(continued)

Table 3 (continued)

	Study details				Population					
Author, date	Publication type/research design	Country (region)	Study period	Data source	Age	Sex	*N*	Prevalence	Incidence	Number or % of cases
Peris-Bonet et al., 2006		Europe	1978–1997	ACCIS database	0–14 years	M and F	19,531		ASR for CNS tumors (1988–1997) = 29.9 per million; ASR for PNET = 6.5 per million (1988–1997)	–
Roldán et al., 2008	Retrospective cohort study	Canada	1975–1996	Alberta Cancer Registry	Age of diagnosis: children M_{age} = 7 years; adults M_{age} = 29.2 years	M>F	2.8 million		–	49 cases of medulloblastoma/PNET
Smoll and Drummond, 2012	Retrospective cohort study	USA	1973–2007	Epidemiology and End Results (SEER) database	Children 1–9 years 10 times more affected by medulloblastoma and 4.6 times more by PNET	M/F = 1.58/1		–	Medulloblastoma = 1.5 per million population, PNET = 0.62 per million population	1,372 cases of medulloblastoma, 530 cases of PNET
Tabatabaei et al., 2012	Retrospective cohort study	Iran	1981–2011	Patient records	1–14 years	M>F	84	–	Brain tumors = 2.76–4.28/100,000 children per year	Medulloblastoma in 42.8% of cases
Thorne et al., 1994	Retrospective population-based study	England (Southwest and Northern)	1976–1991	Bristol Registry of Childhood Cancer	0–14 years	M and F	20.0 million child yrs		1976–1984 = 9.6 per million per year; 1985–1991 = 1.7 per million per year	1976–1984 = 16 cases of medulloblastoma 1985–1991 = 2 cases of medulloblastoma

ASR age-standardized incidence rate, *CNS* central nervous system, *PNET* primitive neuroectodermal tumor

Several studies from North America provided estimates of prevalence and/or incidence rates of cerebellar tumors. Using data from the Surveillance, Epidemiology, and End Results (SEER) database, Smoll and Drummond [50] estimated the incidence rates, ratios, and time trends of medulloblastoma and PNET in children and adults in the United States. Between 1973 and 2007, 1,372 people were diagnosed with a medulloblastoma and 530 with a PNET. The overall incidence rate of medulloblastoma and PNET was estimated at 1.5 and 0.62 per million, respectively; children (1–9 years of age) were ten times more likely to be diagnosed with these tumors than adults (i.e., 6.0 vs. 0.6, respectively). Children were also 4.6 times more likely to be afflicted by a PNET than adults. During childhood, boys were 1.58 times more likely than girls to be diagnosed with a medulloblastoma. Those categorized as "black" were 0.61 times more likely than those classified as "white" to be diagnosed with a medulloblastoma, and this was significant in children and adults [50]. Roldan and colleagues [58] examined 21 years of data (1975–1996) from the Alberta Cancer Registry, a population-based cancer registry for the province of Alberta in Canada, which had a population of 2.8 million in 1996. An addition has been made to clarify that 61% of the total sample of 49 cases were males. The mean age at the diagnosis for children was 7 years and for adults was 29.2 years.

Although some genetic disorders (i.e., Gorlin syndrome, Turcot syndrome, Li-Fraumeni syndrome [LFS]) are associated with an increased risk of medulloblastoma, the etiology is unknown for most patients [59]. Because the highest incidence rate is reported during childhood, very early life experiences may be contributing factors in the development of brain tumors [51]. A meta-analysis conducted by Harder and colleagues [60] confirmed that high birth weight was associated with increased risk for medulloblastoma. Infection during pregnancy and deficient social environment may also be significant risk factors for cerebellar tumors. For example, in a case-control study in England, children of mothers with a documented viral infection during pregnancy had an 11-fold increased risk of malignant nervous system tumor compared to children whose mothers did not have such a history during their pregnancy [61]. Lack of social contact in the first year of life is associated with increased risk of developing a central nervous system tumor in childhood, and the effect is greater for medulloblastoma/PNET [62].

The role of diet as a potential risk or protective factor in brain tumors has been investigated in several studies [e.g., 63, 64, and 65]. In rodents, maternal dietary intake of N-nitroso compounds (NOC) and NOC precursors (e.g., sodium nitrite, amines, and amides) during pregnancy is believed to increase the risk of brain tumor in offspring (e.g., [66]). A large international collaborative case-control study on childhood brain tumors reported that foods associated with increased risk of brain tumors were cured meats, eggs/dairy, and oil products; however, yellow-orange vegetables, fresh fish, and grains reduced the risk significantly [64].

Studies based on a very small sample sizes have also reported that exposure to electromagnetic fields is a potential risk factor for childhood brain tumor [67]. However, in the large-scale United Kingdom (UK) Childhood Cancer Study, the authors found that exposure to electromagnetic fields was not linked to childhood brain tumors [68]. A recent large Canadian study examined the contribution of

maternal occupational exposure to extremely low-frequency magnetic fields shortly before and during pregnancy on the incidence of childhood brain tumors. A significantly increased risk was observed for astroglial tumors as well as for all childhood brain tumors, but no association was specifically assessed for medulloblastoma/PNET [69].

