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ASSIGNMENT: WRITE A CONCISE REVIEW ON THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM AND HIGHLIGHT THE GENETIC BASES OF KNOWN CEREBELLAR DISORDERS

The internal structure of the cerebellum reflects an intriguing paradox; its cytoarchitecture is relatively simple and repeated throughout, yet the connections between its neurons are wired into a complex array of gene expression domains and functional circuits. The developmental mechanisms that coordinate the establishment of cerebellar structure and circuitry provide a powerful model for understanding how functional brain networks are formed. Two primary germinal zones generate the cells that make up the cerebellum. Each zone expresses a specific set of genes that establish the cell lineages within the cerebellar anlage. Then, cohorts of differentiated projection neurons and interneuron progenitors migrate into the developing cerebellum. Thereafter, a number of remarkable patterning events occur including transformation of the smooth cerebellar surface into an intricately patterned series of folds, formation of three distinct cellular layers, and the demarcation of parasagittal gene expression domains. Together, these structural and molecular organizations are thought to support the proper connectivity between incoming afferent projections and their target cells. After birth, genetic programs and neural activity repattern synaptic connections into topographic neural networks called modules, which are organized around a longitudinal zone plan and are defined by their molecular, anatomic, and functional properties. WIREs Dev Biol 2013, 2:149–164. doi: 10.1002/wdev.65

The cerebellum has long been recognized for its role in motor co-ordination, but it is also increasingly appreciated for its role in complex cognitive behavior. Historically, the cerebellum has been overwhelmingly understudied compared to the neocortex in both humans and model organisms. However, this tide is changing as advances in neuroimaging, neuropathology, and neurogenetics have led to clinical classification and gene identification for numerous developmental disorders that impact cerebellar structure and function associated with significant overall neurodevelopmental dysfunction. Given the broad range in prognosis and associated medical and neurodevelopmental concerns accompanying cerebellar malformations, a working knowledge of these disorders and their causes is critical for obstetricians, perinatologists, and neonatologists so that cerebellar malformations can be recognized by neuroimaging and clinical characteristics during the prenatal and postnatal periods.

Cerebellar malformations are now widely diagnosed during pregnancy and associated with significant morbidity and mortality in the newborn period and throughout life. Given the broad range in prognosis and associated medical concerns, a working knowledge of these disorders and their causes is essential for obstetricians, perinatologists and neonatologists. For clinicians, it is most relevant to organize cerebellar malformations by their clinical and imaging features, which then directs additional diagnostic testing, medical monitoring for associated complications, and counseling about prognosis, treatment and recurrence risk. Distinguishing genetic disorders from similar conditions caused by extrinsic factors, such as infection, stroke, or prematurity, is particularly important to provide quality patient care. Cerebellar malformations may be classified as predominantly involving the cerebellum or involving both the cerebellum and brainstem. They may occur in isolation or as part of broader syndromes involving multiple systems. Though the cerebellum has long been recognized for its role in motor co-ordination, it also shapes the functions of other brain regions, especially cognition and affect, by processing external sensory and internally generated information to influence neocortical circuit refinement. Thus, not surprisingly, most cerebellar malformations are associated with neurodevelopmental issues affecting multiple domains: motor, communication, cognition, emotional regulation, and executive function. Human cerebellar development begins around the ninth gestational week and continues beyond birth. This protracted developmental timeline makes the human cerebellum particularly vulnerable to insult, especially during 24–40 weeks of gestation, when considerable neurogenesis in the external granule cell layer results in a five-fold increase in cerebellar size. Malformations that arise early in development typically affect both cerebellum and brainstem, whereas, later in development, cerebellar malformations have less effect on the pons. Here we present some of the most frequently occurring and best understood human cerebellar malformations and their genetic causes.

