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Added Value of MR Spectroscopy and Diffusion Weighted Imaging in Pediatric Leukodystrophy

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Abstract:

Background: Leukodystrophies in paediatric populations pose significant diagnostic challenges due to their heterogeneous presentation and diverse underlying aetiologies. Magnetic resonance spectroscopy (MRS) and diffusion-weighted imaging (DWI) have emerged as promising tools for enhancing diagnostic accuracy in such cases. This study aimed to assess the added diagnostic value of MRS and DWI in paediatric leukodystrophies. **Methods:** A retrospective cohort of 40 pediatric patients displaying clinical symptoms suggestive of leukodystrophies underwent comprehensive evaluations, including clinical assessments and dedicated MRI studies incorporating MRS and DWI. Radiological data obtained from MRI scans were correlated with clinical diagnoses and laboratory findings to identify characteristic patterns associated with different types of leukodystrophies. **Results:** The mean age of the studied patients was 3.1 years (±0.89), with a distribution of 45% males and 55% females. Types of leukodystrophies included Canavan disease (20%), Leigh disease (40%), metachromatic leukodystrophy (25%), and adrenoleukodystrophy (15%). In patients with Canavan disease, the NAA/Cr ratio ranged from 2.3 to 3.2 (mean ± SD: 2.8 ± 0.34), while in Leigh disease, it ranged from 1.1 to 1.5 (mean ± SD: 1.3 ± 0.14). Similarly, Cho/Cr ratios varied across different types of leukodystrophies, with mean values ranging from 0.9 to 2.5. All patients with Canavan disease, Leigh disease, metachromatic leukodystrophy and adrenoleukodystrophy exhibited positive lactate doublet. DWI revealed diffusion restriction in 22.5% of patients. **Conclusions:** The integration of MRS and DWI into diagnostic protocols for pediatric leukodystrophies enhances our ability to characterize metabolic and structural abnormalities associated with different disease entities.

Keywords: Pediatric leukodystrophies; Magnetic resonance spectroscopy; Diffusion-weighted imaging; Diagnostic accuracy; Metabolic abnormalities.

Introduction

Leukodystrophies are hereditary illnesses characterized by delayed onset or regression of developmental milestones. They are caused by aberration in myelin production, either due to enzyme shortage or storage disease. Clinical manifestations, imaging results, and pathology vary for each type of leukodystrophy[(1)].

Leukodystrophies' symptoms can appear as early as 6 months after birth, with earlier onset leading to greater impairment. They cause more than 30% mortality by 8 years of age. It can develop at any age from preterm infants and neonates to late adulthood and have been reported across all ethnicities and regions of the world [(2)].

Magnetic resonance spectroscopy (MRS) is used to analyse the resonance frequencies of various metabolites being emphasized in the aberrant signal locations, including choline, creatine, and N-acetyl aspartate. During the normal process of myelination in newborns, which typically takes two years to complete, the white matter of the paediatric brain exhibits different peaks of metabolites on MRS at various times [(3)].

Diffusion weighted imaging (DWI) is a specialized magnetic resonance imaging (MRI) technique that measures the random motion of water molecules within tissues. It provides unique information about the microstructure and cellularity of tissues, making it particularly useful in diagnosing and characterizing various medical conditions, especially in the field of neuroimaging and oncology [(4)].

There is no definite cure for leukodystrophies, but a diagnosis can aid with family genetic testing and decreasing illness morbidity and mortality rates. Using MRI and DWI together is effective in diagnosing suspected leukodystrophies and can help distinguishing different types of leukodystrophies and pathological versus normal myelination [(5)].

The aim of this study was to verify the added value of MRS and DWI in the diagnosis of paediatric leukodystrophy.

Patients and Methods:

Study Population:

This retrospective cohort study involved the examination of 40 patients exhibiting clinical indications suggestive of leukodystrophies, such as delayed developmental milestones, behavioural issues, or cognitive disorders. These patients were recruited from the inpatients' and outpatients' clinic of the Radiodiagnosis Department of Benha University Hospital, between December 2021 to December 2023. Official permission was obtained from the Faculty of Medicine, Benha University, and the research protocol received approval from the ethical committee within the faculty of medicine {MD 32-10-2021} to ensure compliance with ethical standards and patient safety. Patients were informed about the potential risks associated with anaesthesia, and their families had a clear understanding of its role in the procedure to ensure informed consent.

