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Original Article

# Patterns of Restricted Diffusion within Corpus Callosum in Neonatal Hypoxic-Ischemic Encephalopathy and its Significance in Predicting the Clinical Outcome

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## Abstract

**Background:** Hypoxic-ischemic encephalopathy (HIE) continues to be a dreadful cause of morbidity and mortality in neonates and is a leading cause of cerebral palsy and other neurodevelopmental deficits. It manifests in different patterns of brain involvement on magnetic resonance imaging (MRI), of which restricted diffusion within the splenium, genu, or body of the corpus callosum has received less attention in the literature. In this review, we will describe a series of cases showing this pattern of injury.

**Materials and Methods:** MRI including diffusion-weighted imaging was performed in 28 neonates with known or clinically suspected HIE, including both premature and term neonates.

**Results:** 11 out of 28 patients demonstrated restricted diffusion in the corpus callosum. Out of these 11 patients, 6 showed restricted diffusion in the entire corpus callosum, 3 showed isolated splenium involvement, 1 had body and splenium signal abnormality, and 1 showed diffusion restriction in the genu and splenium.

**Aims:** The aim is (1) to study the patterns of restricted diffusion in corpus callosum in neonatal HIE and (2) to demonstrate that corpus callosum involvement is associated with extensive brain insult.

**Conclusions:** Cytotoxic lesions of the corpus callosum in neonate with HIE are associated with extensive brain injury and emerges to be an early neuroradiologic marker of adverse outcome. Splenium of corpus callosum is the most vulnerable location for ischemic injury. Corpus callosal injury is more common among term than preterm neonates.

**Key words:** Corpus callosum, Hypoxic-ischemic encephalopathy, Magnetic resonance imaging, Restricted diffusion, Splenium

## INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) is a major cause of mortality and morbidity in newborns. The pattern of brain injury depends on factors such as brain maturity, duration, and severity of the insult. The pattern of injury is of four types, i.e., involvement of the watershed areas, basal ganglia-thalamus, total injury (maximal basal ganglia-thalamus and watershed), and focal-multifocal injury (presence of strokes and/or white matter injury alone).[1] Restricted diffusion within the corpus callosum is not frequently studied in HIE. Restricted diffusion of the corpus callosum on magnetic resonance imaging (MRI) is due to acute cytotoxic edema within the affected area. Cytotoxic lesions of the corpus callosum (CLOCCs) are secondary lesions associated with various entities including epilepsy,[2] the usage as well as sudden withdrawal of antiepileptic drugs,[3] ischemia,[4] multiple sclerosis; Marchiafava-Bignami syndrome, cerebral trauma, neoplasm, AIDS dementia complex, and infections such as influenza, herpes, salmonella, varicella zoster, rotavirus,[5] HIV, tubercular meningitis, and hemolytic-uremic syndrome with encephalopathy, neonatal hypoglycemia,

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demyelination disorders, and many other conditions. This study is to show the pattern of restricted diffusion within the corpus callosum on MRI in neonatal HIE.

## MATERIALS AND METHODS

This study was conducted at the Department of Radiodiagnosis, MGM Hospital, Warangal, Telangana State, between January 2018 and July 2018. We studied 28 neonates, 5 preterms, and 23 term infants, with known or clinically suspected HIE. Patient's history and clinical staging by Sarnath were documented before MRI. This was a prospective, observational study conducted among patients of both sexes. The study was carried out using GE BRIVO 1.5T MRI system with the 8-channel pediatric head coil. Following sequences (time of relaxation/time of echo/flip angle/field of view) were acquired as a part of the study: Axial T1-weighted spin echo images (500/14/90/256/4 mm), axial spin-echo T2-weighted images (4000/98/180/256), and isotropic diffusion-weighted images (DWI) (b 0, 1000), with apparent diffusion coefficient (ADC) maps. Before the MRI study, the procedure was explained to the parents/guardians of the patient, and a written informed consent was obtained. Sedation was given, either orally (syrup pedicloryl-½ h before the study) or intravenously (ketamine/propofol), before the start of the study, as deemed appropriate by the attending anesthetist.

## RESULTS

Restricted diffusion on DWI within corpus callosum was noted in 11 out of 28 patients (40%) [Table 1]. Signal abnormality in the rest of the brain parenchyma was also recorded.

