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*Research Article*

# Cerebellar Vermis Injury in Severe Neonatal Hypoxic-Ischemic Encephalopathy

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## Abstract

Background/Objectives: Cerebellar vermis abnormalities often accompany more extensive hypoxic-ischemic encephalopathy lesions in full-term newborns. However, these abnormalities have received little attention until now. This study presents a small case series of affected newborns, focusing on vermis lesions and associated brain injuries.

Methods: Newborns underwent an initial conventional Magnetic Resonance Imaging (MRI) scan of the brain, typically within the first few days after the acute insult. A late conventional brain MRI was obtained between the third and fifth months of life. Images were analyzed independently by a child neurologist and a neuroradiologist on our team and the results were compared. Findings: Cerebellar vermis involvement was confirmed in all cases. Interestingly, the hippocampus, dorsal brainstem, cerebellum and globus pallidus were particularly affected, though this is rarely reported or described.

Conclusion: Cerebellar vermis injury is often associated with severe Hypoxic-Ischemic Encephalopathy (HIE) in term neonates. In addition to previous reports, we describe new, widespread lesions in cerebral regions that are functionally and metabolically linked with the vermis.

**Keywords:** Cerebellar Vermis; Hypoxic-Ischemic Encephalopathy (HIE); Hypoxic-Ischemic Encephalopathy; Term Neonates; Globus Pallidus; Hippocampi

## Introduction

Hypoxic-Ischemic Encephalopathy (HIE) in term neonates can result in severe and irreversible brain damage. Initially, brain lesions associated with HIE were studied using ultrasounds and CT scans because these methods can be used during the acute injury stage. However, it was not until the advent of Magnetic Resonance Imaging (MRI) that these lesions could be accurately and effectively examined for their distribution, severity and clinical correlations. A useful clinical distinction of neonatal HIE is classification into three stages: Stage 1 is characterized by jitteriness and irritability, as well as a normal electroencephalographic (EEG) pattern. Stage 2 is characterized by hypotonia, lethargy and multifocal seizures within the first 12 hours after birth. It also exhibits EEG periodicity or delta wave activity. Stage 3 is characterized by diffuse flaccidity, stupor or coma and suppression of brainstem activity. This stage exhibits an EEG burst-suppression or isoelectric pattern [1]. Two major neuroimaging patterns of injury emerged in full-term neonates with Hypoxic-Ischemic Encephalopathy (HIE). The first pattern, associated with prolonged partial asphyxia, showed diffuse cortical injury and often resulted in multicystic encephalomalacia. In this pattern, the thalami and basal ganglia were spared. The second pattern was associated with acute, nearly total asphyxia. Due to their active metabolism, the thalami and basal ganglia were injured, while the cerebral cortex was relatively preserved [2,3]. Neuroimaging in HIE has primarily focused on supratentorial brain structures [4,5]. However, recent literature increasingly suggests that the developing cerebellum is vulnerable to injury during severe neonatal asphyxia, even after the introduction of therapeutic

hypothermia [6-15]. Historical experimental studies have demonstrated that complete asphyxia injures the cerebellum and brainstem nuclei [16]. Rare neuroimaging and pathological studies have revealed various forms of cerebellar involvement associated with different patterns of severe basal ganglia and thalamic injury. These include dentate nucleus involvement and most notably, vermis and Purkinje cell damage [7,8,10,3-15]. Neuroimaging has revealed vermis atrophy accompanied by hypointense T1-weighted abnormalities and hyperintense T2-weighted and Fluid-Attenuated Inversion Recovery (FLAIR) abnormalities, primarily affecting the anterior vermian lobe [7,8]. Furthermore, new imaging techniques, particularly Diffusion Tensor Imaging (DTI), have revealed occult cerebellar injuries that could be easily confirmed by neuropathological examination [10]. Thus, although the cerebellum and vermis have only recently received significant attention, it is clear that severe hypoxia-asphyxia regularly affects these particular infratentorial structures in neonates, especially in cases of severe and protracted hypoxia-asphyxia. However, clinical and neuroimaging studies of vermian involvement in HIE are scarce. Here, we present cases of vermian involvement in several infants with a history of severe HIE. Our aim is to confirm vermis involvement and its association with other rare or undescribed brain lesions.