Inclusion Criteria:

The study included paediatric patients aged between 6 months and 12 years who displayed clinical symptoms indicative of leukodystrophies, subsequently confirmed to exhibit a leukodystrophy pattern. Participation in the study required willingness from the patients.

Exclusion Criteria:

Patients with negative MRI findings for leukodystrophy or those who declined

participation in the study were excluded from the research.

Methodology:

All subjects underwent comprehensive assessments, including a full clinical evaluation, review of the patients' laboratory test results, review of prior radiological investigations, and a dedicated magnetic resonance imaging (MRI) study.

MRI Protocol:

The MRI scans were conducted using a machine with a minimum strength of 1.5 tesla and included conventional MRI sequences such as axial T2, T1, and FLAIR; coronal T2; and sagittal T1. Additionally, diffusion-weighted imaging (DWI) with B-values of 0 and 1000 and magnetic resonance spectroscopy (MRS) utilizing short and intermediate echo times (TE) of 35 and 144 milliseconds, respectively, with both single and multivoxels were performed.

The radiological data obtained were correlated with the patients' laboratory findings and clinical diagnoses to identify patterns and potential indicators of leukodystrophy.

Primary Outcome:

The primary objective was to assess the roles of MRS and DWI in diagnosing paediatric leukodystrophy to enhance diagnostic accuracy and treatment planning.

Secondary Outcome:

Early detection and accurate diagnosis of paediatric leukodystrophy aimed to facilitate proper management and reduce disability rates among affected children.

Statistical analysis:

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD). Qualitative variables were presented as frequency and percentage (%).

Results:

Table 1: Demographic data of the studied patients

		N=40
Age (years)	**Mean ± SD**	**3.1 ± 0.89**
	Range	**16 m – 4y**
Gender	**Male**	**18 (45%)**
	Female	**22 (55%)**

The age of the studied patients ranged from 16 months to 4 years with a mean value (± SD) of 3.1 (±0.89) years. Regarding gender, 18 (45%) patients were males, and 22 (55%) patients were females.

Table 2: Types of leukodystrophies of the studied patients

	N=40
Canavan disease	**8 (20%)**
Leigh disease	**16 (40%)**
Metachromatic leukodystrophy	**10 (25%)**
Adrenoleukodystrophy	**6 (15%)**

Regarding types of leukodystrophies, 8 (20%) patients had Canavan disease, 16 (40%) patients had Leigh disease, 10 (25%) patients had metachromatic leukodystrophy and 6 (15%) patients had adrenoleukodystrophy.

Table 3: Relation between Lactate doublet and different diseases of the studied patients

		Lactate doublet
Canavan disease (n=8)	**Positive**	**8 (20%)**
Leigh disease (n=16)	**Positive**	**16 (40%)**
Metachromatic leukodystrophy (n=10)	**Positive**	**10 (25%)**
Adrenoleukodystrophy (n=6)	**Positive**	**6 (15%)**

Among patients with Canavan disease (n=8), 100% tested positive for lactate doublet, as did all patients with Leigh disease (n=16), metachromatic leukodystrophy (n=10) and adrenoleukodystrophy (n=6).

Table 4: Diffusion restriction of the studied patients

		N=40
Diffusion restriction	**Positive**	**9 (22.5%)**
	Negative	**31 (77.5%)**

Regarding diffusion restriction, 9 (22.5%) patients showed restricted diffusion (positive), and 31 (77.5%) patients showed facilitated diffusion (Negative).

