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Magnetic Resonance Imaging Findings in Delayed Milestones Associated with Additional Clinical Features in Pediatric Patients

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ABSTRACT

Background: Rare, but the delay in the process of achieving milestones has a devastating effect, with a vast number of etiologies associated with it. This study aimed to identify the brain MRI findings in patients showing additional clinical features with developmental delay and the development of a correlation between clinical findings and MRI findings.

Methods: This cross-sectional study included 22 patients with developmental delay at Liaquat University of Medical and Health Sciences, Hyderabad, from August 2022 to August 2024, using non-probability consecutive sampling. Clinical histories, examinations, and brain MRIs using a 1.5 Tesla scanner were conducted. Data were analyzed in SPSS v26. Descriptive statistics, Chi-square or Fisher's exact test were applied, and a p-value <0.05 was considered statistically significant for associations between clinical features and MRI findings.

Results: The study included 22 patients, evenly distributed between genders (11 males and 11 females). The majority, 10 (45.5%), were aged 2–5 years. The most common clinical manifestations were epilepsy (14, 63.6%, p = 0.01), gait disturbance (13, 59.1%, p = 0.03), gross developmental delay (9, 40.9%, p = 0.04), visual and auditory disturbances (7, 31.8%, p = 0.02), motor disturbances (7, 31.8%, p = 0.05), neurological deficits (7, 31.8%, p = 0.04), and speech deformities (6, 27.3%, p = 0.03). Some cases also had associated radiological abnormalities. A p-value < 0.05 was considered statistically significant.

Conclusion: Patients of delayed milestones that are exposing additional clinical features are likely to have some kind of abnormalities on MRI scan despite of their etiological variables.

Keywords: Clinical Features, Developmental Delay, Cognitive Function, Developmental Milestones .

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INTRODUCTION

Human development is a continuous process from conception to maturity, influenced by genetic, environmental, nutritional, and health factors. These influences can delay the achievement of key developmental milestones, which are assessed across motor skills (gross and fine), social interactions, and language abilities [1,2,3,4]. Developmental delay is estimated to affect 5–10% of children, with 1–3% of cases occurring in those under the age of five. In the United States and Canada, this translates to 40,000–120,000 affected children out of approximately four million annual births [5]. Developmental delays may become apparent during infancy, early childhood, or the early school years. Rather than being diagnoses, these delays are symptoms of various underlying causes, such as genetic disorders, metabolic or vascular conditions, malformation syndromes, trauma, infections, toxins, or environmental factors [5,6,7,8,9]. At least 89% of patients with developmental delays present additional features, including epilepsy, neurological deficits, abnormal head size, facial dysmorphism, cleft lip or palate, sensory impairments, motor disturbances, and social or cognitive challenges[10].

Brain MRI is an essential component for individuals having developmental delays, it can help to show abnormalities in upto 60–84% of cases, primarily in the ventricles and corpus callosum. This underscores the significance of neuroimaging in detecting structural anomalies [1, 4, 8, 10]. Delay in reaching developmental milestones could significantly affect overall development and future potential of the child and may stem from variety of causes.

The objective of this study was to determine the patterns of brain MRI abnormalities among patients with developmental delay with other clinical signs and symptoms and to examine the association of clinical features with MRI findings. Detailed characterisation of these parameters from this cohort provides important information about the nature and prevalence of brain anomalies and will assist in early diagnosis, follow up, prognostication, and parent counselling with regards to recurrence in future pregnancies. With the growing importance of neuroimaging in pediatric neurology, we undertook this prospective study in 81 consecutive patients attending a Pediatric OPD of a tertiary care hospital emphasizing on radiological assessment on MRI and review of literature.

METHODS

This was a cross sectional descriptive study including 22 patients with clinical findings of developmental delay presenting at Liaquat University of Medical and Health Sciences, Hyderabad. The current sample size was based on the number of patients available for study within a limited time

and with limited resources. The sampling technique was non-probability consecutive. It was a one-year study (Aug, 23, 2022 to Aug 2024) after approval from ERC **(Ref: LUMHS/REC/-601).**

Patients' ages ranged between 3 months and 12 years, new patients with a developmental delay were referred for a brain MRI. Inclusion criteria included offer 3months to 12 years old, presenting for the first time with a developmental delay and referred for brain MRI. Exclusions were made for known genetic disorders (e.g., Down syndrome, Turner syndrome), metabolic diseases (e.g., rickets, scurvy), protein-energy malnutrition, and abnormal infections (e.g., lobar pneumonia, tonsillitis), as well as diseases of developmental delay without further neurological abnormalities. Detailed clinical histories and physical examinations were carried out. Brain MRI data were acquired with a GE 1.5 Tesla magnetic resonance imaging scanner. T1W, T2W, FLAIR, DWI, and ADC images were obtained. Anatomical structures such as the ventricles and corpus callosum were examined and MR findings were correlated with clinical characteristics.