Several epidemiological investigations have examined the association between parental exposure to pesticide and childhood brain tumors, with the majority reporting positive associations. For example, in a recent population-based case-control study, the association between brain cancer in children and parental exposure to pesticides in occupational and residential settings was investigated [70]. The researchers reported very weak association between PNET for any of the pesticide classes or exposure sources considered. However, Rosso and colleagues [71] found an association between household exposure to chemicals and medulloblastoma/PNET in children registered with Children's Cancer Group (USA and Canada), particularly for pesticides used in lawn care. A European study found an increased risk of PNET with parental exposure to polycyclic aromatic hydrocarbons (OR = 2.0, 95% CI: 1.0, 4.0) and high maternal exposure to solvent (OR = 3.2, 95% CI: 1.0, 10.3) during the 5-year period before birth [72].

Fetal Alcohol Spectrum Disorders (FASD)

Fetal alcohol spectrum disorders (FASD) are a group of conditions that occurs when alcohol was consumed during pregnancy. FASD are divided into several subgroups: fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD) [73]. Alcohol has irreversible effects on the central nervous system, including abnormal functioning of the amygdala, thinning of the corpus callosum, and reduced brain volume with specific reductions in the frontal lobe, striatum and caudate nucleus, thalamus, and cerebellum [73]. Growth deficiency (height and weight), central nervous system and neurological damage (memory problems, hearing loss, poor gait), and facial dysmorphism (a smooth philtrum, small palpebral fissures, and thin vermilion) are common features of patients with FASD [74].

A recent systematic review of FASD prevalence published in 2013 found significant variations in the reported prevalence estimates across the reviewed studies [75]. Ospina and Dennett [75] classified the 54 studies into six categories based on FASD (or subtypes) prevalence for a specific population. The FASD prevalence estimates for communities based on population-level data range from 0.2 to 5 per 1,000 population. Studies of FASD prevalence in school settings also reported variable estimates, ranging between 0.5 and 10.7%. The reported estimates of FASD prevalence among children in care were found to be much higher than the estimates for school settings or communities, ranging between 30.5 and 52%. A limited number of studies from North America examined FASD prevalence in correctional systems, providing estimates between 9.8 and 23.3%. The majority of studies that examined estimates of FASD prevalence in aboriginal populations were conducted in Canada.

The pooled estimate of FAS prevalence in aboriginal people based on six studies was 0.2% or 2 FAS cases per 1,000 population. The FASD prevalence in other specialized settings, for example, in special education settings, was found to be much higher. The pooled prevalence estimate of FAS was 4.9% (95% CI: 2.5, 7.3), and the pFAS prevalence was 5.4%. The great variation observed in the reported estimates could be in part due to the differences in the characteristics of the populations studied (e.g., age, sex, race/ethnicity, aboriginal status), diagnostic criteria used, methods of case ascertainment, and years of data used.

Popova and colleagues [76] conducted a systematic review and meta-analysis of FASD comorbidity in 2016. The authors identified 428 comorbid conditions in persons with FASD. The identified comorbid conditions extended over 18 of 22 chapters of the ICD-10. The comorbid conditions with the highest prevalence were those related to peripheral nervous system and special senses, conduct disorder, receptive language disorder, chronic serous otitis media, and expressive language disorder.

Cerebellar Malformations

Cerebellar Agenesis

Cerebellar agenesis is an extremely rare condition with complete absence of the cerebellum or with only a small portion of the cerebellum (subtotal cerebellar agenesis) [77, 78]. Primary cerebellar agenesis has a high mortality rate and is typically identified during autopsy. Cerebellar agenesis negatively affects motor skill development, but may improve with age, and has been associated with abnormalities of non-motor functions, such as expressive language, affective behavior, neurological abnormalities, and working memory [79].

Our initial search of studies providing estimates of prevalence and/or incidence, or number of cases, resulted in only one article describing one new case of complete primary cerebellar agenesis [79]. Yu and colleagues [79] described the clinical presentation and subsequent imaging tests of a 24-year-old female, who was married with a daughter, and was living in China. Review of the article revealed seven other publications describing eight living cases of cerebellar agenesis, ranging in age from 4 months to 59 years [77, 80–85]. Interestingly, some individuals with total or subtotal cerebellar agenesis were described as being asymptomatic and having typical neurobehavioral, mental, and physical functioning [81]. See Table 4 for a summary of study statistics.

