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A study of magnetic resonance imaging and spectroscopy of brain in children with developmental delay

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Abstract
Background: Developmental delay denotes significant delay in one or more developmental domains. It has an estimated prevalence of 1-3% worldwide. Brain magnetic resonance imaging appears to be the most promising neuroimaging technique in the evaluation of patients with developmental delay.
Aims and Objectives: Our study aims to identify the spectrum of abnormalities in brain magnetic resonance imaging in children with developmental delay and categorize the morphologic abnormalities. Secondly, the role of Proton Magnetic Resonance Spectroscopy (MRS) to ascertain the magnitude and severity of various neuro-metabolite ratios in children with normal brain imaging will also be studied.
Materials and Methods: Our study involves the evaluation of 100 children presenting with developmental delay to the Department of Radio diagnosis, SP Medical College Hospital between July 2020 and July 2021. The children were evaluated with a standard MRI protocol. Clinical and demographic parameters were noted. The various involved brain structures were studied systematically and the morphologic abnormalities were categorized.
Results: The prevalence of abnormal MRI findings was 78% among the evaluated children. Our study showed predominant involvement of the white matter (50%), ventricles (37%) and corpus callosum (24%). The relative proportion of various morphologic abnormalities was Neurovascular diseases (50%), Congenital and developmental (12%), Non-specific findings (11%), Neoplastic and cystic lesions (3%) and combined etiology (2%). 10 children with a normal MRI were subjected to MR Spectroscopy which revealed no significant difference in the neuro metabolite ratios among the patients.
Conclusion: MR imaging has good sensitivity in diagnosing various disorders of developmental delay. Careful evaluation of the MRI helps identifying the probable etiology in most if not all cases. Proton MR Spectroscopy is an emerging technique in evaluating children with developmental delay and should be incorporated in the standard MRI protocol in cases where it is feasible. Hence, appropriate diagnosis on MRI helps in guiding the physician to plan further patient management.

Keywords: Developmental delay, children, magnetic resonance imaging, neurovascular diseases, magnetic resonance spectroscopy

Introduction
Development is a continuous process which begins from conception and continues throughout an individual's life. Developmental delay denotes significant delay in one or more developmental domains. It poses a social stigmata upon the child and his or her family. Developmental delay has an estimated prevalence of 1-3% worldwide [1]. Developmental delay needs careful evaluation to ascertain the etiology which is evident in around 50-70% of the cases. The evaluation of developmental delay is complex and involves various modalities including cytogenetic testing, biochemical and hormonal assays, enzyme assays, electroencephalography (EEG) and neuroimaging. Magnetic resonance imaging has evolved over the years as one of the most sensitive modality in imaging a child with developmental delay. Around 60% of the children with developmental delay have an abnormal MRI [1]. Further, MRI provides detailed anatomical evaluation of the brain and also provides information on the extent of myelination and its associated micro structural changes. Appropriate categorization of patients based on neuroimaging guides the clinicians in further evaluation of the child which helps them at arriving at a diagnosis more promptly and with ease. Identifying the involved brain structures and the associated morphologic abnormalities

also help in appropriately categorizing the patients which has a significant impact on patient management.

Study Design
This is a prospective, descriptive study involving a sample size of 100 children presenting with developmental delay. The children are referred to the Department of Radio diagnosis, S.P Medical College Hospital for neuroimaging as a part of their evaluation.

Study Period
Between July 2020 and July 2021.

Study Duration
One year.

Inclusion And Exclusion Criteria
Inclusion Criteria
Children with developmental delay aged between 6 months and 10 years, referred to our department for Brain Magnetic Resonance Imaging to evaluate the cause of developmental delay.

Exclusion Criteria
1. Children younger than 6 months and older than 10 years of age.
2. Children with progressive neurodevelopmental disorders.
3. Children with congenital CNS infections, meningitis and encephalitis.
4. Children with recognized syndromes including chromosomal disorders.

Study Protocol
Preliminary Screening
The children presenting with developmental delay will be evaluated clinically by a paediatrician with expertise in developmental paediatrics and will be referred for brain Magnetic Resonance Imaging to the Department of Radiodiagnosis. The commonly used scales to assess developmental delay include DENVER II (revision of the Denver Developmental Screening Test, DDST)
and Trivandrum Developmental Screening Chart.
The clinical and demographic details of the patient were noted down. Informed consent for neuroimaging will be obtained from the parents or legal guardian of the child.