**Material and Methods**

In our small study of thirteen full-term newborns with severe HIE, the duration of the condition varied. All of the participants exhibited respiratory, systemic and neurological symptoms, including early epileptic tonic and atonic seizures, within the first few hours of life. Their condition was primarily caused by intrapartum cardiocirculatory insufficiency. All of the newborns required total ventilatory assistance. During the earliest hours and days when respiratory and neurological conditions permitted, the newborns underwent brain transfontanellar sonography, as well as their first CT scan and MRI. These investigations revealed common results of initial, topographically undefined brain damage. Brain imaging was performed using a 1.5 Tesla magnetic resonance device. Main T1-weighted, T2-weighted and Fluid-Attenuated Inversion Recovery (FLAIR) images were obtained. While the initial investigations revealed generalized brain damage, late brain MRIs of three - to five - month-olds produced the best results, as summarized in Table 1.

| Patient n° | Cortex | Thalamus | Globus pallidus | Putamen | Vermis | Cerebellum | Brainstem | Hippocampus | White matter |
|---|---|---|---|---|---|---|---|---|---|
| 1 | ++ | ++ | ++ | + | ++ | + | + | + | + |
| 2 | + | ++ | ++ | ○ | ++ | ○ | ○ | ○ | + |
| 3 | ○ | ++ | ++ | ○ | ++ | ○ | ○ | ○ | ○ |
| 4 | ++ | ++ | ++ | + | ++ | + | + | + | + |
| 5 | ○ | + | + | + | ++ | ○ | ○ | ○ | ○ |
| 6 | + | ++ | ++ | ○ | ++ | ○ | ○ | ○ | + |
| 7 | ++ | ++ | ++ | ○ | ++ | ○ | ○ | ○ | + |
| 8 | ○ | ++ | ++ | ○ | ++ | ○ | ○ | ○ | ○ |
| 9 | ++ | ++ | ++ | ○ | ++ | + | + | + | + |
| 10 | + | ++ | ++ | ○ | ++ | ○ | ○ | ○ | + |
| 11 | ○ | ++ | ++ | ○ | ++ | ○ | ○ | ○ | ○ |
| 12 | + | ++ | ++ | + | ++ | + | + | ○ | + |
| 13 | + | ++ | ++ | ○ | ++ | ○ | ○ | ○ | + |
| Legends: + mild lesion; ++ severe lesion; ○ no apparent lesion | | | | | | | | | |

**Table 1:** Brain involvement in 13 newborns with HIE.

**Results**

Late brain MRI images revealed significant and symmetrical signal abnormalities in the basal ganglia and thalami, which were

present in all cases. Of the basal ganglia regions, the globus pallidus was the most frequently affected, followed by the putamen. The thalami were always affected (Fig. 1). Only newborns with severe, long-standing HIE showed cerebral hemispheric white matter damage. In these cases, the corresponding cerebral cortex also showed ischemic injury. Additionally, a peculiar injury consisting of a bilateral, hyperintense, transverse, horizontal signal was observed in the cerebellar hemispheres of a few newborns. The vermis itself showed more severe and extensive signal abnormalities. Occasionally, there was initial vermis folia atrophy, which was only visible on late MRI images (Fig. 2). Abnormal tissue damage in the form of bilateral, symmetric signals was observed in the hippocampus of three out of thirteen newborns, generally progressing to late atrophy. The brainstem, particularly the dorsal pons and midbrain, was also affected in the most severe cases of HIE and exhibited pathological hyperlucency. Vermian involvement typically affected the antero-superior folia. It also extended into the mid and posterior compartments (Fig. 3).