Dandy-Walker Malformation

Dandy-Walker malformation (DWM) is a complex developmental anomaly involving the fourth ventricle and cerebellum, characterized by an enlargement of the fourth ventricle, vermian agenesis (partial or complete), and posterior fossa cysts

Table 4 Prevalence, incidence, and/or number of cases reported in studies examining the epidemiology of cerebellar malformations

	Study details				Population					
Disorder Author, date	Publication type, research design	Country (region)	Study period	Data source	Age	Sex	*N*	Prevalence	Incidence	Number of cases or families
Cerebellar agenesis										
Sener and Jinkins, 1993	Case report	Texas, USA	–	University of Texas Health Science Center	58 years	F	–	–	–	1 case
Sener, 1995	Case report	–	–	–	6 years	1F;1M	–	–	–	2 cases
Tekin et al., 2002	Case report				7 years	F	–	–	–	1 case
Timmann et al., 2003	Case report	Germany	–	–	59 years	F	–			1 case
Van Hoof and Wilmink, 1996	Case report				46 years	M	–	–	–	1 case
Velioglu et al., 1998	Case report	–	–	–	22 years	M	–	–	–	1 case
Yu et al., 2014	Review, Case report	China	–	General Hospital of Jinan Military Command	24 years	F	–	–	–	1 case
Dandy-Walker malformation										
Di Bella and Pizzo, 2010	Original research, retrospective	Italy (Catania)	1999–2009	–	Pediatric	–	5,000	32/10,000	–	16 cases
Hakami and Majeed-Saidan, 2011	Retrospective analysis of prospectively collected data	Saudi Arabia	2001–2010	Neonatal Intensive Care Unit in Riyadh Military Hospital, Riyadh	–	–	94,210	2.3/10,000	–	–
Kontopoulos et al., 2008	Retrospective	Florida, USA	1997–2005	–	–		600 monochorionic twins	–	1/8,000–10,0000 live births	10 cases

McClelland et al., 2015		USA (22–36 states)	1997–2003	Kids' Inpatient Database	–		–		1.36/1,000	–
Ohaegbulam and Afifi, 2001	Retrospective analysis of prospectively collected data	Saudi Arabia (Northern)	1989–1999	Population of military personnel and their dependants	–		45,274 live births	–	1/10,000 live births per year; males (1.24/10,000), females(0.78/10,000)	–
Joubert syndrome										
Akhondian et al., 2013	Case report	Iran	–	–	12, 10, 3 years	2F; 1M	3	–	–	3 cases in one family
Brancati et al., 2010	Review	–	–	–	–	–	–	–	1:18,000–1:100,00	
Hakami and Majeed-Saidan, 2011	Retrospective analysis of prospectively collected data	Saudi Arabia	2001–2010	Neonatal Intensive Care Unit in Riyadh Military Hospital	–	–	94,210	1.7 per 10,000	–	–
Lissencephaly and cerebellar hypoplasia										
Koul et al., 2006	Case report	Oman	1993–2003	NR	15 days to 6 years	4F; 8M	40	–	–	12 cases; family history of developmental delay in 2/7 cases
Ozyurek and Kose, 2005	Case report	Turkey	–	–	3 years	M	1	–	–	1 case
Pontocerebellar hypoplasia										
Alkan et al., 2009	Retrospective study of MRI and CT images	Turkey	2002–2008	–	8.9 years (30 weeks gestation – 17 years)	22F; 23F	45	–	–	12 cases

(continued)

Table 4 (continued)

	Study details				Population					
Disorder Author, date	Publication type, research design	Country (region)	Study period	Data source	Age	Sex	*N*	Prevalence	Incidence	Number of cases or families
Grellner et al., 2000	Case report	Germany	–	–	1.5 years	M	1	–	–	1 case
Zafeiriou et al., 2013	Retrospective cases study	Greece	–	Tertiary hospital	24–28 weeks (mean, 25.8 weeks)	7F; 5MF	12	–	–	12 cases observed in extreme prematurity
Gómez-López-Hernández (GLH) syndrome										
Abdel-Salam et al., 2014	Case report	Egypt	–	–	24 months	M	1	–	–	1
De Mattos et al., 2014	Review, case report	Brazil	–	–	Minutes old	M	1	–	–	1
Erzin et al., 2016	Letter, case report	Turkey	–	–	24 years	M	1	–	–	1
Fernandez-Jaen et al., 2009	Review, case report	Spain	–	–	14 months; 6 years	M	2	–	–	2
Gomy et al., 2008	Review, case report	Brazil	–	–	12 years; 29 years	M	2	–	–	2
Kobayashi et al., 2015	Case report	Japan	–	–	42 weeks gestational age; then at 4 and 39 years	F	1	–	–	1
Poretti et al., 2008	Case report	Switzerland	–	–	38 weeks gestation to 39 years	2F;2 M	4	–	–	4 cases
Rush et al., 2013	Case report	USA	–	–	4–11 years	3F;1M	4	–	–	4 cases
Saricam et al., 2015	Case report	Turkey	–	–	16 years	F	1	–	–	1 case