Sedation
Infants and younger children will be sedated using Syrup Triclofos (Syp pedicloryl) 50 mg/kg just before imaging the child. In children inadequately sedated with the above drug, IV midazolam 0.1
mg/kg/dose under strict clinical supervision and monitoring will be used for sedation.
Older children who were well cooperative for the imaging procedure were imaged unsedated.
Necessary emergency equipment and drugs were made available in the MRI room.

MRI Protocol
All patients will be evaluated using a 1.5 Tesla MRI system **(Magnetom Symphony, Siemens Healthcare).** The patients were placed in the supine position and the head was placed securely in the receiver coil. The scan was performed under the supervision of a qualified Radiologist in the workstation.
The following sequences will be performed in all patients.
T2 axial TR/TE 5400ms/111ms, slice thickness 5 mm, slices 20, FOV 230 mm, DF 30% T2 coronal TR/TE 3500ms/116ms, slice thickness 3 mm, slices 18, FOV 230 mm, DF 20% T1 mpr sagittal TR/TE 1450ms/3.93ms, slice thickness 3 mm, FOV 230 mm, DF 50% FLAIR axial TR/TE 8110ms/114ms, slice thickness 5 mm, slices 19, FOV 230 mm, DF 30% T1 tir coronal TR/TE 6200ms/70ms, slice thickness 3 mm, slices 18, FOV 230 mm, DF 20% DWI and ADC map TR/TE 3600ms/98ms Gradient echo sequence TR/TE 540ms/19ms, slice thickness 5 mm, FOV 230 mm, DF 30%, flip angle 20 degrees T1 axial TR/TE 310ms/7.7ms, slice thickness 5 mm, slices 19, FOV 230 mm, DF 30% The children with a normal MRI of the brain were subjected to Proton MR spectroscopy. Multivoxel MR spectroscopy with the voxels placed in the subcortical white matter of the frontal and parieto-occipital lobes bilaterally (TR/TE 1400ms/135ms) was performed. The following neurometabolite ratios were calculated.
1. N-acetylaspartate (NAA)/creatine (Cr)
2. Choline (Cho)/Cr

Categorization of the patients
Step 1:
The children were categorized based on their gestational age into preterm, term and late preterm [2] based on the following criteria:

Definition
Preterm Born at 37 weeks gestation or less
Late preterm Born between 34-0/7 and 36-6/7 weeks of gestation

Term Born between beginning of week 38 and end of week 41 of gestation
STEP 2:
The following brain structures were systematically evaluated based on a study by Widjaja *et al.* [3]
1. Ventricles
2. Corpus callosum
3. Gray matter
4. White matter
5. Limbic system
6. Basal ganglia
7. Brain stem
8. Cerebellum
9. Cranial vault

Step 3
The proportion of patients with a normal MRI were noted. The various abnormal MRI findings and their corresponding diagnosis were categorized based on a study by Williams *et al.* [4]. The various morphologic abnormalities were categorized into one or more of the following categories
1. Normal
2. Nonspecific findings like cavum septum pellucidum, cavum vergae, ventriculomegaly, prominent Virchow-Robin spaces (VRS), prominent cisterna magna etc.
3. Neurovascular including periventricular leukomalacia, hypoxic -ischemic injury, encephalomalacia, atrophy, gliosis etc.,

4. Congenital and developmental including vascular malformations
5. Neoplastic and cystic lesions
6. Combined or multifactorial

The results were analyzed systematically and relevant observations were made. All data were analyzed with a statistical software package – Statistical Package for the Social Sciences (SPSS), version 16.0 for Windows.

Results

Out of 100 children presenting with developmental delay in our study, 61% had associated seizures. The proportion of children with associated seizures in a study by Widjaja *et al.* [3] was 26% wherein 90 children with developmental delay were evaluated with a brain MRI. The percentage of children with seziures in a study by Momen *et al.* [24] and Koul *et al.* [29] was 53% and 43% respectively.

The proportion of children with an abnormal MRI presenting with developmental delay only was 12% versus 88% of children with developmental delay "plus" associated with an abnormal MRI. This was compared to other relevant studies. In a study by Ali *et al.* [20], 89% of children with developmental delay "plus" had an abnormal MRI. Similarly in a study by Widjaja *et al.*, 88% of children with developmental delay "plus" were associated with abnormal MRI.