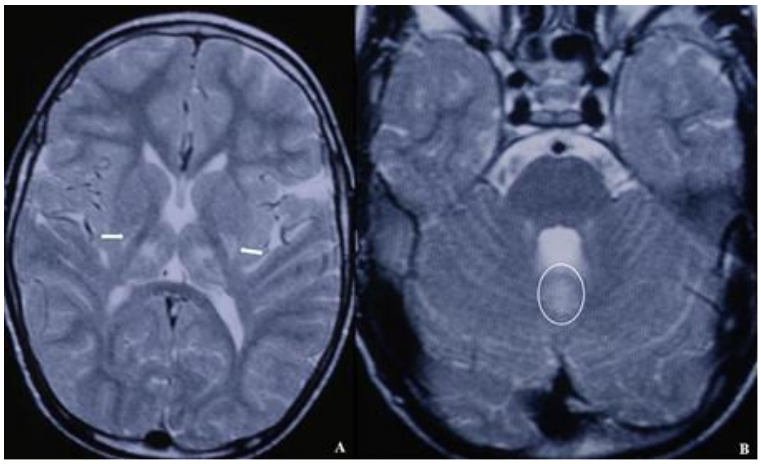


**Figure 1:** Example of brain MRI in newborns with moderate HIE. In newborns with less severe HIE, thalamic and basal ganglia involvement is constant. In general, the globus palliduus appears to be affected more often than the putamen (white arrows). The extent of the abnormal signal in the vermis generally parallels that of the basal ganglia, though it may be abnormally large in a few cases of less severe HIE (empty circle). Axial T2 SE MRI (Panel A and B; Patient No. 5).

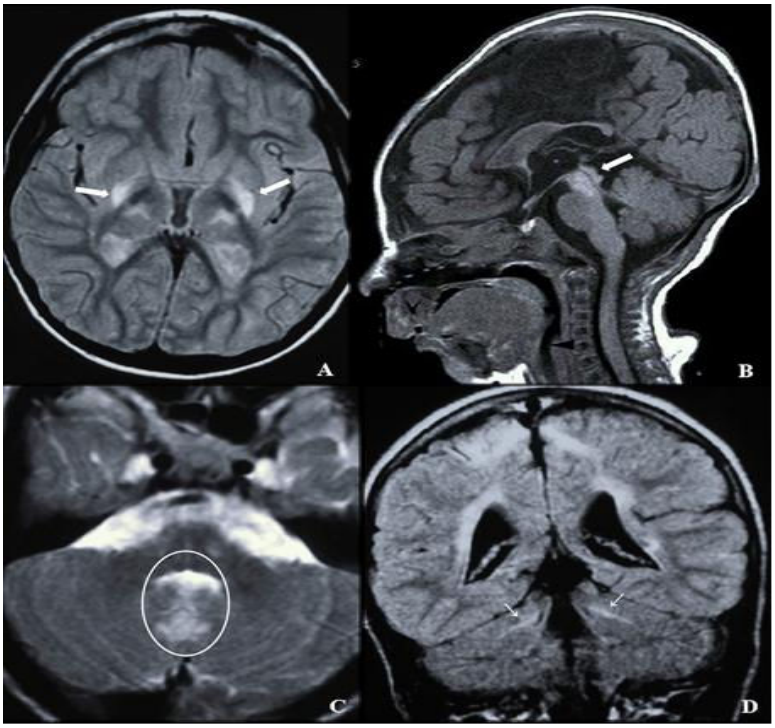


**Figure 2:** Examples of brain MRI in newborns with more severe HIE. In patients with more severe HIE (Patient No. 12), the abnormal signal extension increases in the thalami and basal ganglia, particularly in the globus pallidus region (Panel A, axial

FLAIR T1 MRI, white arrows). Additionally, anterior vermian damage extends further posteriorly (Panel C, axial T2 SE MRI, empty circle) and involvement of the dorsal midbrain and pons becomes evident (Panel B, sagittal T1 SE MRI, white arrow). Panel D (coronal FLAIR T1 MRI) shows involvement of the hemispheric and paracentral white matter. A new finding is the presence of thin stripes of symmetrical abnormal signals in both anterior cerebellar hemispheres, indicating white matter damage (small thin arrows).