Schell-Apacik et al., 2008	Case report	Germany	–	–	3.67 and 15.67 years	M	1	–	–	1 case
Sukhudyan et al., 2010	Case report	Armenia	–	–	1.5–20 years	M	6	–	–	6 cases
Rhombencephalosynapsis (RS)										
Arisoy et al., 2016	Case report	Turkey	–	–	19 weeks	–	–	–	–	1 fetus
Passi et al., 2015	Case report	India	–	–	4 years	M	1	–	–	1 case
Weaver et al., 2013	Retrospective, case report	USA	–	–	10 months–10 years	3F; 6 M	9	–	–	6 cases of RS; 3 cases of partial RS
Sener et al., 2000	Retrospective review of MRI examinations	Turkey	–	–	1 day–18 years	–	3,000	13 per 10,000	–	6 cases reported (3 months–8 years, 3F, 3 M)
Utsunomiya et al., 1998	case report	Japan	–	–	3 years, 4 years	2 M	–	–	–	2 cases
Chiari malformation										
Di Bella and Pizzo, 2010	Original research, retrospective	Italy (Catania)	1999–2009	–	Children	M/F	5,000	32 per 10,000	–	12 cases (0.24%)
Dughal et al., 2014	Prospective observational	Pakistan (Lahore)	2010–2012	–	Infants with anomalies	33F;47M	80	–	–	2 cases (3%)
Ghavami and Abedinzadeh, 2011	Original	Iran (East Azarbaijan)	2005–2008	–	–	–	22,500 pregnant women	–	–	41 fetuses
Lee et al., 2015	Retrospective review of surgical records	Korea	1991–2012		12–250 months	–	–	–	–	54 cases

(continued)

Table 4 (continued)

	Study details				Population					
Disorder Author, date	Publication type, research design	Country (region)	Study period	Data source	Age	Sex	*N*	Prevalence	Incidence	Number of cases or families
Meadows et al., 2000	Retrospective analysis of MR images	USA (Maryland)	1994–1997	Imaging report database, Johns Hopkins Hospital	0–70 years of age	–	22,591	7.8 per 10,000	–	0.77% CMI
Sakushima et al., 2012	Survey	Japan	2008–2009	Nationwide postal survey	38 ± 23.5 years	56.5%F; 42.1%M	708	–	–	CMI: 48.0%; CMII: 8.1%
Schanker et al., 2011	Case report	USA	–	–	20–62 years	5F;1M	–	–	–	CMI: 3 family pairs (2 mother-daughter; 2 father-daughter)
Tectocerebellar dysraphia										
Agrawal et al., 2010	Case report	India	–	Datta Meghe Institute of Medical Sciences	3 months	M	1	–	–	1
Anik et al., 2010	Case report	Turkey	–	Kocaeli University	5 months	F	1	–	–	1
Chowdhary et al., 1989	Original research, case report	Saudi Arabia	–	King Faisal University	1 week to 5 months	3F, 1M	4	–	–	4 cases
Friede, 1978	Case report	Switzerland	–	University of Zürich	2 months, 8 years, newborn	1F; 2M	3	–	–	3 cases
Krishnamurthy et al., 2008	Case report	India	–	Maulana Azad Medical College	7 months	M	1	–	–	1 case
Poretti et al., 2011	Case report	USA	–	The Johns Hopkins School of Medicine	4 years	F	1	–	–	1 case

CMI Chiari type I malformations, *CMII* Chiari type II malformations

[86–88]. Hydrocephalus is a common finding in DWM cases and can lead to death if not treated quickly [89].

A number of studies conducted in the United States [90, 91], Italy [92], and Saudi Arabia [93] have examined the epidemiology of DWM. All of the studies had retrospective designs, with sample sizes ranging between 129 and 14,599.

Di Bella and Pizzo [92] examined the health records of 5,000 children referred to a pediatric radiology unit at the University Hospital of Catania, Italy, for diagnostic procedures over a 10-year period (January 1999–October 2009). The authors found 16 cases of DWM, ranging in age from 1 month to 9 years (ten males, six females). Thus, based on this study, the prevalence of DWM was estimated at 32 per 10,000 population.

In a retrospective analysis of prospectively collected data on all newborns admitted to the neonatal intensive care unit in Riyadh Military Hospital, Riyadh, Saudi Arabia, Hakami and Majeed-saidan [93] reported that 22 infants were identified with Dandy-Walker anomaly (incidence, 2.3 per 10,000). This rate was higher than that estimated in a population of military personnel and their dependents in the Northern region of Saudi Arabia. Ohaegbulam and Afifi [94] identified all infants diagnosed with DWM during an 11-year period (1989–1999) from a cohort of 45,274 live births. The incidence of DWM was 1 per 10,000 live births per year and was higher for males (1.24 per 10,000) than for females (0.78 per 10,000).

In the United States, the incidence of DWM has been estimated at 1.36 per 1,000 in study examining data from the Kids' Inpatient Database containing information from hospitals in 22–36 states covering 1997–2003 [89]. Another US study reported that the incidence of DWS in complicated monochorionic twins was approximately 200 times higher than that expected for the general population [90]. DWS was also more likely to occur in the smaller twin and more likely to be restricted in growth. Other research has shown that DWM is associated with maternal non-Hispanic black ethnicity, a history of infertility treatment, preterm birth, low birthweight, and twin births [95], but these findings have been inconsistent [96]. See Table 4.