This further emphasizes the association of abnormal MRI in children with developmental delay "plus" disorders.

The proportion of children with normal and abnormal MRI findings in our study was 22% and 78% respectively. This was compared with other similar studies in literature. In the study by Ali *et al.* [20] the proportion of children with an abnormal MRI was 68%. Other studies including Momen *et al.* [24], Widjaja *et al.* [3] and Koul *et al.* [29] had the following percentage of children with an abnormal MRI; 59%, 84% and 81% respectively.

The various involved brain structures were compared with other studies. Our study showed abnormalities of the white matter in 50% of children. The corpus callosum, ventricles, gray matter, basal ganglia, limbic system and brain stem were involved in 24%, 37%, 13%, 5%, 3% and 2% of children respectively.

In a study by Widjaja *et al.* [3], the white matter was abnormal in 26% of the children. The corpus callosum, ventricles, gray matter, basal ganglia, limbic system and brain stem were involved in 44%, 48%, 4%, 2%, 6% and 4% of children respectively. Our study showed an increased proportion of children with involvement of the white matter compared to the above mentioned study.

The categories based on the morphologic abnormalities on MRI were compared with the relevant studies. In a study by Ali *et al.* [20], the most common abnormality encountered was Neurovascular disesaes like hypoxic ischemic encephalopathy (31%). Our study reported a slightly higher percentage of children in this category (50%). The rest of the categories were comparable to the above- mentioned study.

In a study by Momen *et al.* [24], the most common categorical abnormality was neurovascular diseases which accounted for nearly 38% of the total cases. This was comparable to our study. The rest of the compared variables showed similar proportions as obtained in our study.

Sample Images

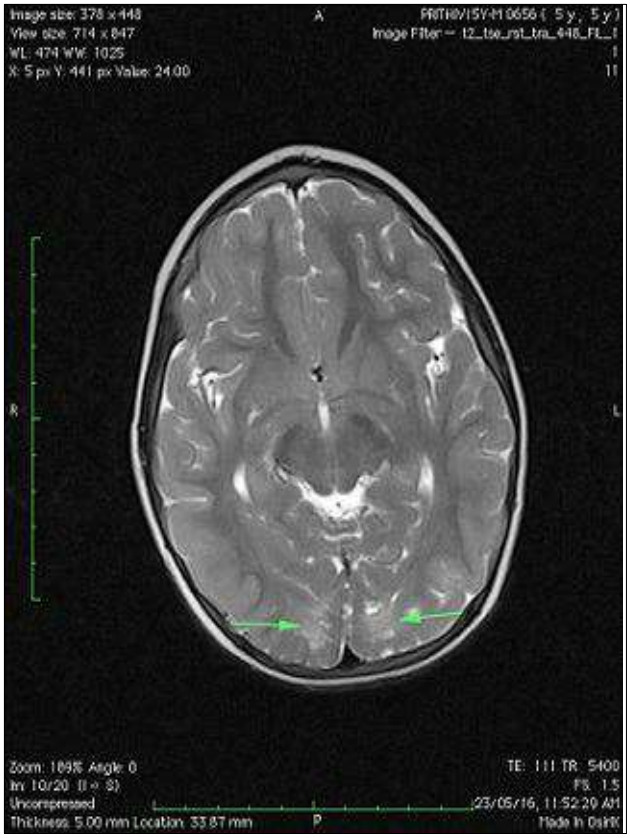

Fig 1: Axial T2 weighted MR images showing paucity of bilateral parietoccipital periventricular white matter with gyral thinning (periventricular leukomalacia) in a case of hypoxic ischemic injury**.**