Epidemiology of cerebellar malformations

There are few population-based prevalence data for cerebellar malformations, due to several factors. Neuroimaging studies are required for diagnosis, but are variably performed depending on the clinical circumstances and resources available. When neuroimaging studies are performed, cerebellar malformations are often under-recognized. Within the few population-based cohorts, patients diagnosed with cerebellar malformations have the most severe clinical features [1]. Finally, cerebellar malformations are found in cohorts of individuals with autism, but rarely listed as a diagnosis. Dandy–Walker malformation (DWM) is frequently reported as the most prevalent cerebellar malformation, but estimated prevalences vary considerably among available studies (1/3000 to 1/30,000) [2]. Thus, the true prevalence for cerebellar malformations collectively, or for specific disorders, is mostly unknown.

Clinical features of cerebellar malformations

The clinical classification of cerebellar disorders provides critical information for accurate prognostic and recurrence risk counseling. The most useful diagnostic categories also guide subsequent evaluation and medical management. Furthermore, a clinical diagnosis may facilitate identification of the underlying genetic cause that can then be used for prenatal diagnosis and carrier testing. Since clinical and neuroimaging features of specific cerebellar malformations overlap considerably, correctly classifying the cerebellar malformation in any particular patient requires a comprehensive approach that integrates pre- and postnatal medical history, physical examination, neuroimaging, and laboratory testing.

Prenatal ultrasound and magnetic resonance imaging (MRI) are now widely used to evaluate the fetal brain, and many cerebellar malformations are recognizable before birth (Fig. 1); however, the sensitivity and specificity of prenatal neuroimaging is not known. Prenatal ultrasound can identify cerebellar hypoplasia, abnormal fluid collections in the posterior fossa, or poor delineation of posterior fossa landmarks. Additional evaluation during pregnancy can involve fetal MRI, genetic amniocentesis, cell-free fetal DNA testing, and evaluation for in-utero infection. Despite thorough evaluation during pregnancy, a specific etiology is often not identified until after birth. For patients who elect to terminate a pregnancy, fetal autopsy after termination without a prolonged interval before delivery provides the best diagnostic information and should be offered.

Fig. 1



Fetal neuroimaging of cerebellar malformations. (A, B) Axial and sagittal views of a 22-week gestation fetus with confirmed VLDLR-related cerebellar hypoplasia. Note that cerebellar hypoplasia more severely affects the vermis; there are no primary fissure and other vermis landmarks on the sagittal view. (C, D) Axial and sagittal views of a 25-week gestation fetus with TSEN54-related pontocerebellarhyplasia. Note marked hypoplasia of the vermis, hemispheres and pons. (E, F) Axial and sagittal views of a 20-week gestation fetus with Joubert syndrome. Note the more severely affected vermis with dysplastic brainstem. (G–I) Axial and sagittal views of a 20-week gestation fetus with POMGNT1-related muscle–eye–brain disease demonstrating cerebellar hypoplasia of vermis and hemispheres, “kinked brainstem” and severe, asymmetric lateral ventriculomegaly. (J–L) Axial and sagittal views of a 20-week gestation fetus with rhombencephalosynapsis demonstrating small cerebellum without an obvious vermis and severe ventriculomegaly with partially absent septum (diagnosis was confirmed by autopsy).

The postnatal clinical presentation of patients with cerebellar malformations is typically non-specific; features include hypotonia, motor delay, nystagmus, and decreased visual attention. Severely affected patients can present with apnea, feeding difficulties, aspiration, spasticity, lack of developmental progress, and seizures. Signs of cranial nerve dysfunction, including abnormal eye movements, ptosis, facial palsy, hearing impairment, and facial/corneal anesthesia, may be observed. Ophthalmologic evaluation may reveal chorioretinal coloboma or retinal dystrophy in patients with Joubert syndrome (JS), various structural eye abnormalities in patients with cobblestone malformations, or other eye movement abnormalities. Mildly affected patients may have relatively isolated cranial nerve dysfunction, as in Duane retraction syndrome and horizontal gaze palsy with progressive scoliosis. Cognitive impairment is frequent, but not universal, among patients with cerebellar malformations, and autistic features are also observed. Not surprisingly, cerebellar malformations are associated with a wide range of neurodevelopmental outcomes.