Joubert Syndrome and Related Disorders (JSRD)

Joubert syndrome and related disorders (JSRD), originally described in 1968 as Joubert syndrome, is primarily an autosomal recessive neurologic disorder characterized by absence or hypoplasia of the cerebellar vermis and a malformation in the brain stem resulting in hypotonia, developmental delay, neonatal respiratory dysregulation, abnormal eye movements, ataxia, polydactyly, and intellectual disability [97–99]. Nephronophthisis (NPHP) or cystic renal dysplasia is seen in approximately one-quarter of cases of Joubert syndrome [100]. An important malformation is the "molar tooth sign" (MTS) – a pathognomonic midbrain-hindbrain malformation [101, 102].

Globally, the incidence of Joubert syndrome has been estimated at 1 per 80,000–100,000 live births, although some researchers suggest that this range may underestimate the actual number of cases of the syndrome [101]. For example, Srour and colleagues [103, 104] suggest that within the French-Canadian population, there is a higher prevalence of Joubert syndrome, particularly in the Saint Lawrence region of the province of Quebec, Canada. Akhonidan and colleagues [105] identified and described the same presentations of Joubert syndrome in three family members in Iran. In a Saudi Arabian study, Hakami and Majeed-saidan [93] (see also Dandy-Walker Malformation) found 22 cases of Joubert syndrome (incidence, 1.7 per 10,000 live births). Thus, it appears that ethnicity can be a risk factor for the condition.

Lissencephaly and Cerebellar Hypoplasia (LCH)

Lissencephaly and cerebellar hypoplasia (LCH) is a rare autosomal recessive disorder in which the cerebellum, cerebrum, and brain stem are affected [106]. Generally, lissencephaly is caused by impairment in neuron migration, which is essential for development of the cerebellar cortex. Consequently, the cerebellar cortex becomes smooth (lack of folia and sulci) [107]. Seizures, hypotony or spasm, and psychomotor retardation are the symptoms of LCH and death typically occurs at an early age. Affected individuals have moderate to severe intellectual disabilities and delayed development. Prevalence of LCH is largely unknown [108]. Koul, Jain, and Chacko [109] examined data from all children in Oman (population 2.3 million) from January 1993 to December 1997 and identified 12 cases of lissencephaly. In another report, researchers in Turkey described a case of Joubert syndrome with lissencephaly [110] but the type of lissencephaly was not reported. Recently, Zika virus infection in pregnant mothers has been suggested as a risk factor for lissencephaly [111].

Pontocerebellar Hypoplasia (PCH)

Pontocerebellar hypoplasia (PCH) is a group of prenatal onset, autosomal recessive, neurodegenerative disorders that affects brain development [112]. Characteristic features of PCH include atrophy of the brain stem, particularly pons (pontine nuclei), and cerebellum, movement problems, intellectual disability, and communication difficulties (i.e., lack of ability to speak) [113]. Affected individuals die during infancy or childhood [114] before the age of 6 years [115].

The condition appears to affect males and females similarly and has been observed in infants born extremely prematurely [116]. About 100 cases of PCH have been reported in the literature [117]. Alkan, Kizilkilic, and Yildirim [118] conducted a retrospective study of the magnetic resonance imaging (MRI) scans and

computed tomography images from 45 children (22 girls, 23 boys; 30 weeks–17 years of age) of cerebellar malformation and found 12 cases with cerebellar hypoplasia. Grellner, Rohde, and Wiski [119] describe one case of PCH type 2 – a 1.5-year-old boy who had severe psychomotor delay and dyskinesia and epileptic seizures. The genetics of PCH are largely understood; as such, in a specific community in the Netherlands, genetic carrier screening has taken place to identify high-risk couples for having children with PCH [120]. Between September 2012 and 2013, Mathijssen and colleagues [120] identified 4 of 92 couples were carriers with a 1-in-4 risk of having a child with PCH type 2 in each pregnancy.

Gómez-López-Hernández Syndrome (GLH)

Gómez-López-Hernández (GLH) syndrome, also known as cerebellotrigeminal-dermal dysplasia, is a neurocutaneous disorder characterized by rhombencephalosynapsis (see Rhombencephalosynapsis section below) and trigeminal anesthesia [121]. GLH manifestations may include alopecia (partial or complete hair loss); hypotonia; wide-spaced eyes; ataxia; impaired pain sensation; low-set, posteriorly rotated ears; short stature; developmental delay; and seizures [122]. Although intellectual disability is typically observed, individuals with normal cognitive function have been described in the literature (e.g., [123]).

Only 34 cases of GLH have been reported worldwide. Cases have been described in Armenia [124], Brazil [125], Egypt [126], Germany [127], Japan [121], Spain [122], Switzerland [128], and Turkey [129, 130]. Because many of the cases described have occurred in Brazil, a "founder effect" has been suggested for GLH in Brazil [125]. Several researchers have argued that GLH may not be as rare as has been previously thought; they suggest that it is under-recognized in the pediatric population because clinical presentation varies in severity [121, 123, 128].