Data was collected with the help of a formatted questionnaire. Data were interpreted by changing percentage into proportions and analyzed in SPSS version 23. The mean and standard deviation were calculated for quantitative variables, and the frequency and percentage were calculated for categorical variables. Associations were determined by chi square or Fisher's exact test as appropriate. $P< 0.05$ was considered as a statistically significant value.

RESULTS

Table 1: Demographic Data of patients

Variables	Number	Percentage(%)
Age		
3 months to 1 year	7	31.8
2 upto5 years	10	45.5
6 up to 8 years	4	18.2
9 upto12 years	1	4.5
Gender		
Male	11	50

Female	11	50
Gestational Age		
Preterm	1	4.5
Term	21	95.5
Obstetric history		
Normal	19	86.4
Bad	3	13.6
Consanguinity		
Present	10	45.5
Absent	12	54.5

A total of 22 patients were enrolled in the study, comprising an equal distribution of 11 (50%) males and 11(50%) females. The majority of cases, 10 (45.5%), presented within the age range of 2 to 5 years. Most patients, 21(95.5%), were delivered at term gestational age, with 19(86.4%) having a normal obstetric history. Furthermore, 12(54.5%) of the participants reported no history of consanguinity. Detailed demographic data are provided for comprehensive reference **(Table 1)**.

Most patients with developmental delay exhibited multiple clinical manifestations. The most common were epilepsy 14(63.6%), gait disturbances 13(59.1%), and gross developmental delay 9(40.9%). Other frequently observed findings included visual and auditory disturbances 7(31.8%), motor impairments 7(31.8%), neurological deficits 7(31.8%), and speech deformities 6(27.3%). A detailed summary of clinical manifestations is provided. **(Figure 1).**

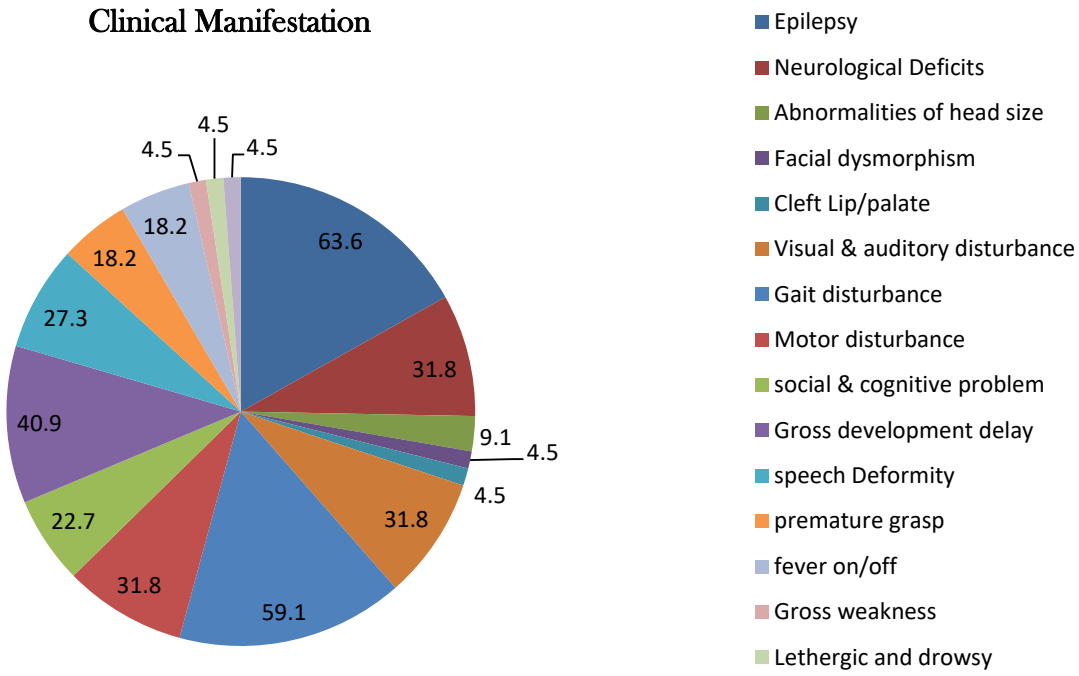

Figure 1: Clinical Manifestations

Table 2: Findings of Magnetic Resonance Scan

Structure	Number	Percentage
Abnormal of Ventricles	11	50%
Changes White matter	14	63.6%
changes Corpus Collasum	5	22.7%
Abnormality of Grey matter	7	31.8%
Abnormality of cerebellum	9	40.9%
Abnormality of the brain stem	3	13.6%
Abnormality of basal Ganglia	1	4.5%
Abnormal sulci	3	13.6%
Bat wing shape ventricle	4	18.2%