Recognizing the clinical features associated with cerebellar dysfunction can aid in identifying patients with cerebellar malformations and trigger the need for neuroimaging; recognizing the idiosyncratic features associated with specific diagnoses may help to differentiate specific cerebellar disorders (Tables 1 and ​and22 and sections below). Extreme prematurity or intrauterine infection may indicate a non-genetic etiology; however, these are usually diagnoses of exclusion. Laboratory testing can also differentiate patients. For example, creatine kinase is elevated in patients with cobblestone malformations, protein glycosylation profiles are abnormal in congenital disorders of glycosylation (CDGS), and hyperglycemia with markedly decreased or absent insulin is seen in patients with PTF1A-related cerebellar and pancreatic agenesis.

Table 1



Typical clinical, imaging, and genetic characteristics of specific cerebellar malformations with known genetic cause.a

Table 2

Typical clinical, imaging, and genetic characteristics of cerebellar malformations without known genetic cause.

Specific malformations with known genetic causes

* Predominantly cerebellar malformations

A malformed cerebellum may be abnormally small, dysplastic, or unusually large. The vermis and both hemispheres may be equally or disproportionately affected. Primary malformations of the pons, midbrain, and supratentorial structures are also seen in a substantial subset of patients. The wide range in morphological presentations results from the diversity of causes, including chromosomal abnormalities, specific genetic syndromes, and extrinsic factors.

* Dandy–Walker malformation

Dandy–Walker malformation (MIM 220200) is a heterogeneous disorder defined by a hypoplastic, upwardly rotated vermis, an enlarged fourth ventricle, and an enlarged posterior fossa with an elevated confluence of sinuses (Fig. 2B). Typically, the cerebellar hemispheres are less affected than the vermis, and the brainstem is normal to moderately hypoplastic. DWM can occur with additional brain abnormalities including agenesis of the corpus callosum (ACC) and hydrocephalus, but more often it occurs as an isolated brain-imaging finding. The clinical features and developmental outcomes vary widely. Patients may exhibit symptoms ranging from intellectual disability to autism or they may be completely unaware of any deficits until diagnosed as adults for unrelated reasons [3]. The recurrence risk in isolated DWM is low at an estimated 1–5% [4], suggesting de-novo, somatic mosaic, or complex genetic causes.

Fig. 2



Sagittal views of cerebellar malformations with known genetic causes. (A) Unaffected individual for comparison. (B) Dandy–Walker malformation (unknown cause) with hypoplastic, rotated vermis and marked enlargement of 4th ventricle and posterior ossa. (C) Cerebellar hypoplasia in a patient with biallelic RELN mutations, demonstrating hypoplastic brainstem and characteristic absent folia of the vermis; note the normal tectum. (D) Tubulinopathy (TUBA1A mutation) with brainstem hypoplasia, vermis hypoplasia, lissencephaly and microcephaly; note the large, dysplastic tectum. (E) Mild cerebellar vermis hypoplasia, abnormal 4th ventricle shape, and small cysts (arrows) in a patient with biallelic LAMA1 mutations. (F) Pontocerebellarhyplasia (PCH) (homozygous TSEN54 mutation) with hypoplastic brainstem and vermis (which is less affected than hemispheres); note the normal tectum. (G) PCH in a patient with congenital diabetes; note the extremely small vermis and flat pons with preserved tectum. (H) CASK-related PCH; note that the pons is not severely affected in this patient. (I) Cerebellar agenesis, with severe pontine and midbrain hypoplasia in a severely affected patient with biallelic WNT1 mutations. (J) Congenital disorder of glycosylation Type 1a due to biallelic PMM2 mutations. (K) TCTN2-related Joubert syndrome with vermis hypoplasia (obscured by hemispheres in this image), horizontal superior cerebellar peduncles, large dysplastic tectum and heterotopia at the dorsal cervicomedullary junction (arrowhead). (L) Muscle–eye–brain disease due to POMGNT1 mutations; note the markedly hypoplastic and dysplastic brainstem, cerebellar cysts, abnormal tectum, and hydrocephalus. Adapted with permission from Doherty et al. [12], except for panel (I) which is from Aldinger et al. [40].