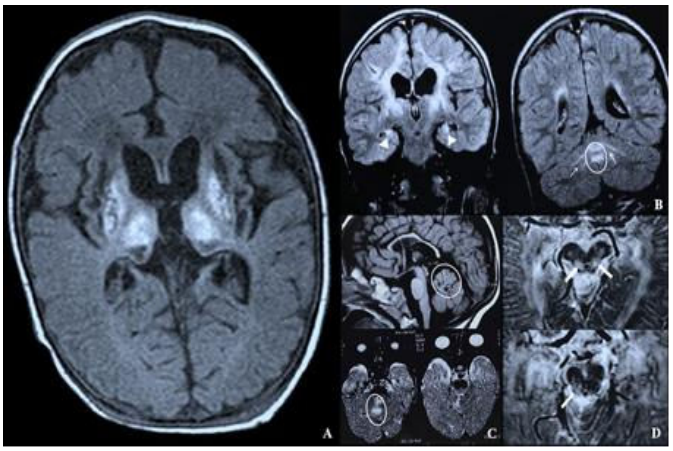


**Figure 3:** Examples of brain MRI in newborns with the most severe HIE. In the case of very severe HIE (Patient No. 4), the thalami and basal ganglia are heavily affected, often symmetrically (Panel A, axial T1 SE MRI). Abnormal signals confirm the extent of the cerebral injury and indicate involvement of the cerebellar vermis and anterior cerebellar hemispheric white matter. They also indicate probable damage to the deep dentate nuclei (small thin arrows and empty circle) and bilateral injury to the hippocampi (white arrowheads) (Panel B, FLAIR MRI). Panel C shows the abnormal vermian signal (C, axial T2 SE MRI, empty circle) and initial atrophy of the superior-anterior third of the vermis (upper half of Panel C, sagittal T1 MRI, empty circle). Panel D clearly demonstrates bilateral involvement of the dorsal pons and midbrain (white arrows) (axial T2 SE MRI).

**Discussion**

Cerebellar abnormalities may accompany HIE in full-term newborns, with the vermis appearing to be the preferred target. Vermian lesions occur when the thalami and basal ganglia sustain severe, symmetrical damage. Occasionally, the deep cerebellar nuclei are maximally involved, often alongside an injury to the posterior pons and midbrain [12,14]. The antero-superior folia of the vermis are primarily affected and Purkinje cells are predominantly damaged [7,8,10,13-15].

Consistent with previous reports, this small case series confirms that HIE involving the thalamus and basal ganglia can result in variable lesions. Therefore, vermian damage may also be variable, subtle and difficult to detect with conventional brain MRIs. However, more sophisticated neuroimaging techniques, such as Diffusion Tensor Imaging (DTI), can reveal vermian lesions in the days immediately following birth [10]. Therefore, DTI has the potential to become the gold standard for early, complete diagnosis of HIE in term newborns. Early neuroimaging that demonstrates the location and extent of brain injury is critical for subsequent therapeutic approaches and prognosis. Recent postmortem histopathological studies have confirmed the selective and early vulnerability of Purkinje cells in vermian lesions of term neonates with HIE. These studies revealed the early necrosis or apoptosis of these cells, as well as the subsequent defective growth of the cerebellar vermis. Consistent with previous reports, this small case series confirmed vermian injury in HIE newborns. The antero-superior vermian compartment was the most affected area. Bilateral thalamic involvement was always present. However, the extent of vermian injury did not systematically correspond to the extent of thalamic damage. This suggests that the extent of vermian injury depends on which thalamic nuclei are damaged despite their tight anatomical and metabolic connections. Indeed, the ventrolateral thalamic nuclei are not always affected, while the pulvinar often. We emphasize the rarely reported hippocampal signal abnormality. Notably, Connolly, et al., case series demonstrates bilateral hippocampal involvement in 10 out of 30 affected neonates [8]. All of these neonates showed vermis injury, as well as paracentral white matter, thalamic and putaminal involvement, cerebral and cerebellar white matter involvement and involvement of the dorsal pons and mesencephalon. Another difference between our cases and previous reports is the consistent and often obvious involvement of the globus pallidus, while the putamen was generally less affected. Our small series of HIE newborns confirms the presence of diffuse abnormal signals in the dorsal pons and midbrain, which occur almost exclusively in the most severely affected neonates with diffuse white matter involvement.