**Table 1: Patterns of corpus callosal involvement in neonatal hypoxic ischemic encephalopathy**

| Patterns of corpus callosal involvement | Number of cases (%) |
|---|---|
| Entire corpus callosum | 6 (55) |
| Splenium | 3 (27) |
| Body and splenium | 1 (9) |
| Genu and splenium | 1 (9) |
| Total | 11 (100) |

Out of these 11 patients, restricted diffusion in the entire corpus callosum was noted in 6 cases which was the most common finding. Out of the 6 cases, 4 cases showed total brain injury pattern of involvement [Figure 1], 1 case showed watershed pattern, and 1 case showed basal ganglia-thalamus pattern of involvement. The splenium of the corpus callosum was the second most common area involved and was seen in 3 patients. Out of 3 patients, 1 showed total pattern of involvement, 1 patient showed watershed pattern [Figure 2], and 1 was isolated splenium involvement [Figure 3]. 1 patient showed combined involvement of the body and splenium with watershed pattern [Figure 4]. Involvement of the genu and splenium was noted in 1 case who had basal ganglia-thalamus pattern of involvement [Figure 5].

Out of 28 patients, 5 neonates were premature neonates. One of these neonates showed corpus callosum injury which showed involvement body and splenium. In our study, corpus callosum injury was found to be more common among term neonates.

In our study, we documented patients with the restricted diffusion of the entire corpus callosum, isolated involvement of the splenium and the genu, isolated involvement of the splenium and the body and isolated splenium involvement. Corpus callosum injury was associated with more severe clinical presentation. Corpus callosal injury was more common among term neonates, and most of the injuries were associated with total (maximal basal ganglia-thalamus and watershed) pattern of brain injury (45%) [Table 2].

## DISCUSSION

The pathophysiologic effects of HIE on corpus callosum are complex. The main underlying pathology in HIE is insufficient cerebral blood flow and decreased oxygen delivery to the brain.

Restricted diffusion of the corpus callosum on MRI represents acute cytotoxic edema within the affected area and could be a generalized response to the underlying hypoxic ischemia. On DWI the affected area of corpus callosum shows restricted diffusion with a corresponding dark signal intensity on ADC.

**Table 2: Incidence of different patterns of brain injury associated with restricted diffusion in corpus callosum**

| Corpus callosal injury | Total brain injury pattern | Watershed pattern | Basal ganglia-thalamus pattern | Isolated splenial restricted diffusion | Total |
|---|---|---|---|---|---|
| Entire corpus callosum | 4 (66) | 1 (17) | 1 (17) | 0 | 6 (100) |
| Splenium | 1 (33) | 1 (33) | 0 (0) | 1 (33) | 3 (100) |
| Body and splenium | 0 (0) | 1 (100) | 0 (0) | 0 (0) | 1 (100) |
| Genu and splenium | 0 (0) | 0 (0) | 1 (100) | 0 (0) | 1 (100) |
| Total | 5 (45) | 3 (28) | 2 (18) | 1 (9) | 11 (100) |