Few genes have been implicated in rare cases of DWM, including genomic imbalances that are part of a congenital syndrome and rare single gene disorders [5–8]. FOXC1-related DWM is associated with multiple congenital anomalies, especially eye malformations consistent with Axenfeld–Rieger syndrome [6]. Congenital anomalies associated with FOXC1-related DWM in severely affected patients overlap with Ritscher–Schinzel, or 3C (cranio-cerebello-cardiac) syndrome. Recently, mutations in CCDC22 were found in X-linked cases of 3C syndrome, suggesting that CCDC22 mutations may be a new cause of DWM [8]. Though these patients were noted to have DWM, limited neuroimaging data were reported to substantiate this diagnosis [8]. ZIC1/4-related DWM is also associated with multiple congenital anomalies, including dysmorphic facial features and abnormal development of the eyelids. Recently, exome sequencing identified autosomal dominant mutations in LAMC1 and NID1 as the cause of DWM with encephalocele in two families [7]. Despite these genetic advances, the genetic cause remains unknown in the majority of DWM patients.

Case reports and small case-series also suggest that extrinsic factors may contribute to DWM. For example, serial fetal prenatal neuroimaging identified evidence of prenatal hemorrhage above the cerebellum in a patient postnatally diagnosed with DWM [9]. Two comprehensive population-based studies suggest that clomiphene citrate exposure and twinning may be additional non-genetic risk factors for DWM. Additional rigorous studies are needed to assess prenatal risk factors for DWM.

Cerebellar hypoplasia Cerebellar hypoplasia (CH) refers to an underdevelopment of the cerebellum. This category of cerebellar malformation is distinct from DWM in that it does not involve a concurrent enlargement of the posterior fossa, and almost all individuals exhibit cognitive and motor impairments. CH is a feature of many different disorders and it is often a non-specific feature associated with genomic imbalances. CH is frequently associated with additional brain abnormalities, including lissencephaly, cortical dysplasia, microcephaly and heterotopia, pointing to specific genetic causes.

The lissencephaly spectrum of brain malformations is caused by defects in either the reelin pathway or microtubule formation and function. Patients with autosomal recessive mutations in RELN have pachygyria and an extremely hypoplastic cerebellum with very little foliation and disproportionate effects on the vermis (Fig. 2C) [10]. Additional clinical features include profound developmental disability, microcephaly, sloping forehead, seizures, and congenital lymphedema. In contrast, patients with autosomal recessive mutations in VLDLR, a reelin receptor, exhibit mild pachygyria and a mildly small cerebellum that retains some foliation [11]. Reelin is transiently expressed by neurons within superficial layers in both the cerebral cortex and cerebellum and regulates radial neuronal migration.

Mutations in the alpha- and beta-tubulins are a major cause of brain malformations, especially lissencephaly, pachygyria, and polymicrogyria, collectively referred to as tubulinopathies. Mutations in TUBA1A, TUBA8, TUBB2A, TUBB2B, TUBB3, TUBB4A, and TUBB are associated with a range of clinical features from isolated congenital fibrosis of the extraocular muscles to severe intellectual disability, quadriplegic cerebral palsy, seizures, cranial neuropathies and hydrocephalus [12,13]. Neuroimaging features include cortical dysgenesis (lissencephaly or polymicrogyria), malformation of cranial nerves, and basal ganglia dysplasia, often with cerebellar and pontine hypoplasia, and defects in the corpus callosum, anterior commissure and internal capsule (Fig. 2D). Dysmorphic features are infrequently reported, and, surprisingly, other organ systems are not affected. Most occurrences are sporadic and due to de-novo mutations, but rare recurrences have been reported due to germline mosaicism and autosomal recessive inheritance [14].

Additional genes and extrinsic exposures have been associated with CH. Mutations in CHD7 account for the majority of patients with CHARGE syndrome (MIM-214800), characterized by Coloboma, Heart defects, choanal Atresia, Retardation of growth and development, Genital and Ear abnormalities [15]. Neuroimaging reveals that more than a third of these patients have a slightly rotated, mildly to moderately hypoplastic cerebellar vermis, a mildly enlarged posterior fossa, and abnormal cerebellar hemisphere foliation [16]. CHD7 loss-of-function disrupts critical gene expression in the isthmus organizer, a transient embryonic structure that directs early cerebellar development [16]. Mutations in OPHN1 are associated with CH, ventriculomegaly, intellectual disability, seizures and mildly dysmorphic facial features that are characteristic in males and occasionally in females [17]. Retinoic acid exposure during early pregnancy has been associated with severe cerebellar vermis hypoplasia with variable effects on the hemispheres. Additional clinical features include microtia, micrognathia, cleft palate, conotruncal heart defects, thymic defects, and retinal abnormalities [18].

