

# The Role of Brain Magnetic Resonance Imaging in the Evaluation of Children with Global Developmental Delay

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## ABSTRACT

**Introduction:** Global developmental delay is diagnosed when there is a significant delay in two or more of the following domains of development: gross motor, fine motor, speech and language, cognition, and social/personal development. The etiology of global developmental delay varies from specific diseases to sequelae of perinatal ischemic insult. Determination of causality may or may not lead to treatment modification but has specific implications with regard to prognosis and counseling of the family. Magnetic resonance imaging is the modality of choice in investigating infants and children with developmental delay.

**Aim:** To study and classify brain magnetic resonance imaging findings in children aged 3 months-18 years who presented with global development delay.

**Materials and Methods:** Clinical records and imaging studies of 90 developmentally delayed children between

the ages of 3 months to 18 years who presented to the Dept of Radio-diagnosis, BMCRI for brain magnetic resonance imaging during September 2013 to August 2014 were analyzed retrospectively.

**Results:** Out of 90 children (male-44, female-46) who presented to us, abnormal findings were present in 65 (male-32, female-33) (72%), of which most (53) of them had features sequelae to ischemic insult such as periventricular leukomalacia, encephalomalacia and thinning of corpus callosum. 10 of the children (male-3, female-7) had structural malformations including corpus callosum agenesis (4), subcortical nodular heterotopia, etc.

**Conclusion:** Out of all 72% children with global developmental delay who underwent Magnetic resonance imaging showed positive findings, showing that MRI can contribute significantly to the determination of causality.

**Keywords:** Birth asphyxia, Encephalomalacia, Leukomalacia

## INTRODUCTION

The estimated prevalence of developmental delay in children is ~5- 10% and the etiologic profile is diverse. Global developmental delay is diagnosed when there is a significant delay in two or more of the following domains of development: gross motor, fine motor, speech and language, cognition, and social/personal development. Global developmental delay is associated with age specific deficits in adaptation and learning skills [1].

Clinically, development can be assessed by various tests, the most reproducible being Denver Developmental Screening Test II. Denver Developmental Screening Test has long been the standard for developmental screening and is applicable to children aged between 2 weeks to 6 years of age. However,

the etiology of developmental delay cannot be identified on the basis of history and physical examination alone. Additional studies to determine include genetic analysis, metabolic and serological testing and neuroimaging [2].

Cognitive and motor development observed in infants and children are a reflection of postnatal brain development. Myelination and synaptogenesis are considered the biological correlates of this developmental process and have been studied extensively. Any delay in neurodevelopment is likely to have a biological correlate [3]. This biologic correlate can be studied to some extent using neuroimaging techniques, particularly magnetic resonance imaging. Magnetic resonance imaging is the modality of choice in investigating infants and children with developmental delay [4]. MRI has a significant

role in diagnosis and early intervention in patients with hypoxic ischemic injury [5].

Previous studies have shown that ~60% of the patients have abnormal brain MRI [3]. A study determining the prevalence of abnormal brain MRI has so far not been carried out among patients presenting to Victoria Hospital, Bangalore Medical College and Research Institute, since our department is the only one possessing MRI scanner and no ethical clearance will be provided by the ethical committee to any studies performed by any other departments without our knowledge or consent.

This study may lead to informed counseling of these developmentally delayed children and their families.

The aim of this study is to determine the prevalence of abnormal brain MRI among developmentally delayed children aged 3 months- 18 years.

## MATERIALS AND METHODS

A Retrospective study (Retrospective analysis of data from PACS) was conducted in Victoria Hospital attached to Bangalore Medical College and Research Institute, Bangalore. Ninety consecutive children aged between 3 months- 18 years with clinical diagnosis of global developmental delay, who were referred for magnetic resonance imaging of the brain as part of their clinical work up were included in the study. The study was conducted between the months of September 2013 and August 2014. Informed consent had been obtained prior to the imaging study. Oral sedation utilizing triclofos (25 mg/kg body weight/dose) or intravenous sedation using midazolam in appropriate doses were administered when required. Institutional ethical committee approval was obtained for this study.