Suggested risk factors for GLH include smoking and cannabis use and the use of other drugs (i.e., valproate, ethosuximide) by mothers during pregnancy [131]. No specific mutation or chromosomal abnormality has been identified for GLH; however, the findings reported by de Mattos and colleagues [125], Gomy and colleagues [132], and Saricam and colleagues [130] suggest an autosomal recessive pattern of inheritance. Erzin and colleagues [129] report the only case of GLH with schizophrenia.

Rhombencephalosynapsis

Rhombencephalosynapsis is a rare midline brain malformation that involves cerebellar vermis absence, fusion (continuity) of the cerebellar hemispheres, and fusion of the dentate nuclei [133]. Rhombencephalosynapsis can occur in isolation or in combination with other anomalies such as Gómez-López-Hernández syndrome (see

above), VACTERL features, and holoprosencephaly [133–135]. Patients suffer from truncal ataxia, limb ataxia, head stereotypies, delayed motor development, abnormal eye movements, and other features determined by supratentorial abnormalities [136].

Some authors suggest that there are only about 30–35 cases of rhombencephalosynapsis that have been identified and described in the literature from 1914 to 1995 [135, 137], but there may be over 100 cases [138] reported in the literature worldwide. A number of studies from the United States [133, 139], Japan [135], India [138], and Turkey [137, 140] have been published. The majority of these studies are case reports describing one or two cases; however, Tully and colleagues [133] describe their comprehensive search for patients with RES in a database of more than 6,800 individuals with brain malformations and other developmental brain disorders. The authors found and described 53 cases of RES and the features of GLH, VACTERL, or other malformations that presented in conjunction with RES. Examination of the MRI scans of 3,000 children, Sener [137] estimated the prevalence of rhombencephalosynapsis to be 0.13% (13 per 10,000), a finding that was higher than expected. Clinicians generally recommend that differential diagnosis should be made from DWM and other anomalies [140].

Chiari Malformations

Chiari malformations are classified by type (types I–IV) based on the severity of the structural defects in the cerebellum, craniocervical junction, and brain stem [141]. In most cases, the posterior fossa is small resulting in downward displacement of the cerebellum and lower medulla together or the cerebellum alone into the spinal canal [142]. Consequently, cerebrospinal fluid can be blocked, and symptoms such as abnormal eye movements, headache, dizziness, muscle numbness, and problems with balance and coordination can be observed [143, 144]. Chiari type II malformations (CMII) are usually identified at or before birth [145] but may go undetected if symptoms are not apparent. This is often the case for Chiari type I malformations (CMI), which is frequency asymptomatic and may not be recognized until adolescence or adulthood [146]. The average age of a CMI diagnosis has been reported to be 24.9 ± 15.8 years [147].

Information on prevalence of Chiari malformations at the population level is lacking. Although several studies have provided estimates of Chiari malformation prevalence (0.01–3.6% of the population), these studies are based on imaging data collected at a single center or hospital and may not reflect the true prevalence of the condition [148, 149]. Nevertheless, these studies are valuable in describing the epidemiology of Chiari malformations. For example, Meadows and colleagues [150] conducted a retrospective examination of more than 22,000 brain MRI scans and estimated the prevalence of CMI at 7.8 per 10,000. The earlier studies from Western countries reported prevalence estimates of 8.2–8.4 per 100,000 [151, 152]. One study based on 2 years of data for newborns admitted to a hospital in Pakistan reported that 3% of all the cases were diagnosed with Chiari malformation [153].

Lee and colleagues [154] retrospectively reviewed 21 years of medical records for pediatric patients who underwent surgery at an institution in Korea for symptomatic CMI. A total of 54 children were identified with symptomatic CMI. Four patients were between the ages of 3 and 27 months, 9 were 3 and 4 years of age, and 41 were 5 and 17 years of age. More males than females were identified in the younger two age groups, but more females than males were identified in the oldest age group. Sakushima and colleagues [155] conducted a survey of hospitals in Japan between August 2008 and July 2009 and found that among a sample of 708 patients with syringomyelia, 48% were diagnosed with CMI and 8.1% with CMII. The authors also reported that Chiari malformation was more common in children than adults.

A few studies examined incidence of Chiari malformations. In one study, 3 years of ultrasound examinations for 22,500 pregnant women from East Azarbaijan in Iran were reviewed to estimate incidence of these conditions [156]. Of the 22,500 pregnancies, 112 (or 0.5%) of fetuses had central nervous system anomalies and 41 had Chiari malformations. Ghavami and Abedinzadeh [156] concluded that Chiari malformations and hydrocephalus were the two most common central nervous system abnormalities in East Azarbaijan in Iran.

While the exact cause of Chiari malformation is unknown, research suggests that genetic factors are the most likely. For example, Schanker and colleagues [149] described a series of three family pairs with CMI and suggested that along with the previously described underlying culprit genes, estrogen may also be a factor in the development of Chiari malformations. CMI has also been found to coexist with ASD, but CMI is often under-recognized in individuals with ASD because symptoms are attributed to autism [157].