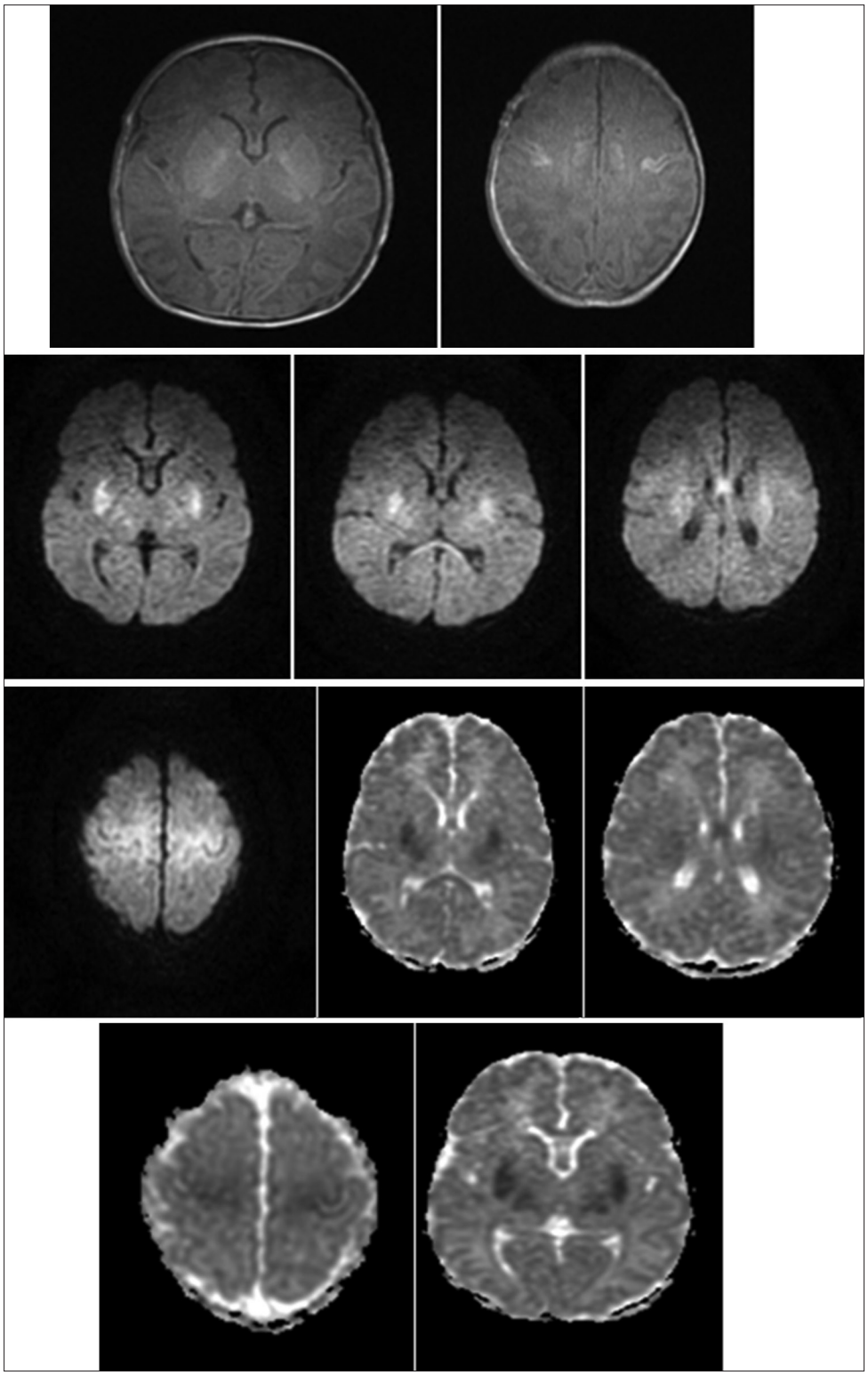

**Figure 1: Magnetic resonance imaging in 8-day full-term female with a neonatal hypoxic injury. Axial T1-weighted image shows abnormally increased signal intensity in bilateral basal ganglia, thalamus, and perirolandic cortex. In addition, there is the absence of normal bright signal in the posterior limb of internal capsule, referred to as "absent posterior limb sign." Axial diffusion-weighted images show hyperintense signal in bilateral basal ganglia, thalamus, perirolandic cortex, bilateral parietal lobes, genu, body and splenium of corpus callosum. Apparent diffusion coefficient maps show hypointense signal in same structures confirming that abnormal signal intensity is due to restricted diffusion**

Glutamate excitotoxicity is one of the important mechanisms that lead to cytotoxic edema. The corpus callosum and the basal ganglia are rich in glutamate receptors and are, therefore, more vulnerable to glutamate neurotoxicity by hypoxic-ischemic injury.[6,7] Seizures[8] and anticonvulsant therapy[9] may also be contributing factors of diffusion restriction within the corpus callosum. Oster *et al*.[10] proposed that repeated and excessive electrical discharges along the commissural fibers during seizures caused transient changes in energy metabolism and ionic transport, resulting in rapidly resolving intramyelinic edema.

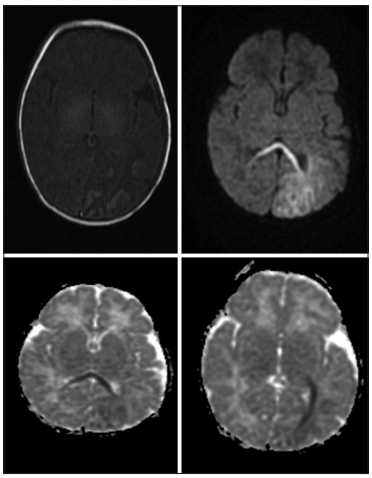

**Figure 2: Magnetic resonance imaging in 5-day-old male with neonatal hypoxic injury. Axial T1-weighted image shows hyperintensity of the left occipital lobe. Axial diffusion-weighted images show restricted diffusion in the splenium of the corpus callosum and left occipital lobe (infarct).**