### Inclusion Criteria

- Children aged between 3 months-18 years who presented with global developmental delay/poor scholastic performance.

### Exclusion Criteria

- Children aged <3 months and >18 years
- Children with known genetic disorder, such as Down's syndrome, Turner's syndrome, etc., associated with delayed developmental milestones
- Contraindication to magnetic resonance imaging- claustrophobia, cochlear implant, pacemaker.
- History of head injury and non-cooperative sick patients.

### Method

Clinical data included basic demographic information (age, sex), birth history, history of admission to NICU and history of seizures. Findings of physical examination included weakness

of limbs, hypo/hypertonia of limbs, abnormal posturing, language and speech deficits and particulars of developmental milestones attained. Significant biochemical and serological information was also noted.

Imaging Protocol and categorization of imaging findings: MRI of the brain was performed using 1.5T Seimens (AVANTO) imaging system. The sequences used were- Axial T1, T2 and FLAIR FSE, T1 sagittal FSE, T2 coronal FSE, DWI, IR coronal and gradient axial.

The imaging findings were categorized into the following groups [3]:

- I. Normal
- II. Neurovascular diseases like hypoxic ischemic injury and non-specific findings: delayed myelination, hypoplasia of corpus callosum, ventriculomegaly.
- III. Recognizable neurodegenerative diseases like tuberous sclerosis, Sturge Weber syndrome.
- IV. Structural malformations- corpus callosum agenesis, heterotopia, Chiari malformations.
- V. Metabolic diseases.

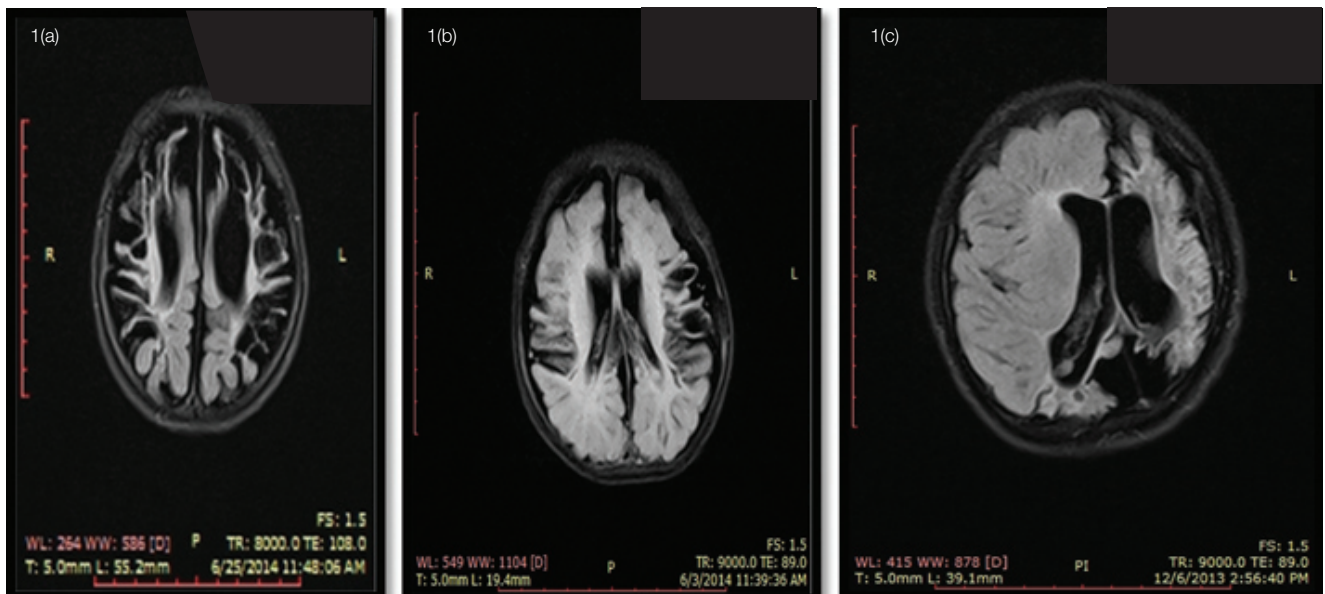
## STATISTICAL ANALYSIS

The required information was gathered and recorded in forms created for this purpose. Frequency was calculated and association between qualitative variables was evaluated using Chi square test. The p value of less than 0.05 was considered significant.