Tectocerebellar Dysraphia

Tectocerebellar dysraphia is an extremely rare congenital malformation consisting of vermian hypoplasia or aplasia, an occipital encephalocele, and dorsal traction of the brain stem, such that the hypoplastic cerebellar hemispheres are rotated around the brain stem to lie ventrolaterally [158]. Very few cases of tectocerebellar dysraphia have been reported in the scientific literature [159]. Children with tectocerebellar dysraphia generally have very low intellectual functioning, and 40–75% die before their first birthday, largely because of hydrocephalus [160].

Tectocerebellar dysraphia is a condition so rare that prevalence and incidence estimates cannot and have not been made. Thus, we examined eight published case reports; these case reports describe the following cases: one 3-month-old boy in India [161], one 5-month-old girl [162], and two cases (8-year-old boy, 2-month-old boy) but the authors also noted three other cases previously described [163], 7-month-old male in India [158], 4-year-old girl in the United States [164], and four cases (three girls, one boy) in Saudi Arabia [165]. Some authors suggest that variants of tectocerebellar dysraphia (e.g., tectocerebellar dysraphism with an occipital encephalocele) are structural manifestations of Joubert syndrome [164].

Other

Cerebellitis

Acute cerebellitis is an inflammatory syndrome characterized by cerebellar dysfunction ([166], as cited in [167]). Vomiting, headaches, tremors, nystagmus, dysarthria, and states of consciousness ranging from sleepiness to coma are common symptoms of severe cerebellitis [168, 169]. Patients with acute cerebellitis may also exhibit broad-based gait disturbance, poor coordination of finger-to-nose movements (dysmetry), and irritability [168]. Cerebellitis typically occurs in early childhood either during or after infection or postvaccination or has autoimmune etiologies.

An important causative pathogen for cerebellitis is varicella zoster virus (VZV), an acute, exanthematous, and highly infectious disease, which causes chickenpox (varicella) in childhood, and shingles (herpes zoster) in later life [168, 170]. In a retrospective study using 10 years of data (October 2003–June 2013) from Bambino Gesu Hospital, Rome, Italy, Bozzola and colleagues [168] found that 48 out of 457 (10.5%) children hospitalized with varicella developed acute cerebellitis. All children were unvaccinated for the virus. The highest frequency of cerebellitis occurred in children aged 1–5 years (60.9%), followed by children aged 5–10 years (34.1%), and those 10+years (5%). Girls and boys were affected equally. See Table 5 for a summary of study statistics.

The majority of the literature describes isolated case reports of the most severe but rare cases of cerebellitis (cf [171]), and these cases are typically associated with viruses other than VZV. Specifically, cases of acute cerebellitis have been associated with the Epstein-Barr virus, mycoplasma pneumoniae, rotavirus, human herpesvirus 7, mumps, influenza, and nonspecific viral infections (see [171] for a review). Hackett and colleagues [172] recently reported a case of a 6-year-old girl with an influenza A (H1N1) infection in Ireland presented with acute cerebellitis. In the United States, Hashemi and colleagues [173] described the first reported case of a 9-year-old boy, who presented with hemorrhagic cerebellitis secondary to *Plasmodium falciparum* infection, after traveling in Tanzania. In their retrospective evaluation of the medical records of 194 patients with Epstein-Barr virus infection who were hospitalized in the Department of Infectious Diseases and Child Neurology at the University of Medical Sciences in Poznan, Poland, between January 2010 and January 2015, Mazur-Melewska and colleagues [174] found two cases of cerebellitis (1.03%). Uchizono, Iwasa, Toyoda, Takahashi, and Komada [175] reported what may be the first case of a 7-year-old girl presenting with cerebellitis following group A streptococcal infection in Japan. Although no genetic causes have been identified for acute cerebellitis, Xu and colleagues [176] reported its occurrence in identical twin boys (aged 15 years) 8 days apart in Shijiazhuang, China; a viral infection, however, could not be ruled out. An important challenge for physicians and epidemiologists is to correctly identify the acute cerebellitis because there is considerable overlap in presentation with acute post-infectious ataxia [28] and opsoclonus-myoclonus syndrome [177].

Cerebellar Stroke

Cerebellar stroke is characterized by complaints of dizziness, vertigo, and vomiting [178]. Pontine compression and acute hydrocephalus secondary to the obstruction of the fourth ventricle may occur as a result of swelling after the infarction, which may further result in decreased level of consciousness and arousal. Cerebellar injury early in life stunts cerebellar growth and negatively affects neurodevelopment (cf [179]).