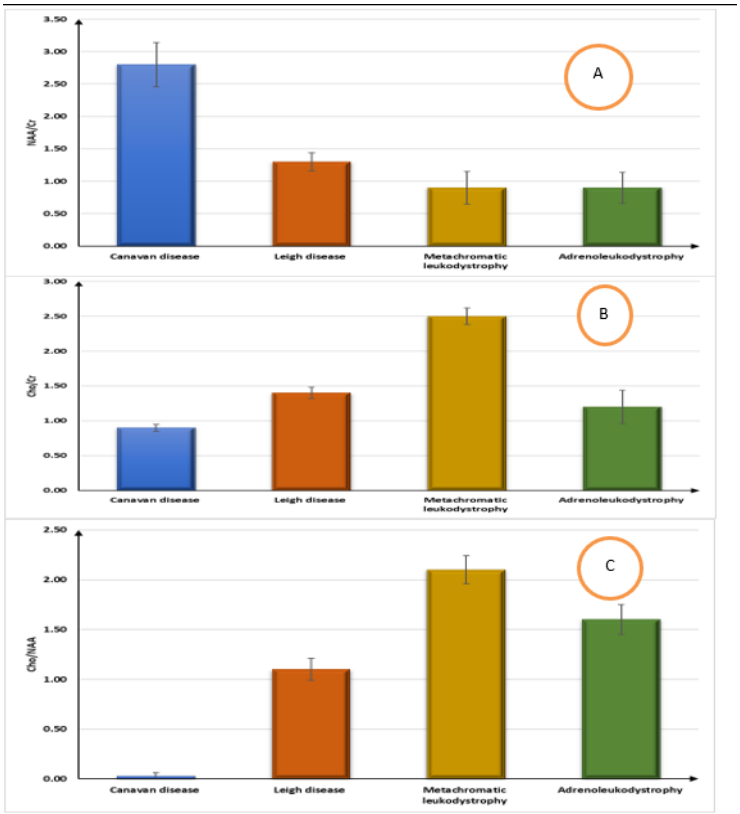


Figure 1: Relation between NAA/Cr, Cho/Cr and Cho/NAA different diseases of the studied patients of the studied patients

(A): NAA/Cr ranged from 2.3 to 3.2 with a mean value (± SD) of 2.8 (±0.34) in patients with Canavan disease, ranged from 1.1 to 1.5 with a mean value (± SD) of 1.3(±0.14) in patients with Leigh disease, ranged from 0.5 - 1.3 with a mean value (± SD) of 0.9 (± 0.25) in patients with metachromatic leukodystrophy and ranged from 0.6 to 1.2 with a mean value (± SD) of 0.9(±0.24) in patients with adrenoleukodystrophy.
(B): Cho/Cr ranged from 0.8 to 0.9 with a mean value (± SD) of 0.9 (± 0.05) in patients with Canavan disease, ranged from 1.3 to 1.5 with a mean value (± SD) of 1.4 (± 0.08) in patients with Leigh disease, ranged from 2.3 to 2.7 with a mean value (± SD) of 2.5 (± 0.12) in patients with metachromatic leukodystrophy and ranged from 0.9 to 1.5 with a mean value (± SD) of 1.2 (± 0.24) in patients with adrenoleukodystrophy.

(C): Cho/NAA ranged from 0.24 to 0.3 with a mean value (± SD) of 0.3 (± 0.03) in patients with Canavan disease, ranged from 0.9 to 1.2 with a mean value (± SD) of 1.1 (± 0.11) in patients with Leigh disease, ranged from 1.8 to 2.2 with a mean value (± SD) of 2.1 (± 0.14)in patients with metachromatic leukodystrophy and ranged from 1.4 to 1.8 with a mean value (± SD) of 1.6 (± 0.15) in patients with adrenoleukodystrophy.