The pathogenetic correlations between supratentorial brain injury and infratentorial lesions, primarily vermian, in term neonates with HIE have been approached inconsistently. The absence of visible vermis injury on conventional MRIs during the first few days of life and the late onset of progressive atrophy and growth failure in the injured vermis are pivotal factors in understanding pathogenesis. One possible explanation is that the pathogenesis of these vermian lesions, which evolve slowly into atrophy, depends on excessive apoptosis. This is plausible because, during this specific developmental stage, the vermis exhibits metabolic activity similar to that of the thalami and basal ganglia [6,7,9,13]. Le Strange, et al., considered impaired cerebellar growth, particularly vermian growth, to be a secondary consequence of perinatal injury to the supratentorial thalamus and basal ganglia [6]. This is significant because the ventrolateral thalamic nuclei have strong anatomical and functional connections with the cerebellum, especially the vermis. These nuclei act as primary relays to the cerebellum. Additionally, Sargent, et al., identified the vermis as one of the most metabolically active regions of the full-term neonate's brain [7]. However, they emphasize the possibility of acute neuronal necrosis and late apoptosis, both of which contribute to vermian atrophy. Annink, et al., demonstrated histological necrosis and altered morphology of Purkinje neurons [13,15]. They also observed signs of neuroinflammation, as evidenced by activated microglia and macrophages. Indeed, cerebral tissue damage can still develop even after therapeutic hypothermia is introduced to protect against energy dysfunction and inflammation. Vermian injury is often overlooked in term HIE neonates. However, a histopathological study of the cerebellar vermis was performed on 14 HIE newborns who underwent autopsy and injury was found in 72% of them [9]. In addition to defects in oxidative phosphorylation and inflammation, Johnston's study further supported neuronal excitotoxicity [17]. In extensive research on the causal role of excitotoxicity in perinatal brain injury, Johnston described the mechanisms by which NMDA and AMPA receptors become overstimulated in newborns with term HIE. Johnston also highlighted how this process intermingles with mitochondrial energy metabolism, secondary depolarization, energy depletion, cytochrome C deficiency and ultimately, caspase activation and apoptosis. Johnston's study advanced our understanding of brainstem involvement by demonstrating that AMPA receptors fail to regulate calcium ion influx into neurons and mitochondria under hypoxic-ischemic conditions.

A similar mechanism may be at play in white matter injury because immature oligodendrocytes primarily express AMPA receptors. Uncontrolled $Ca^{2+}$ influx in these cells can lead to cell death. Interestingly, topiramate and hypothermia can rescue normal AMPA receptor activity and prevent cell death. However, as mentioned above, altered Purkinje neuron morphology is evident through histopathological examination, even in HIE newborns protected by hypothermia.

**Conclusion**

In severe HIE in term neonates, damage to the antero-superior cerebellar vermis, as revealed by late MRIs, is much more prevalent than commonly recognized or demonstrated by conventional neuroimaging techniques. Conventional neuroimaging is crucial in demonstrating vermian involvement over time, usually after many weeks of life. Among the infratentorial structures, the dorsal pons and midbrain may often be affected. However, injury to the anterior cerebellar hemispheric white matter is rare, as demonstrated by some of our cases. Injury to the ventrolateral thalamus and putamen is recognized as a prerequisite for vermian damage. Interestingly, however, in our small series of thirteen HIE neonates, the globus pallidus exhibited more common, symmetrical alterations than the putamen. Furthermore, confirming hippocampal abnormalities in our cases not only increases the amount of affected cerebral tissue, but may also play a critical role in the future epilepsy of long-surviving newborns. More sophisticated neuroimaging procedures, particularly Diffusion Tensor Imaging (DTI), can detect vermian lesions in the early hours of life. These procedures may allow for a more precise therapeutic approach than hypothermia alone.

**Conflict of Interests**

The authors declare that they have no conflicts of interest.

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**Author Contributions**

The authors contributed equally to the work.

**Institutional Review Board Statement**

This study was conducted in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association.

Furthermore, the manuscript did not need the approval of the Ethical Committee of our University Administration as this is not a requirement for the publication of a single case provided that it is of definite interest to the scientific community (Regulations of the Ethical Committee of "Area Vasta Emilia Nord", Italy, approved on September 22, 2020).

**Informed Consent Statement**

Informed consent was verbally obtained from the parents of all subjects involved in the study.

**Data Availability Statement**

Data and Materials are available from the authors upon reasonable request.

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