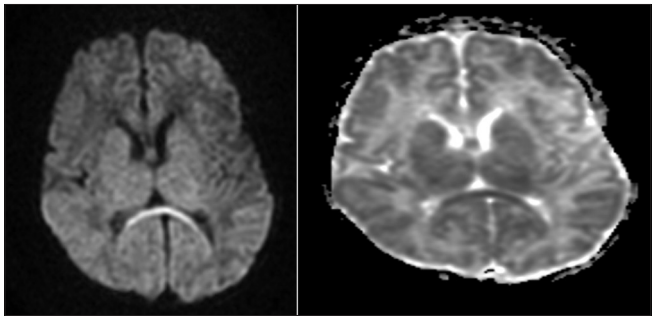

**Figure 3: Magnetic resonance imaging in 3-day-old female with neonatal hypoxic injury. Axial diffusion-weighted image shows hyperintensity of the isolated splenium of corpus callosum, and apparent diffusion coefficient map shows hypointense signal ("Boomerang sign").**

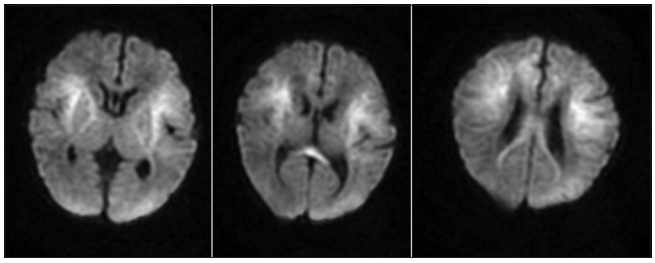

**Figure 4: Magnetic resonance imaging in 4-day-old female with neonatal hypoxic injury. Axial diffusion-weighted image shows restricted diffusion in bilateral parietal lobes, external, and internal capsule, body and splenium of corpus callosum.**

Complex interdependent mechanisms increase cytokine levels and, ultimately, glutamate levels in the brain.[11,12] With an insult to brain, macrophages are recruited which release the inflammatory cytokines interleukin-1 (IL-1) and IL-6, beginning the cascade that leads to cytokinopathy. This cytokinopathy causes massively increased levels of glutamate in the extracellular space. Compared with those in other brain areas, the neurons, astrocytes, and oligodendrocytes of the corpus callosum have a higher density of receptors, including cytokine receptors, glutamate, and other excitatory amino acid receptors, toxin receptors, and drug receptors.[7] The excitotoxic action of glutamate on receptors on corpus callosum, sodium-potassium pumps, and aquaporins results in an influx of water into both astrocytes and neurons. This water is trapped within the cells, which results in cytotoxic edema and hence restricted diffusion on MRI. The splenium of corpus callosum is particularly more vulnerable to cytokinopathy[13] [Table 3].

As the corpus callosal lesions with reduced diffusion (low ADC value) are caused by cytotoxic edema,[14,15] the term CLOCCs are used.

Involvement of the splenium, based on signal changes, can be divided into two types according to its shape and extent: Oval, circumscribed, with well-defined borders usually located in the midline, or wider, more extensive less regular lesions involving the entire splenium ("Boomerang sign").[4]

A study by Takenouchi *et al*.[16] on restricted diffusion within the corpus callosum in HIE, reviewed images of 34 infants. 10 of the 34 (29%) infants demonstrated restricted diffusion within the splenium of the corpus callosum, with a significantly higher incidence of severe neurodevelopmental delay or death, compared to infants without restricted diffusion in the splenium of the corpus callosum. Our study showed similar results with 10 out of 28 infants (35%) manifesting adverse outcome. 1 of 28 patients showed isolated splenium involvement and was associated with good neurodevelopmental outcome.[16]

**Table 3: Incidence of restricted diffusion within genu, body, splenium in corpus callosal injury**

| Restricted diffusion | Number of cases (%) |
|---|---|
| Genu | 7 (63) |
| Body | 7 (63) |
| Splenium | 11 (100) |