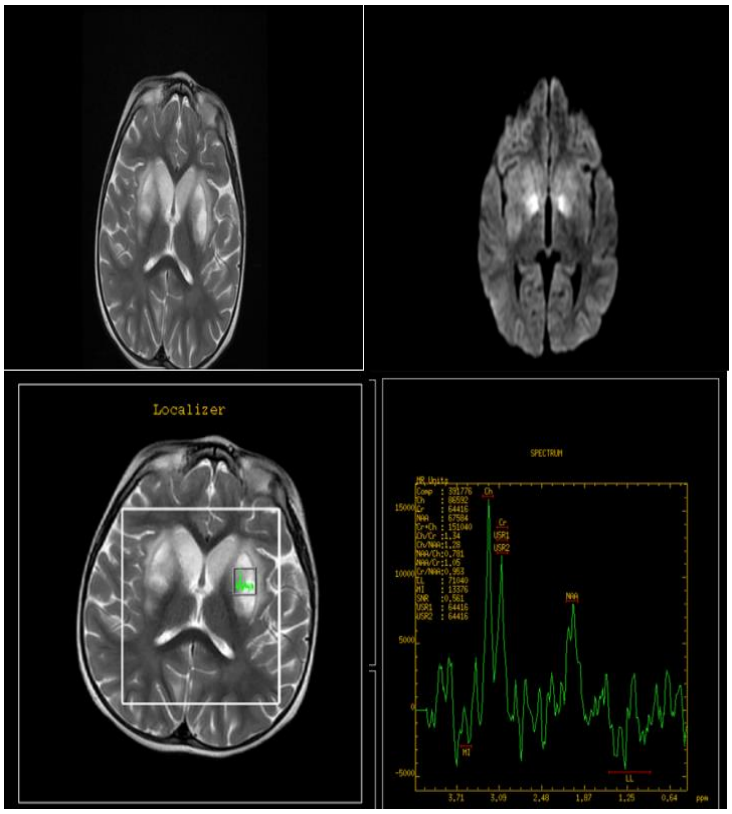


Figure 2: A case of Leigh disease with axial T2 image show widening of the cortical sulci and bilateral symmetrical hyperintense signal involving the basal ganglia, diffusion restriction seen, suggesting acute form, MR spectroscopy revealed elevated lactate doublet with mildly reduced NAA peak.