## RESULTS

In this study, 90 children with developmental delay were studied. Out of 90 children, 44(48.8%) were male and 46(51.2%) were female. Patients were divided into four age groups: 3months to 4 years, 5 to 8 years, 9 to 12 years and 13 to 18 years. Brain MRI findings were reported as normal in 25 cases (27.7%) and abnormal findings were seen in 65 cases (72.3%). Among the cases with abnormal brain MRI, 53(58.8%) had findings that were categorized as group II and constituted the largest group [Table/Fig-1a-1c]. The patients belonging to this group had neurovascular diseases and non-specific findings of delayed neurodevelopment. This was the largest group in each age group as well as in both genders. For example, among 55(61.1%) children aged 3 months to 4 years, majority (38-68.1%) belonged to group II.

Among 44(48.7%) male patients with developmental delay, 32(72.7%) had abnormal brain MRI and among 46(51.2%), female patients 33(71.7%) had abnormal brain MRI. There is no relation between abnormal brain MRI and gender. The p value is 0.916. Most of the male (28-63.6%) and female (24-52.2%) patients had abnormal findings that belonged to group II [Table/Fig-2].



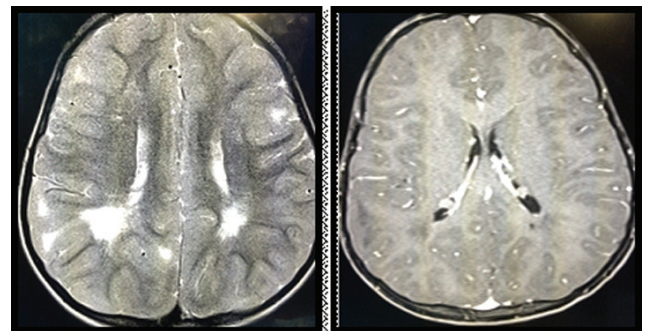
**[Table/Fig-1]:** Group II- 1(a) and 1(b) show encephalomalacic changes in two different patients. 1(c) shows neuroparenchymal atrophy involving left cerebral hemisphere in another patient.

Age	Normal		Abnormal				
	I	II	III	IV	V		
3 months-4 yrs	11 (20%)	38(68.1%)	-	6 (10.9%)	-		
5-8 years	6 (33.3%)	8 (44.4%)	1 (5.5%)	3 (16.6%)	-		
9-12 years	6 (66.6%)	3 (33.3%)	-	-	-		
13-18years	2 (35%)	4 (50%)	-	1 (12.5%)	1 (12.5%)		
<b>Total</b>	<b>25 (27.7%)</b>	<b>53 (58.8%)</b>	<b>1(1.1%)</b>	<b>10 (11.1%)</b>	<b>1 (1.1%)</b>		
<b>Gender</b>							
Male	12 (27.3%)	28 (63.6%)	1 (2.3%)	3 (6.8%)	0		
Female	13 (28.3%)	25 (54.3%)	0	7 (17.4%)	1 (2.2%)		
<b>Total</b>	<b>25 (27.7%)</b>	<b>53 (58.8%)</b>	<b>1 (1.1%)</b>	<b>10 (11.1%)</b>	<b>1 (1.1%)</b>		

**[Table/Fig-2]:** Age and gender categorization of brain MRI findings.

Group III included children with recognizable syndromes, such as tuberous sclerosis. Only one (1.1%) male child aged between 5-8 years had tuberous sclerosis. On brain magnetic resonance imaging, tuberous sclerosis is characterized by cortical hamartomas, enhancing sub-ependymal nodules and radial bands in deep white matter [Table/Fig-3a-3b].