Cerebellar hyperplasia

Cerebellar hyperplasia, or macrocerebellum, is a rare neuroimaging finding that occurs in isolation, or is coincident with a variety of neurodevelopmental disorders, including genomic imbalances and specific overgrowth syndromes, including megalencephaly–capillary malformation (MCAP) and megalencephaly–polydactyly–polymicrogyria–hydrocephalus (MPPH) (reviewed by Poretti et al. [19]). Recently, significant progress has been made in understanding the pathophysiology that leads to brain overgrowth in MCAP/MPPH. Clinical features of MCAP/MPPH include seizures, capillary malformations, macrocephaly, and polydactyly, and diagnosis is often based on cerebral cortical overgrowth and polymicrogyria [20,21]. Though cerebellar size is normal at birth, patients often develop a macrocerebellum with normal posterior fossa size. This may progress into cerebellar ectopia/Chiari I malformation, causing clinically associated symptoms (posterior headache, dysphagia, stridor) and hydrocephalus. It is unknown whether the cerebellar overgrowth is a feature of generalized brain overgrowth, or whether there are distinct mechanisms that specifically influence cerebellar overgrowth. Most MCAP and MPPH patients have activating de-novo mutations in PIK3R2 and PIK3CA, respectively, that result in increased cell growth [20,21]. Mutations affecting the PI3K–AKT–mTOR pathway are found in a variety of cancers, opening the possibility of using drugs in development for cancer treatment to reduce brain overgrowth and neurological issues in patients with MCAP/MPPH.

 Cerebellar dysplasia

Any part of the cerebellum can be dysplastic, from small focal regions within one hemisphere to abnormal foliation throughout the cerebellum [22]. Hypoplastic cerebella are frequently also dysmorphic, as observed in tubulinopathies and cobblestone malformations. Chudley–McCullough syndrome (CMS; MIM 604213) is an autosomal recessive disorder in which patients have striking disorganization of the inferior cerebellar hemisphere folia and additional brain abnormalities, including frontal polymicrogyria with subcortical heterotopia, corpus callosum hypogenesis, and arachnoid cysts. Clinical presentation includes severe neonatal sensorineural hearing loss and hydrocephalus that may require shunting in some patients. Surprisingly, these patients typically are not dysmorphic, lack additional congenital anomalies, and have relatively mild developmental problems [23]. CMS is caused by biallelic truncating mutations in GPSM2 that encodes a GTPase regulator required for correct orientation of stem cell divisions in multiple tissues [24]. The cerebellar dysplasia present in CMS is likely due to abnormal cell division, but the precise mechanism remains unknown. Poretti–Boltshauser syndrome (PBS; MIM 150320) is characterized by cerebellar dysplasia, cysts, and vermis hypoplasia (Fig. 2E) with and without retinal dystrophy and is caused by mutations in LAMA1 [25,26]. The superior cerebellar peduncles are long in some patients, though their appearance differs from the classic molar-tooth appearance that defines JS. The clinical features of PBS include motor and speech delay with variable cognitive impact [25,26]. Finally, cerebellar dysplasia with cysts is a prominent feature in cobblestone malformations and GPR56-related brain malformations.

CONCLUSION

Distinguishing different cerebellar malformation conditions is important for prognostic and recurrence risk counseling, medical monitoring for complications, and treatment decisions.

Diagnosis requires a multidisciplinary team approach including perinatologists, neonatologists, neurologists, and geneticists.

Cerebellar malformations are often caused by de-novo dominant mutations as well as autosomal recessive and X-linked mechanisms.

Cerebellar malformation conditions have overlapping neuroimaging and clinical phenotypes.

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