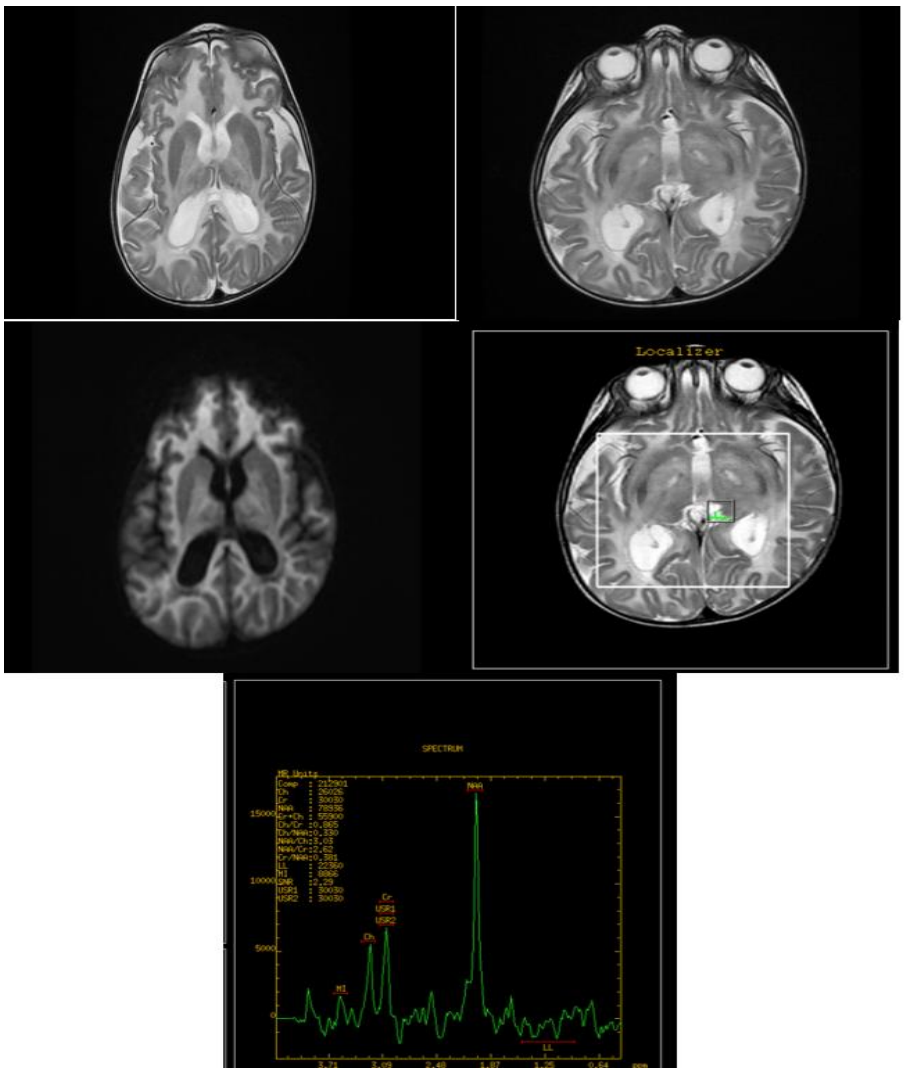


Figure 3: A case of canaven disease with axial T2 images show bilateral symmetrical entire white matter hyperintense signal with sparing of the putamen and caudate nucleus seen. No diffusion restriction however MR spectroscopy revealed evidently elevated NAA peak with relatively decreased choline and creatine peaks.

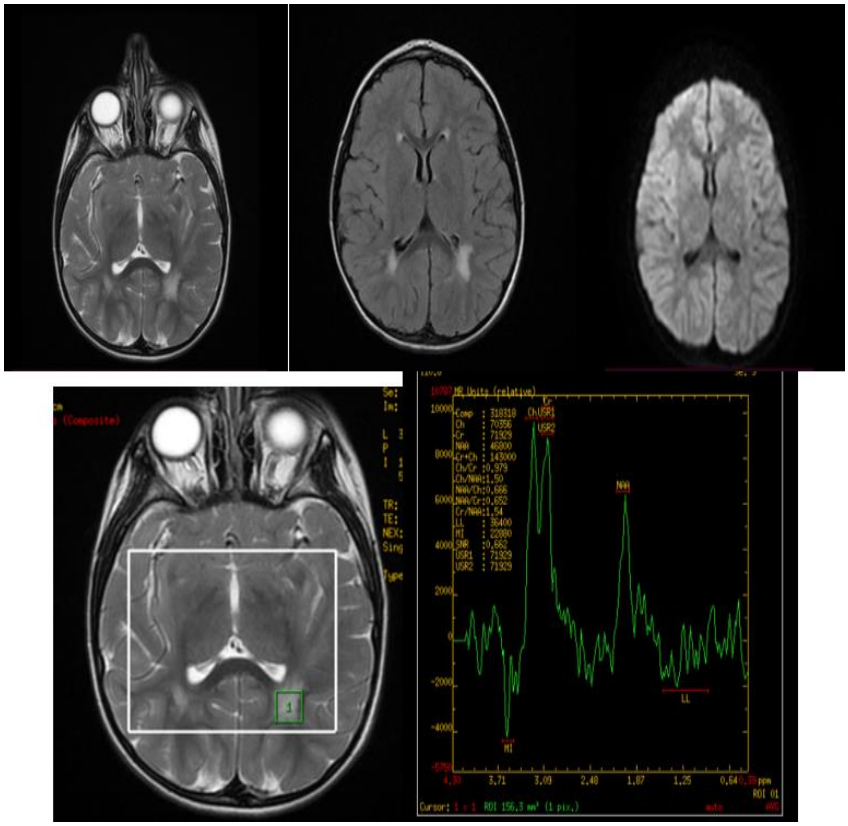
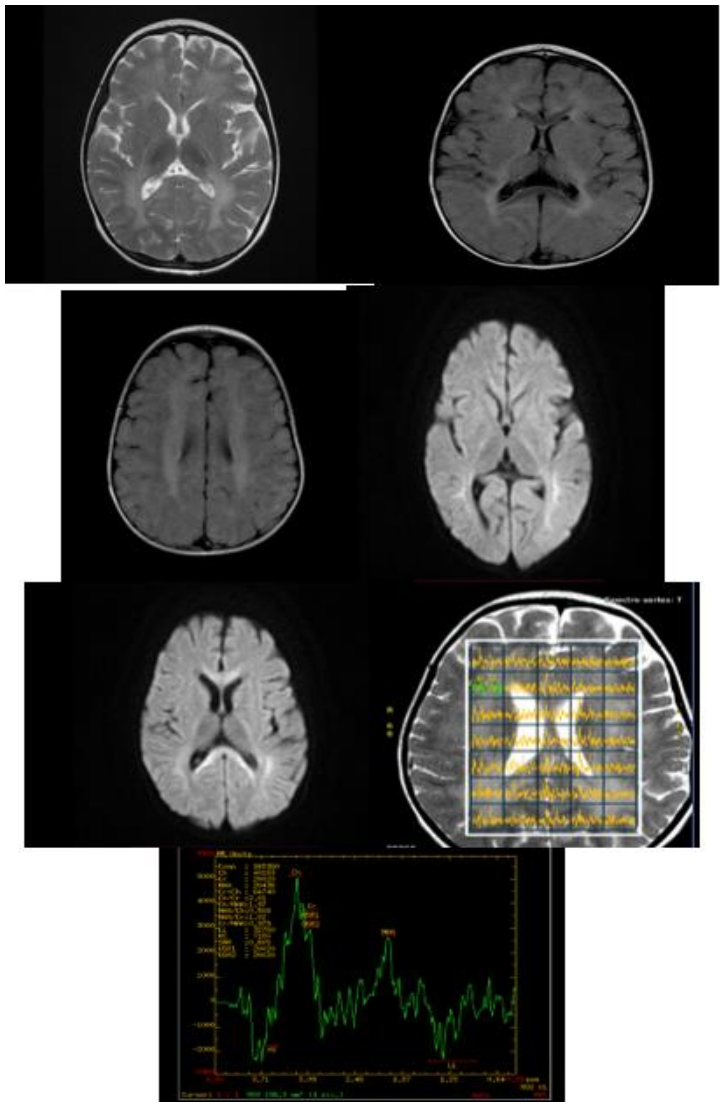