Group IV includes patients with structural malformations of the brain. 10 out of 90 (11.1%) patients had structural brain malformations. Among them, 4 had corpus callosum agenesis and there was 1 patient each with subcortical nodular heterotopia, Chiari I malformation, Joubert syndrome, mega



**[Table/Fig-3a-b]:** Show T2 hyperintense cortical and subcortical hamartomas, enhancing subependymal nodules and disorganized white matter forming radial bands.

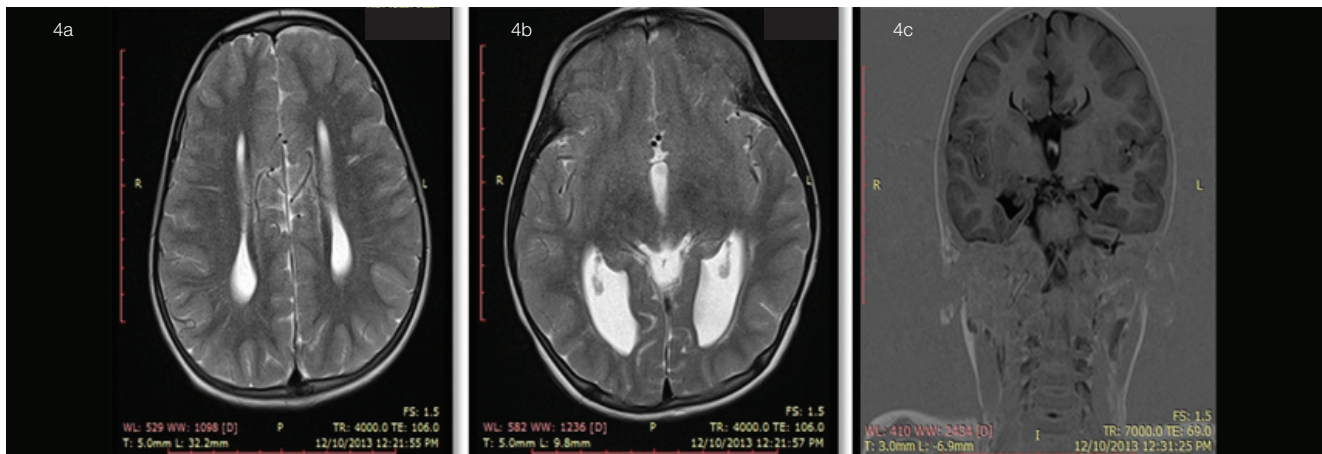
cisterna magna, pachygyria, unilateral obstruction of foramen of Monro [Table/Fig-4a-c, 5a-c].

Group V includes patients with suspected metabolic disease including lysosomal storage disorders that have specific findings on brain MRI. Out of 90 patients 1 had brain MRI findings suggestive of metachromatic leukodystrophy.