Molar tooth appearance	1	4.5%
Absence of cerebellar Vermis	3	13.6%
Deep & wide interpedunclar Cisterns	1	4.5%

Regarding the Magnetic Resonance Scan findings of patients that are present either singular or mix and mostly affected structures is white matter except Corpus Callosum 14 (63.6 %) **(Table 2).**

Table 3: Additional Radiological Findings

MRI findings	Number	Percentage
Atrophic brain	3	13.6%
Canavan Disease findings	1	4.5%
Sigmoid sinus thrombosis	1	4.5%
Chiari II malformation	1	4.5%
Congenital malformation	1	4.5%
Dandy walker malformation/variant	2	9.1%
Delayed myelination, demylination	2	9.1%
Dysplastic changes	2	9.1%
Enlarged subarachnoid space	3	13.6%
Hypoxic Ischemic Encephalopathy	1	4.5%
Joubert Syndrome	1	4.5%
Sinusitis	3	13.6%
Peri-ventricular leukomalacia	1	4.5%
Prominent Cisterna Megna	1	4.5%
Subdural hematoma	1	4.5%
Tonsiler herniation	1	4.5%

Additional radiological findings were found along with a predesigned questionnaire and listed **(Table 3).**

Table 4: Correlation of MRI Findings with Clinical Features

Structure	Epilepsy n / p-value	Neurological Deficit n / p-value	Gait Disturbance n / p-value	Developmental Delay n / p-value	Visual & Auditory Disturbance n / p-value	Motor Deficit n / p-value	Speech Deformity n / p-value
Abnormalities of the ventricles	8 / 0.375	6 / 0.022	8 / 0.193	-	3 / 0.647	6 / 0.022	4 / 0.338
White matter changes (except CC)	9 / 0.933	3 / 0.166	8 / 0.806	-	5 / 0.604	3 / 0.166	4 / 0.856
Corpus callosum changes	3 / 0.848	2 / 0.655	2 / 0.323	✓ / 0.431	1 / 0.519	1 / 0.519	1 / 0.678
Abnormalities of grey matter	4 / 0.665	3 / 0.448	2 / 0.047	-	1 / 0.228	1 / 0.228	1 / 0.350

Abnormalities of the cerebellum	6 / 0.806	4 / 0.290	5 / 0.779	-	2 / 0.421	4 / 0.290	2 / 0.658
Abnormalities of the brainstem	2 / 0.907	-	1 / 0.329	-	2 / 0.163	-	-
Abnormalities of the basal ganglia	1 / 0.439	-	1 / 0.394	-	1 / 0.134	-	-
Abnormal sulci	1 / 0.240	2 / 0.163	1 / 0.329	-	1 / 0.952	-	1 / 0.800
Dilation of ventricles (bat-wing shape)	2 / 0.531	1 / 0.746	2 / 0.683	-	1 / 0.746	2 / 0.388	1 / 0.910
Absence of cerebellar vermis	2 / 0.907	2 / 0.163	2 / 0.774	-	-	2 / 0.163	1 / 0.800
Deep & wide interpedu	-	1 / 0.134	1 / 0.394	-	-	1 / 0.134	-

ncular cisterns							
Molar tooth appearance	-	-	1 / 0.394	-	-	1 / 0.134	-

Pooled analysis of MRI findings with physical correlates suggests that ventricular and corpus callosum abnormalities are commonly identified in patients referred for developmental concerns and can be associated with clinical neurological and cognitive impairment. In particular, ventricle abnormalities were strongly associated with both neurologic dysfunction and motor deficit, indicating that morphologic alterations in ventricular size or shape might affect motor and neural function, presumably as the result of increased ICP or distortion of adjacent brain structures. Changes in the development of the corpus callosum were significantly related to gross developmental delay, consistent with the hypothesis that disruptions to inter-hemispheric transfer may result in loss of function on more global cognitive and motor measures. Gray matter atrophy were also borderline significantly associated with gait disturbances which implicate its possible contribution to motor coordination impairment. Though WM changes, cerebellar pathology, and other brain structural abnormalities including brainstem, basal ganglia, and sulci were common, a statistically significant correlation with specific clinical symptoms was not found in this cohort. In addition, there were no significant correlates identified for speech deformities or sensory (visual, auditory), which could be attributed to non-structural functional impairment or the power changes from small sample sizes. In summary, our results underscore the role of ventricle and corpus callosum abnormalities as central structural correlates of clinical dysfunction in children with developmental delay.