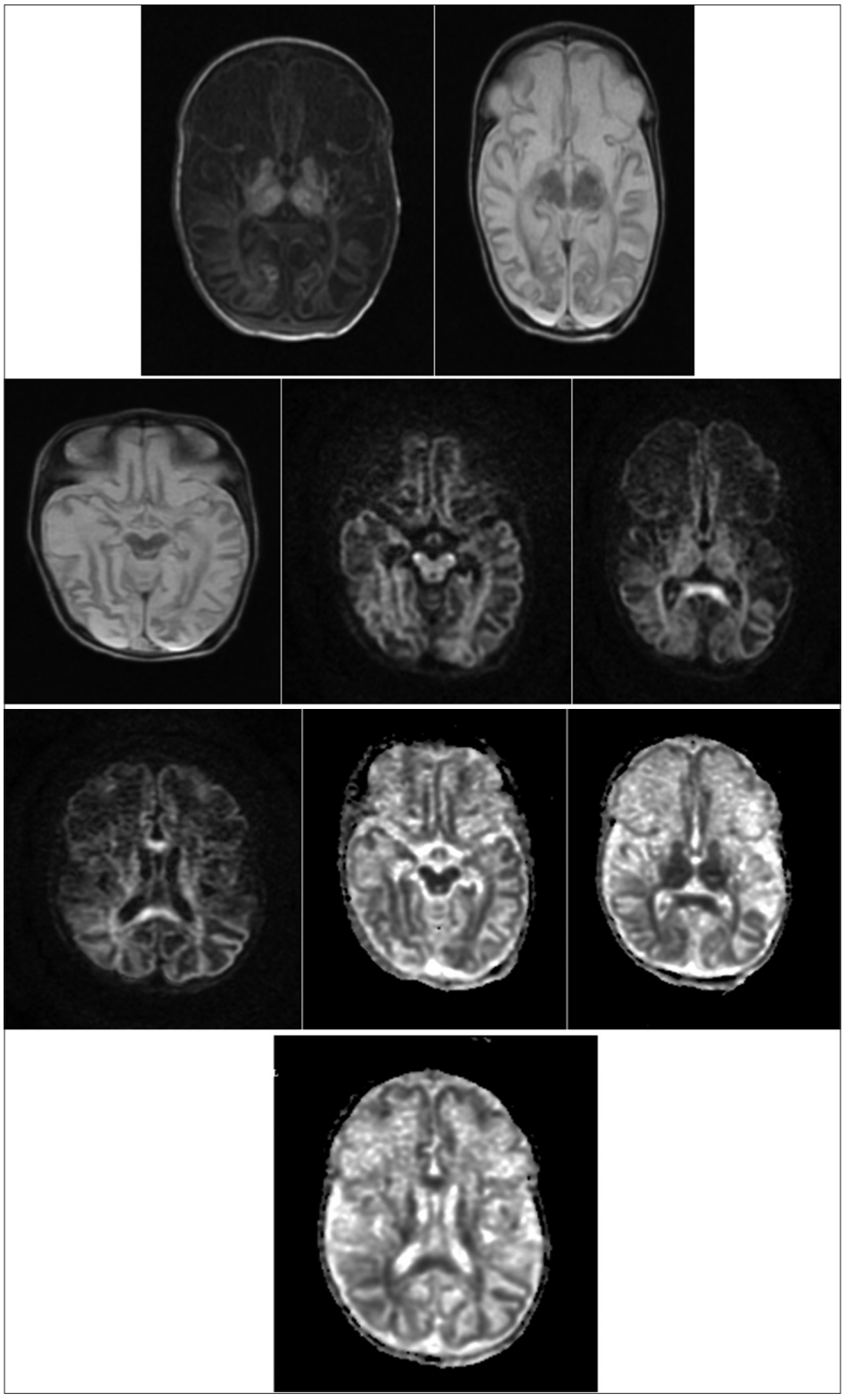

**Figure 5: Magnetic resonance imaging in 13-day-old male with neonatal hypoxic injury. Axial T1-weighted image shows abnormally hyperintense and atrophied basal ganglia, thalamus. The white matter shows abnormal signal intensity and cystic encephalomalacia with thinned out cortex. Axial T2-weighted image shows the corresponding hypointensity of basal ganglia and thalamus and hyperintense white matter suggestive of severe cystic encephalomalacia. Axial diffusion-weighted images show hyperintense signal in basal ganglia, thalamus anteromedial midbrain, splenium, and genu of corpus callosum. Apparent diffusion coefficient maps show hypointense signal in same structures confirming that abnormal signal intensity is due to restricted diffusion**

A study by Nagy *et al*.[17] showed that corpus callosal injury in teenagers with a history of moderate neonatal hypoxic ischemia injury was associated with worse neuropsychological performance. Thus, perinatal corpus callosal injury is an important marker of poor neurological outcome.

## CONCLUSION

We present a series of neonates, term, and preterm of both sexes, with HIE who underwent MRI. Restricted diffusion within the corpus callosum is a part of the spectrum of injury patterns in HIE, which is often associated with extensive brain injury and splenium of the corpus callosum is the most vulnerable location for ischemic injury. It serves as an early neuroradiologic marker of adverse neurologic prognosis.

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