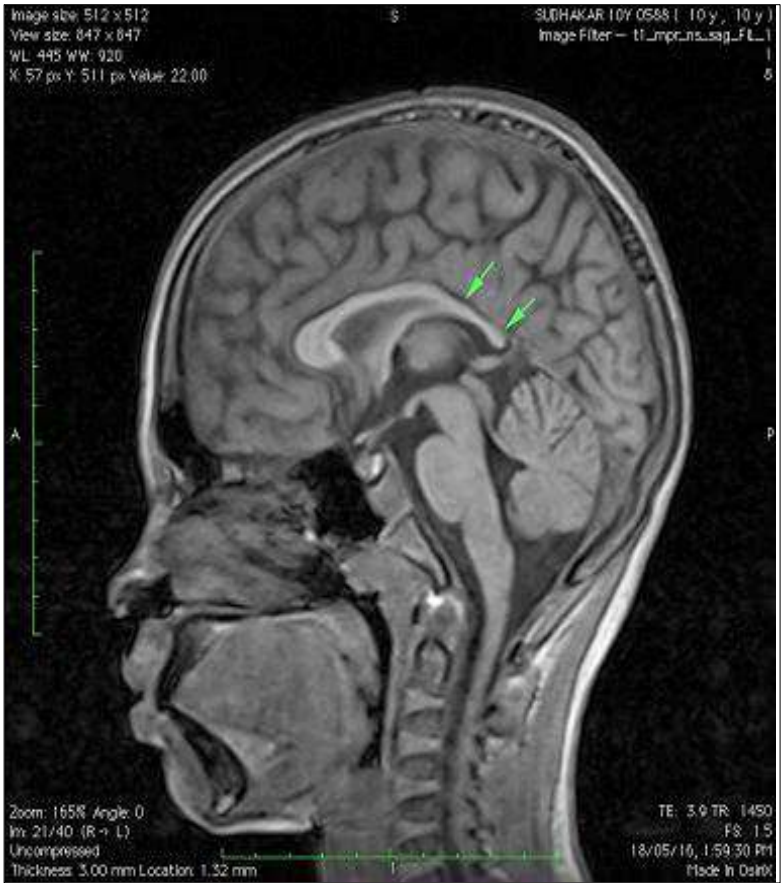

Fig 2: Sagittal T1 weighted MR image shows thinning of posterior body and splenium of corpus callosum (arrows) as a sequalae of hypoxic ischemic injury. Child also had features of periventricular leukomalacia.

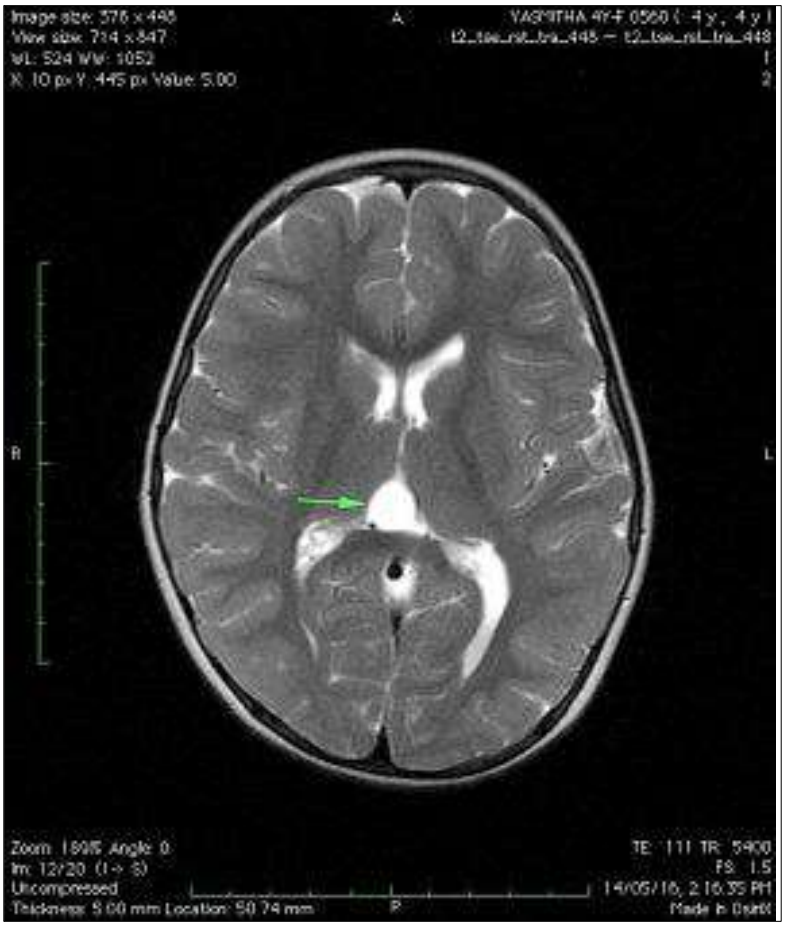

Fig 3: Axial T2 weighted MR image shows a CSF intensity lesion seen in the floor of the III ventricle (arrows). The lesion showed no restricted diffusion. Features consistent with "Arachnoid cyst".