DISCUSSION

Twenty-two patients with developmental delay and additional clinical features were evaluated. Referrals from the pediatrics and neurosurgery wards, they underwent magnetic resonance imaging (MRI) in the radiology department. Consistent with the "developmental delay plus" concept from previous studies, all patients showed MRI abnormalities. This contrasts with earlier findings, which reported abnormalities in only 89% of such cases[10]. It may be due to a difference in inclusion criteria,

as we excluded the cases that were shown to have only a developmental delay without any additional clinical features. Besides, if developmental delay is associated with neurological signs and symptoms, MRI findings will proportionally increase the yield of etiological factors that contribute to the condition [5,6,7,8,9]. This study doesn't discuss the etiological factors related to the condition; despite, it is the presentation of etiological factors that leads to certain changes in neural tissue.

Every patient exhibited some type of abnormality on MRI scans, with the highest proportion (45.5%) presenting at 2 to 5 years of age. The majority (95.5%) were born at term, and no significant gender differences were noted. These results differ from earlier research, which identified a peak presentation between 3 and 12 months of age and a male predominance[1,10]. Some studies show that it can help in calculating prognostic information of children with neonatal seizures, and some highlight that early language delay predicts more predisposition to autistic behaviors in young children and developmental delay[11,12,13]. Some do point out the additional features, but without the frequency of its presentation[10]. As in this study, most of the patients present with Epilepsy (63.6%), Gait disturbance (59.1 %), Gross developmental delay (40.9%), visual and auditory disturbance (31.8%), motor disturbance (31.8%), multiple neurological deficits (31.8%), and speech deformity (27.3%).

This study highlights diverse changes observed in MRI scans, which predominantly involve the white matter (63.6%) while sparing the corpus callosum in most cases. Notable findings include ventricular abnormalities (50%), cerebellar anomalies (40.9%), gray matter irregularities (31.8%), and corpus callosum alterations (22.7%). The corpus callosum changes encompass agenesis, colpocephaly, thinning, and abnormalities of the splenium and genu. Interestingly, these results contrast with earlier studies that predominantly reported changes in the ventricles and corpus callosum[9.10].

Associated condition in this study, like brain atrophy, Canavan disease, Chairi II malformation, Congenital malformation, Dandy walker malformation, demyelination, Joubert Syndrome, Hypoxic Ischemic encephalopathy, Enlarged subarachnoid space with subdural hematoma or without and Sigmoid sinus thrombosis with Sinusitis, all are historically proven associations with developmental delay in literature without its etiological perspective[14,15,16,17,18,19,20,21].

As literature shows, the epilepsy findings in relation to its etiological factors and general findings are not conclusive and show 40% structural abnormalities relevant to its etiology[22]. It can be used as a prognostic variable in the development of delayed child[12]. Besides its association with Canavan disease, sigmoid sinus thrombosis, congenital malformation, Dandy-Walker malformation,

demyelination, dysplastic changes, and enlarged subarachnoid space have already been shown in the literature [23,24,25].

CONCLUSION

Patients of delayed milestones who are exhibiting additional clinical features are likely to have some kind of abnormalities on MRI scan despite their etiological variables. The temporal sequence of additional clinical features is required to be developed, but due to low resources in our country, some other and convenient method is required to rule out the more significant causes of these symptoms and their treatment promptly.

ETHICAL APPROVAL

The study received ethical approval from Liaquat University of Medical and Health Sciences Jamshoro, Hyderabad under reference number LUMHS/REC/-609

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CONFLICT OF INTEREST

None

AUTHORS CONTRIBUTIONS

R.M. was responsible for the study design and methodology, as well as drafting the manuscript. **A.K.** contributed by collecting data and performing the statistical analysis. **A.R.** handled referencing, performed data calculations, contributed to manuscript writing, and was involved in data analysis and interpretation of results. **V.D.** assisted in data analysis and conducted the literature review. **M.K.L.** contributed to manuscript writing and participated in data analysis.

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