

## Review

## Cerebellar disruptions and neurodevelopmental disabilities



Thangamadhan Bosemani, Andrea Poretti\*

Section of Pediatric Neuroradiology and Division of Pediatric Radiology, Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

## S U M M A R Y

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The vulnerability of the cerebellum during prenatal life to disruptive events such as hemorrhage and infection leads to a wide variety of morphological abnormalities. This review discusses various prenatal cerebellar disruptions including cerebellar agenesis, unilateral cerebellar hypoplasia, cerebellar cleft, global cerebellar hypoplasia, and vanishing cerebellum in Chiari type II malformation. For each entity, we discuss the definition, potential pathomechanism, clinical findings including neurocognitive and behavioral problems, neuroimaging features, and management. Accurate recognition of cerebellar disruptions and their differentiation from malformations is important in terms of diagnosis, prognosis, and genetic counselling.

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## 1. Introduction

The cerebellum undergoes a protracted development, from the early prenatal period at about four weeks of gestation extending into the first postnatal years [1]. The embryogenesis/histogenesis of the cerebellum is a highly complex process that is programmed/determined by a large number of genes and may be summarized in four basic steps: (i) characterization of the cerebellar territory in the hindbrain; (ii) formation of two compartments of cell proliferation, giving rise to the Purkinje cells and the granule cells; (iii) inward migration of the granule cells; and (iv) differentiation of cerebellar neurons [1]. The complexity and protracted duration of cerebellar development makes it vulnerable to a wide range of injuries including both primary malformations and acquired/secondary disruptions.

A malformation is defined as a non-progressive, congenital morphologic anomaly of a single organ or body part due to an alteration of the primary development [2]. A disruption is defined as a non-progressive, congenital morphologic anomaly due to the breakdown of a body structure that had a normal developmental potential [2]. Disruption refers to an event or sequence of events that typically occur during prenatal life. The timing and nature of the disruptive event may directly injure or destruct the cerebellum and/or impair/alter the

subsequent sequences of development with resultant perturbation of normal growth and development. There are many potential causes of disruption including vascular, infectious, teratogenic, and mechanical [2]. During prenatal life, the pathomechanism for disruption is attributable to the vulnerability of the cerebellum predominantly to hemorrhage and infection (Table 1) [2,3].

Both primary malformations and acquired/secondary disruptions result in morphological changes (mal-formed) of the cerebellum and brainstem and are typically referred to as “malformations” independent of the cause or pathomechanism. However, disruptions have a very low recurrence risk compared to true malformations. Hence, it is imperative to distinguish malformations from disruptions for genetic counseling, as well as for diagnostic and prognostic purposes. Also, disruptions in rare instances may have a genetic predisposition. For instance, dominant mutations in *COL4A1* lead to changes in the basal membrane of capillaries resulting in microangiopathy. Microangiopathy increases the risk for hemorrhage and/or ischemia in the brain, resulting in porencephaly or unilateral cerebellar hypoplasia [4].

In recent decades, studies from adults with acquired cerebellar diseases such as low-grade cerebellar tumors, cerebellar stroke, and cerebellitis showed that the cerebellum plays a key role not only for motor functions, but also for neurocognitive functions and behavior. The cerebellar cognitive affective syndrome highlights the cerebellar involvement in: (i) executive functions such as planning, setshifting, verbal fluency, abstract reasoning, and working memory; (ii) spatial perception including visual–spatial organization and memory; (iii) language deficits such as

\* Corresponding author. Address: The Johns Hopkins School of Medicine, Charlotte R. Bloomberg Children's Center, Sheikh Zayed Tower, Room 4174, 1800 Orleans Street, Baltimore, MD 21287-0842, USA. Tel.: +1 410 9556454; fax: +1 410 5023633. E-mail address: [aporetti@jhmi.edu](mailto:aporetti@jhmi.edu) (A. Poretti).

**Table 1**  
Cerebellar vulnerability.<sup>a</sup>

Category	Cerebellar vulnerability
Neonatal hypoxic–ischemic injury	+
Postnatal infections	+
Prematurity (<30 weeks of gestational age)	+
Prenatal infections (particularly CMV)	++
Prenatal hemorrhages	+++
Toxicity/selected drugs	+++
Metabolic disorders	++++

CMV, cytomegalovirus.

<sup>a</sup> Reproduced with permission from Poretti et al. [51].

agrammatism and dysprosodia; and (iv) behavior including blunting of affect or disinhibited and inappropriate behavior [5]. Neurocognitive deficits and behavioral problems consistent with the cerebellar cognitive affective syndrome have also been shown in children with acquired cerebellar diseases (e.g. low-grade tumors and cerebellitis) as well as cerebellar malformations (e.g. Joubert syndrome and rhombencephalosynapsis) [6,7]. The pattern of neurocognitive and behavioral impairment in children with prenatal cerebellar disruptive lesions is reminiscent of cerebellar cognitive affective syndrome, but, as discussed later in more detail, it seems to be less specific than in patients with postnatally acquired cerebellar lesions or cerebellar malformations.

In this review, following a short introduction about the role of neuroimaging in the diagnostic work-up of children with suspected prenatal cerebellar disruptions, we discuss the morphological spectrum of prenatal cerebellar disruptions including cerebellar agenesis, global cerebellar hypoplasia, unilateral cerebellar hypoplasia, cerebellar cleft, and vanishing cerebellum related to Chiari type II malformation. For each entity, we review the presumptive underlying pathomechanism, clinical presentation, key neuroimaging features, long-term neurodevelopmental outcome, and potential therapy.

