Seminars in Fetal & Neonatal Medicine 21 (2016) 321–332

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Review

The genetics of cerebellar malformations

Kimberly A. Aldinger [a], Dan Doherty [a, b, *]

[a] Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA, USA
[b] Division of Genetic Medicine, Department of Pediatrics, University of Washington, Seattle, WA, USA

Keywords:
Cerebellum
Neuroimaging
Magnetic resonance imaging
Genetics
Brain malformation
Neurodevelopment

SUMMARY

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. Here we present an update on the genetic causes for cerebellar malformations that can be recognized by neuroimaging and clinical characteristics during the prenatal and postnatal periods.

1. Introduction

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.

2. Epidemiology of cerebellar malformations

Few population-based prevalence data for cerebellar malformations exist, 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,

* Corresponding author. Address: Divisions of Genetic and Developmental Medicine, Department of Pediatrics, University of Washington, Seattle, WA 98105, USA. Tel.: +1 206 221 5465, +1 206 616 3788; fax: +1 206 543 3184.
E-mail address: ddoher@uw.edu (D. Doherty).

http://dx.doi.org/10.1016/j.siny.2016.04.008
1744-165X/

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 (1/3,000 to 1/30,000) [2]. Thus, the true prevalence for cerebellar malformations collectively, or for specific disorders, is mostly unknown.

3. 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.

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 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 2 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.

4. Specific malformations with known genetic causes

4.1. 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.

4.1.1. 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.

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 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. Rigorous studies are needed to assess prenatal risk factors for DWM.

4.1.2. 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