Prenatal Cerebellar Disruptions

Neuroimaging Spectrum of Findings in Correlation with Likely Mechanisms and Etiologies of Injury

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KEYWORDS

• Cerebellar disruption • Neuroimaging • Prenatal • Hemorrhage • Cerebellar hypoplasia • Unilateral cerebellar hypoplasia • Cerebellar agenesis • Vanishing cerebellum

KEY POINTS

- The complex and protracted duration of development (from 4 weeks' gestation to 2 years postnatally) results in a high vulnerability of the cerebellum for acquired injury.
- In the last decades, progressing pre- and postnatal anatomic and functional neuroimaging techniques (ultrasound scan and MR imaging) have led to an improved recognition, classification, and understanding of the spectrum of cerebellar disruptions, which include various forms of cerebellar agenesis, unilateral cerebellar hypoplasia, cerebellar cleft, global cerebellar hypoplasia, and vanishing cerebellum associated with Chiari type II malformation.
- Similar disruptive processes may cause a spectrum of cerebellar disruptions as revealed by neuroimaging.
- Timing and chronicity of injury in relation to the stage of cerebellar development impacts the phenotype of cerebellar disruption.
- The recognition of cerebellar disruptions and differentiation from inborn errors of cerebellar development (so-called malformations) is important in terms of diagnosis, prognosis, treatment, and genetic/parental counselling.

INTRODUCTION

The embryogenesis/histogenesis of the cerebellum is a highly complex process that is programmed/determined by a large number of genes and can be summarized in 4 basic steps: (1) characterization of the cerebellar territory in the hindbrain, (2) formation of 2 compartments of cell proliferation giving rise to the Purkinje cells and the granule cells, (3) inward migration of the

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granule cells, and (4) differentiation of cerebellar neurons.[1,2] The cerebellum develops over a long period, extending from the early embryonic period at approximately 4 weeks of gestation into the first postnatal years.[1] The high complexity and long duration of development makes the cerebellum vulnerable for a wide range of pathologic conditions/injuries including inborn errors of development (primary malformations) and acquired/secondary disruptions. Both inborn errors of development (primary malformations) and acquired/secondary disruptions result in morphologic changes (malformed) of the cerebellum and brainstem and are usually named malformations independent on the cause and pathomechanism. The term *malformation*, however, has a more specific significance and implies an alteration of the primary developmental program as pathomechanism of the morphologic anomaly.

Disruptions are defined as nonprogressive, congenital morphologic anomalies caused by the breakdown of a body structure that had a normal developmental potential and was initially normally developing until injured.[3] The timing and nature of the disruptive event/agent may either directly injure or destruct the cerebellum or impair/alter the subsequent sequences of development with resultant perturbation of normal growth and development. There are several possible causes of disruptions, including vascular (eg, hemorrhage and ischemia), infectious, teratogenic, and mechanical.[3] In the prenatal period, the cerebellum is particularly vulnerable to infections and hemorrhages (**Table 1**).[4] In contrast to true malformations (inborn errors of development), disruptions are acquired lesions with low recurrence risk.

Table 1
Cerebellar vulnerability

Category	Cerebellar Vulnerability
Neonatal hypoxic-ischemic injury	+
Postnatal infections	+
Prematurity (<30 wk gestational age)	+
Prenatal infections (particularly CMV)	++
Prenatal hemorrhages	+++
Toxicity/selected drugs	+++
Metabolic disorders	++++

From Poretti A, Prayer D, Boltshauser E. Morphological spectrum of prenatal cerebellar disruptions. Eur J Paediatr Neurol 2009;13(5):405; with permission.

The differentiation between malformations and disruptions is important for genetic counseling and for diagnostic and prognostic purposes. A genetic predisposition for disruptive lesions may, however, be present. For example, dominant mutations in *COL4A1* lead to changes in the basal membrane of capillaries resulting in microangiopathy.[5] Within the brain, the microangiopathy increases the risk for hemorrhage or ischemia and subsequent porencephaly or unilateral cerebellar hypoplasia on follow-up.[6,7] Furthermore, homozygous mutations in *NED1* are found to cause the fetal brain disruption sequence characterized by severe microcephaly, scalp rugae, and prominent occipital bone.[8]

High-quality anatomic and functional neuroimaging plays a key role in the early and correct diagnosis and differentiation of the many morphologic cerebellar abnormalities that may be seen in the pre-, peri- and postnatal period. In particular, neuroimaging may help differentiate between malformations and disruptions. For example, abnormalities (eg, hypoplasia or dysplasia) involving only 1 cerebellar hemisphere are most likely the sequela of a prenatal disruptive event such as a hemorrhage. High-resolution anatomic MR imaging sequences remain of essential importance for the evaluation/characterization of the normal or abnormal pre- and postnatal posterior fossa contents, which include the cerebellum and brain stem. Advanced, functional neuroimaging techniques such as diffusion tensor imaging (DTI) and susceptibility weighted imaging (SWI) may render additional crucial information to better elucidate certain aspects of the pathogenesis of the encountered cerebellar disruptions. DTI allows exploration of the internal derangement of the fiber architecture. SWI is highly sensitive for blood, blood products, and calcifications and may be of particular help in supporting the notion of a disruptive pathomechanism related to infections or hemorrhages.[9] Additional, less frequently applied techniques include ^{1}H magnetic resonance spectroscopy, and perfusion weighted imaging. Finally, pre- and postnatal ultrasonography with dedicated posterior fossa imaging should not be forgotten as a valuable, widely available, safe, low-cost bedside alternative imaging technique that can be used in critically sick or unstable children. In skilled hands, advanced ultrasound units can give highly diagnostic imaging data, which, because of the ease of serial data collection, allow us to follow and explore the dynamics of cerebellar injury.

This article discusses the morphologic spectrum of prenatal cerebellar disruptions including various forms of cerebellar agenesis, unilateral