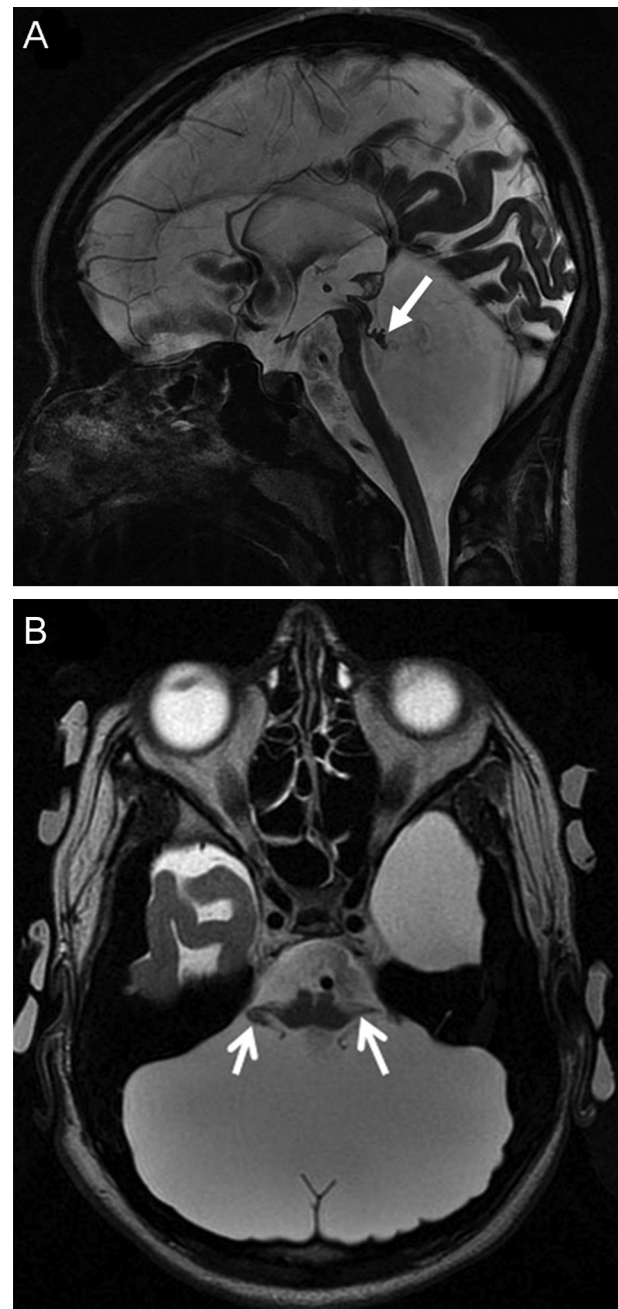
## 2. Role of neuroimaging in the diagnostic work-up of prenatal cerebellar disruptions

Neuroimaging plays a key role in the accurate diagnosis, characterization and differentiation of morphologic abnormalities of the cerebellum during the pre-, peri- and postnatal period, including prenatal cerebellar disruptions. In addition, neuroimaging helps to differentiate disruptions from malformations. For instance, morphologic abnormalities (e.g. hypoplasia and/or dysplasia) involving only one cerebellar hemisphere is most likely sequela of a prenatal disruptive event such as hemorrhage. Magnetic resonance imaging (MRI) is the modality of choice, offering both conventional anatomical and advanced functional pulse sequences. High-resolution anatomical MRI 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 brainstem. Advanced, functional neuroimaging techniques such as diffusion tensor imaging (DTI) and susceptibility-weighted imaging (SWI) may offer additional important information to better evaluate certain aspects of the pathogenesis of cerebellar disruptions. DTI enables the interrogation of the internal derangement of the white matter fiber architecture. SWI is highly sensitive for blood, blood products, and calcifications, and may be of help in confirming a disruptive pathomechanism related to infection or hemorrhage [8]. Additionally, less frequently applied techniques include <sup>1</sup>H-magnetic resonance spectroscopy (MRS), and perfusion-weighted imaging (PWI). Finally, pre- and postnatal ultrasonography (US) remains a valuable, widely available, safe, low-cost imaging technique. US is utilized as a screening tool for evaluation of anatomical and/or morphological

abnormalities during the prenatal period. During postnatal life, US is a portable, bedside imaging technique for the evaluation of critically sick or unstable neonates [9]. Noteworthy, the evaluation of the posterior fossa using US improved significantly with the introduction of the mastoid fontanel view.

## 3. Cerebellar agenesis

Cerebellar agenesis (CA) is an extremely rare condition characterized by near-complete absence of the cerebellum [3]. CA is



**Fig. 1.** Cerebellar agenesis in a 15-year-old girl who presented with severe intellectual disability and tetraspasticity. (A) Sagittal T2-weighted magnetic resonance (MR) image shows near-complete absence of cerebellar structures except for a rudimentary remnant of the anterior cerebellar vermis (arrow), an enlarged posterior fossa, and marked hypoplasia of the pons. (B) Axial T2-weighted MR image shows rudimentary cerebellar tissue (arrows) projecting lateral to the brainstem. (Reprinted with permission from Poretti et al. [3].)

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