As is true of other cerebellar disorders, cerebellar stroke is unusual in children (see [180]). When cerebellar infarction does occur, these cases are described in the research literature (see Table 5). For example, Lin and colleagues [180] reported a case of a 12-year-old boy presenting with vomiting, gait disturbance, and headache; cerebellar stroke was confirmed with magnetic resonance angiography. Interestingly, the boy had no history of neck manipulation, trauma, or other relevant medical history. In their retrospective evaluation of 977 childhood (<16 years of age) cases of malaria in England and Wales reported between January 2004 and December 2008, Garbash and colleagues [181] found that one child developed cerebellar infarction. Estimating incidence and prevalence has been described as difficult because symptoms, such as ataxia, are not seen clearly during a bedside examination [178]. The overall incidence of cerebellar stroke across all ages is estimated to be 1.5% (M_{age} = 65 years) (see [182]). Thakkar and colleagues [43] reported that of the 120 cases of acute ataxia that occurred in children (0–18 years of age) that were seen at Children's Hospital of Pittsburgh between January 2003 and December 2013, cerebellar stroke was identified in two (1.7%) cases. See Table 5.

Risk factors for cerebellar stroke typically include trauma, drugs, and central nervous system infection (see [183]). When trauma has been sustained through sport, stroke may occur in boys 6.6 times more than in girls [183] and may occur with sudden movement [184]. Other risk factors include congenital cervical anomaly and vascular or connective tissue disease. After reviewing pediatric cases of vertebral artery dissection (VAD) described in the literature, Hasan and colleagues [183] reported a high incidence of associated cervical anomalies (i.e., 10/68 cases). Although rare, cerebellar stroke may occur in children and young adults who overdose on tricyclic antidepressants [185]. Thoon and Chan [186] have also reported one case of stroke in the left cerebellum in a 10-year-old girl following influenza vaccination during influenza season. Another important risk factor for cerebellar infarction is prematurity [179, 182]. Khair and colleagues [182] described a case of a 4.5-year-old girl, who was one member of a quadruplet born at 28 weeks gestation, presenting with a number of symptoms indicative of cerebellar stroke. Cerebellar infarction was subsequently confirmed with an MRI. Cerebellar injury is important to identify as it has important implications for long-term cognitive development [179].

Table 5 Prevalence, incidence, and/or number of cases reported in studies of investigating other cerebellar conditions

	Study details				Population					
Disorder Author, date	Publication type, research design	Country/ region	Study period	Data source	Age	Sex	*N*	Prevalence	Incidence	Number of cases or families
Cerebellitis										
Hackett et al., 2013	Case report	Ireland	–	–	6 years	F	1	–	–	1 case associated with influenza A
Hashemi et al., 2015	Case report	US	–	–	9 years	M	1	–	–	1 case associated with *Plasmodium falciparum* infection
Mazur-Melewska et al., 2015	Retrospective evaluation, case report	Poland	2010–2015	University of Medical Sciences	5.1 years	84F; 110M	194 with Epstein-Bar Virus	–	–	2 cases (1.03%)
Uchizono et al., 2013	Case report	Japan	–	–	7 years	F	–	–	–	1 case associated with group A streptococcal infection
Xu et al., 2008	Case report	China	–	Third Hospital, Hebei Medical University	15 years	2M	–	–	–	2 cases likely associated with a viral infection

Cerebellar stroke										
Garbash et al., 2010	Retrospective	UK (England, Wales)	January 2004–December 2008	Pediatric Intensive Care Unit Audit Network (PICANet)	Children (<16 years)	–	977 malaria cases	–	–	1 case of cerebellar stroke
Kawakami et al., 2009	Case report	Japan	–	–	8 years	M	1	–	–	1 case associated with trauma during sport
Khair et al., 2014	Review, case report	Qatar	–	–	4.5 years	F	1	–	1.5%	1 case, premature birth
Lin et al., 2007	Case report	Taiwan	–	–	12 years	M	1	–	–	1 case
Thakkar et al., 2016	Original research, retrospective	USA (Pittsburgh)	January 2003–December 2013	–	0–18 years	–	120	1.7% among cases of ataxia	–	2 cases
Thoon and Chan, 2012	Case report	Chinese-Thai	–	–	10 years	F	1	–	–	1 case associated with influenza

Conclusions

For many cerebellar disorders, prevalence and incidence rates are unknown, or the values have been underestimated; this is true both at the global and regional levels. Scant epidemiological information can be partly attributed to lack of comprehensive healthcare systems in various parts of the world (see [27]), making diagnosis at an early age difficult or impossible. Fetal loss may also contribute to inaccurate epidemiologic measure, because prevalence and incidence are typically estimated using living individuals [187]. Underestimates may also be the result of cases of cerebellar disorder not being classified accurately in published studies; as such, they may be excluded from analysis (see [30]). In a similar vein, in an effort to include a greater number of affected individuals in epidemiological studies, groups of patients may be relatively heterogeneous in composition (see [30]). Thus, case studies become a very important means with which to communicate the various signs, symptoms, comorbidities, and complications associated with a certain disorders, particularly for those cerebellar disorders that have been described as extremely rare (e.g., cerebellar agenesis, tectocerebellar dysraphia). Further population-based epidemiological studies are important for determining the impact of cerebellar disorders worldwide and providing information regarding the causes and appropriate treatments for these disorders.

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