Figure 4: A case of ALD with axial T2 and FLAIR images show symmetric T2 hyperintense signal in the posterior supratentorial white matter bilaterally. No definite restriction within the DWIs. MR spectroscopy shows elevated lactate peak, NAA and creatine are abnormally low while the choline is elevated. This is a nonspecific marker of parenchymal injury.

Figure 5: A case of MLD with axial T2 and FLAIR images show diffusely increased signal in the periventricular and deep white matter extending from the lateral ventricles in the classic ‘‘tigroid’’ pattern with sparing of the subcortical U fibers. Restricted diffusion was seen in the DWIs. MR spectroscopy revealed reduced NAA with relatively high Cho peak.



Discussion:

In our study, the mean age of the patients was 3.1 (±0.89) years, with 45% being males and 55% females. A similar cross-sectional study on 110 patients was conducted, and reported a mean age of 5.24 (±1.89) years, with a slightly higher proportion of males (50.91%) compared to females (49.09%) [6].

Supporting our findings, it was observed that 18 patients diagnosed with metachromatic leukodystrophy, with ages ranging from 18 months to 8 years, and they reported a male predominance [7]. Conversely, it was found in a retrospective study on 10 patients with Leigh syndrome a female predominance, with ages ranging from 3 months to 10 years old [8] . A systematic review was conducted identifying 303 cases of metachromatic leukodystrophy, noting a higher prevalence among females, particularly in late infantile or juvenile subtypes[9].

However, a median age of 36 months ± 54 inter-quartile range was reported in the prospective study on 26 children with leukodystrophies, with a male predominance[10]. Overall, while leukodystrophies can affect both genders, there is generally no significant difference in prevalence between males and females.

The distribution of leukodystrophies in our study showed that 20% of patients had Canavan disease, 40% had Leigh disease, 25% had metachromatic leukodystrophy, and 15% had adrenoleukodystrophy. This partially concurred with the findings of the study which reported percentages of 17.27%, 22.73%, 10.91%, and 37.27% for the respective diseases[6]. Conversely, lower percentages were found, with 15%, 23%, 11.5%, and 31% for Canavan, Leigh, metachromatic leukodystrophy, and adrenoleukodystrophy, respectively[10] (figure 2).

Leukodystrophies represent a diverse group with varying clinical and genetic characteristics, contributing to differences in reported disease types across studies. Our findings suggest that metabolic ratios obtained through magnetic resonance spectroscopy (MRS) may aid in the differential diagnosis of leukodystrophies. Specifically, the NAA/Cr ratio varied across different types, with elevated levels observed in Canavan disease and decreased levels in Leigh disease, metachromatic leukodystrophy, and adrenoleukodystrophy [11]. (figure 3).