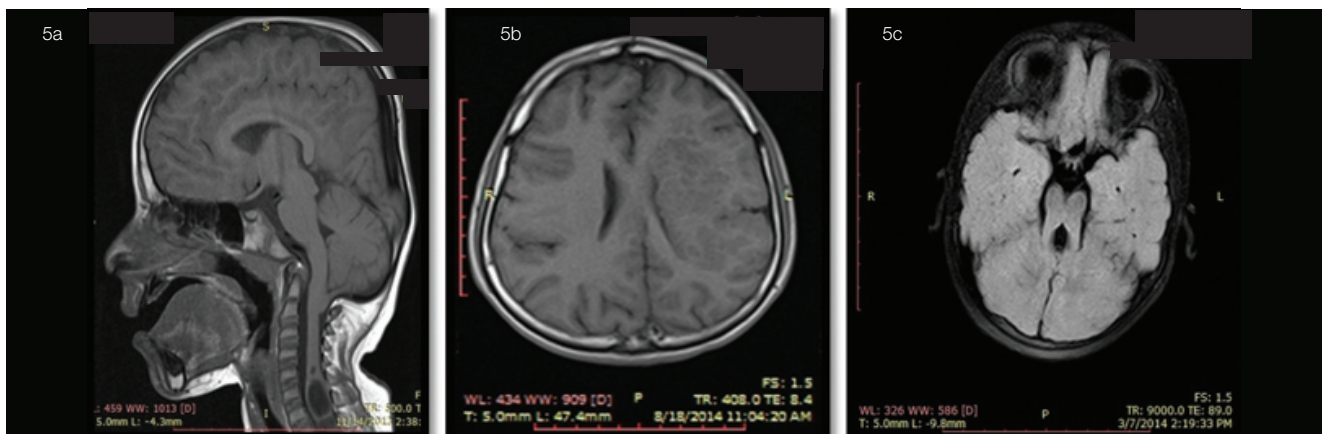
Two other areas that were evaluated in our study include presence of seizures and history of neonatal complications as shown in [Table/Fig-6&7] respectively. 28(75.6%) out of 37 patients with history of seizure disorder had abnormal MRI findings whereas 70% of patients with no history of seizure disorder had abnormal findings on MRI [Table/Fig-7]. The p value is 0.541.

19(70%) out of 27 patients with history of complications at birth or neonatal period had abnormal MRI whereas 73% of





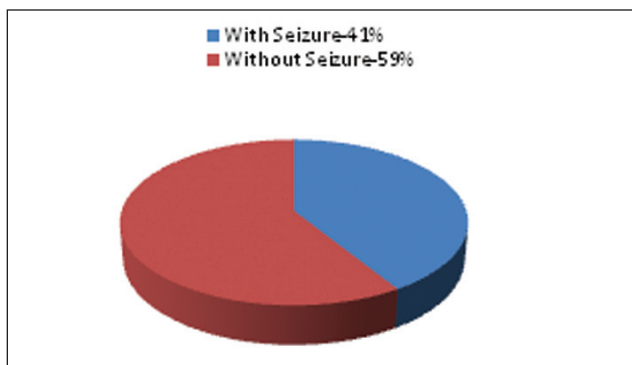
[Table/Fig-4a-c]: Show the classical findings of corpus agenesis which includes parallel lateral ventricles, high riding 3rd ventricle and colpocephaly respectively.



[Table/Fig-5a-c]: 5a: Chiari I malformation with tonsillar herniation, 5b: Subcortical nodular heterotopias and 5c; Joubert syndrome.

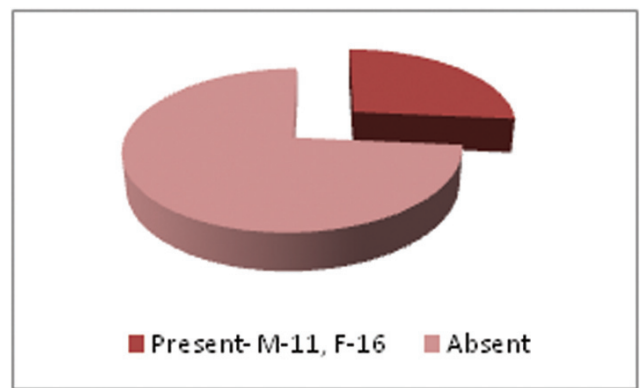
	Normal		Abnormal MRI		Total
	Male	Female	Male	Female	
With seizure disorder	5	4	17	11	37
Without seizure disorder	7	9	15	22	53
Total	12	13	32	33	90

[Table/Fig-6]: Presence of seizure disorder.



[Table/Fig-7]: Presence of seizure disorder.

patients without such history had abnormal findings on MRI [Table/Fig-8]. The p value is 0.797.



[Table/Fig-8]: History of neonatal complications in study group.