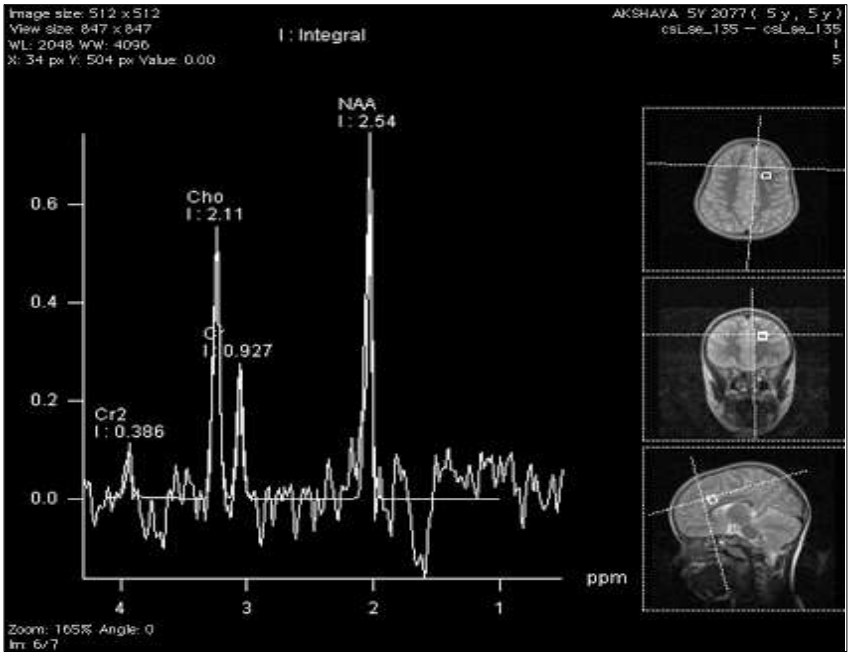

Fig 4: Multivoxel MR Spectroscopy with voxels in bilateral frontal and parieto-occipital white matter (frontal region shown in figures) shows normal neuro metabolite ratios.

Conclusion

The current study was undertaken to evaluate the spectrum of abnormalities on MRI in children with developmental delay. The role of MR Spectroscopy in children with normal MRI was also studied.

Out of the 100 children evaluated in our study around 35 children were in the age group 3-5 years. The children were categorized based on gestational age with 39% of the children being preterm. Further, these children had an associated abnormal MRI in most cases. It was also noted that 61% of the children had associated seizures. It was inferred that the children with associated seizures had a larger proportion of abnormal MRI (56 out of the 61 children with seizures).

Among the rest of the children, 24% presented with one or more neurological deficits. It was also noted that there existed a significant correlation between the occurrence of an abnormal MRI and the presence of additional clinical features along with developmental delay (developmental delay "plus").

Among the 80 children presenting with developmental delay "plus", 69 had an abnormal MRI.

The various involved brain structures were also studied systematically. The white matter (50%), ventricles (37%) and corpus callosum (24%) were involved in most cases. Around 78% of the children had an abnormal MRI in our study.

The various MRI abnormalities were categorized. The category of Neurovascular diseases showed the highest proportion of children in our study (50%) with an increased incidence in the age group 3-5 years. Most of the cases were a sequel to hypoxic ischemic injury.

MR Spectroscopy in children with normal MRI revealed no significant difference in the neuro metabolite ratios among the children evaluated. Since MR Spectroscopy adds to the time period of the conventional MR protocol and is by far dependant on the patient being motionless for the entire duration of the study, this limits its use in younger children and infants due to motion artifacts and risk of prolonged sedation.

MRI has good sensitivity in diagnosing various disorders associated with developmental delay. Careful evaluation of the MRI helps identifying the probable etiology in most if not all cases. Additional clinical variables also add to the diagnostic accuracy of MRI.

MR Spectroscopy is an emerging technique in evaluating children with developmental delay. Proton MR Spectroscopy should be included in the standard imaging protocol while evaluating older children with developmental delay.

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