Consistent with our results, previous studies have highlighted the diagnostic value of NAA/Cr ratio in differentiating specific leukodystrophies. In 2019, researchers reported elevated NAA/Cr ratio in Canavan disease[12], while in 2015, similar results were found across different studies[10]. Additionally, decreased NAA/Cr ratio in Leigh disease was observed, supporting our findings and indicating the potential of MRS in characterizing metabolic alterations associated with leukodystrophies [8].

Elevated NAA/Cr ratio in Canavan disease was noted, reinforcing the consistency of our findings with previous research. These observations collectively underscore the utility of MRS in identifying metabolic changes specific to different leukodystrophies, aiding in their diagnosis and management[13].

Our findings indicate variations in Cho/Cr ratio across different leukodystrophies, with mean values (± SD) of 0.9 (± 0.05) in Canavan disease, 1.4 (± 0.08) in Leigh disease, 2.5 (± 0.12) in metachromatic

leukodystrophy, and 1.2 (± 0.24) in adrenoleukodystrophy. The Cho/Cr ratio serves as a diagnostic indicator in these neurological disorders, with elevated levels observed particularly in metachromatic leukodystrophy due to increased choline-containing compounds resulting from astrocytic proliferation, demyelination, and gliosis. These pathological processes reflect active inflammation and demyelination in affected brain regions, coupled with depleted energy stores leading to reduced Cr levels and consequently elevated Cho/Cr ratio [14,15].

In contrast, Cho/Cr ratio in Leigh disease can vary depending on disease stage and severity, influenced by factors such as neuronal damage and mitochondrial dysfunction. While our study observed elevated Cho/Cr ratio in Leigh disease, previous reports [10,8] also noted decreased Cho/Cr ratio in this condition, indicating variability in MRS findings. Additionally, a low Cho/Cr ratio in a case of metachromatic leukodystrophy was reported, further emphasizing the diverse metabolic profiles associated with different leukodystrophies[16].

In our study, Cho/NAA ratios varied across different types of leukodystrophies, with mean values (± SD) of 0.3 (± 0.03) in Canavan disease, 1.1 (± 0.11) in Leigh disease, 2.1 (± 0.14) in metachromatic leukodystrophy, and 1.6 (± 0.15) in adrenoleukodystrophy. The interpretation of Cho/NAA ratios depends on the clinical context and brain region examined, with healthy brain tissue typically exhibiting ratios between 1.0 and 2.0 [17]. In Canavan disease, the decreased Cho/NAA ratio is attributed to the marked elevation of NAA levels, while in other leukodystrophies, ratios may vary based on genetic mutations and affected brain regions [18]. (Figure 4)

Lactate doublet was observed in all patients across different types of leukodystrophies, including Canavan disease, Leigh disease, metachromatic leukodystrophy, and adrenoleukodystrophy, with the highest prominence noted in Leigh disease. This pattern in MRS indicates disruptions in cellular metabolism, potentially due to anaerobic metabolism or impaired mitochondrial function, leading to lactate accumulation. Presence of lactate doublet is not specific to leukodystrophy and can be seen in various neurological conditions with metabolic disturbances [19]. (Figure 5)

DW revealed varied diffusion properties among patients, with 22.5% showing restricted diffusion and 77.5% showing facilitated diffusion within areas of abnormal signal intensity. DWI provides valuable insights into underlying pathological processes, although its utility in leukodystrophy diagnosis may be limited when used alone. It was suggested that DWI, while valuable for follow-up and assessing response to treatment, is not sufficient for a definitive diagnosis, emphasizing the importance of combining MRI, MRS, and DWI for comprehensive evaluation in leukodystrophy diagnosis[20].

Conclusions:

When assessing paediatric leukodystrophies, the combination of MRS and DWI with conventional MRI offers a thorough understanding of the brain's microstructural and metabolic alterations. Treatment planning and patient prognosis are aided by these techniques, which are critical to the diagnosis, characterization, and tracking of disease development.

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