## DISCUSSION

Global developmental delay occurs in ~5-10% of children. The causes of developmental delay are innumerable. The causes

of developmental can be classified as- genetic/syndromic (Down's syndrome, Fragile X syndrome, tuberous sclerosis, neurofibromatosis, etc.), metabolic (phenylketonuria, urea cycle disorders), endocrine (congenital hypothyroidism), traumatic, environmental causes (lack of stimulation), perinatal or congenital neuroinfections (cytomegalovirus, toxoplasmosis), cerebral dysgenesis, toxins (fetal alcohol syndrome) and perinatal asphyxia [6, 7].

The determination of cause is important for a number of reasons including prognostication, surveillance and prevention of secondary disability, potential treatment, and appropriate genetic counseling [7].

Apart from clinical history, physical examination, chromosomal analysis and biochemical testing, neuroimaging plays an important role in the etiologic profiling of these developmentally delayed children. Evidence based guidelines by McDonald et al., consider neuroimaging as a second line of investigation in the evaluation of global developmental delay in pre- school children. The yield of neuroimaging is highly variable ranging from 9 to 80%. However, the yield of a neuroimaging study increases when it is done in presence of specific problems such as microcephaly, seizure disorder or focal neurologic deficit [8].

In a study on pre-school children by Tikaria S et al., conducted in a tertiary care hospital in India to investigate the diagnostic possibilities, they found that a stepwise approach yielded the diagnosis in 73% of the cases. Further, the severity of the developmental delay did not affect the aetiological yield. They found that chromosomal disorders, hypoxic ischemic encephalopathy, cerebral dysgenesis and multiple malformation syndromes were the most common causes. They also emphasized that a stepwise approach is more useful especially in developing countries where advanced cytogenetic analysis and molecular analysis is not easily available [9]. Similar study was conducted by Fayyazi A et al., with an etiological yield of 75% [10].

Out of the 90 patients who presented to us, a staggering 65(72%) had abnormal findings on brain MRI. Various other studies have shown differences in the percentage of patients who had abnormal findings on brain MRI [Table/Fig-9]. The wide variation is likely due to patient selection [9].

Studies	Abnormal MRI Findings (in percentage)
Present study	72%
Momen et al., [3]	58.6%
Ali AS et al., [6]	68%
Koul et al., [11]	71.8%
Widjaja et al., [12]	84%
Bouhadiba et al., [13]	48.6%

**[Table/Fig-9]:** Comparison between present study and other studies showing yield of abnormal MRI findings.

Most of the patients with abnormal brain MR had findings that could be classified as group II (53-58.8% of all children) - which included non-specific findings and neurovascular sequelae to ischemic insult. Also, a wide variety of congenital malformations/ cerebral dysgenetic disorders and recognizable neurodegenerative diseases of the brain can also lead to delayed development. These are demonstrable on brain MRI.

The frequency of normal brain MRI was higher in the older age groups, whereas the frequency of abnormal brain MRI was found to be the highest in the age group 3 months- 4 years(44-48.8%). This is probably because children with developmental delay are identified more frequently when they are younger and probably evaluated earlier. Also some findings such as delayed myelination are recognized in younger children and normalize later in life.

No gender significant difference was observed between normal and abnormal brain MRI.

No significant association was found with history of seizure disorder/complications in the neonatal period with abnormal brain MRI. The p value was 0.541 and 0.797 respectively.

The main drawback of the present study was the smaller sample size and the shorter time period. We also did not correlate our findings with abnormal electroencephalographic studies.

## CONCLUSION

Neuroimaging is a second line of investigation in children with delayed developmental milestones with a high diagnostic yield when evaluating specific clinical features. This is corroborated in our study, in which there was a high proportion of abnormal brain MRI. Magnetic resonance imaging due to its inherent soft tissue resolution also gives a specific diagnosis in many cases. Advanced magnetic resonance imaging techniques such as diffusion tractography and functional imaging may also be capable of demonstrating which domains of development are preferentially affected.

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