ORIGINAL ARTICLE

Frequency of Different Types of Leukodystrophy in Children Using Magnetic Resonance Spectroscopy

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ABSTRACT

Objective: To determine the frequency of different types o leukodystrophy (LD) in children using magnetic resonance spectroscopy**.**
Study design: Observational study.
Place and Duration of Study: Department of Radiology, Allied Hospital, Faisalabad from July 2022 to December 2022.
Methodology: Total 130 patients of age 2 months to 15 years and either sex coming for MRI examination either for diagnosis of leukodystrophy were selected. Proton Magnetic Resonance Spectroscopy 1H-MRS was performed for all patients for diagnosis of LD.
Results: In this study, frequency of different types of leukodystrophy in children using magnetic resonance spectroscopy were as follows; Krabbe disease in 15 (11.54%), Canavan's disease in 23 (17.69%), adrenoleukodystrophy LD in 48 (36.92%), Leigh disease in 30 (23.08%) and metachromatic LD in 14 (10.77%).
Conclusion: This study concluded that MRS should be used in every patient with clinical leukodystrophies because it is cost effective as compared to other available tests.
Keywords: *Leukodystrophies, Magnetic resonance spectroscopy, Krabbe disease, Canavan disease*.

INTRODUCTION

Leukodystrophies (LD) are genetic disorders that primarily affect white matter of Central nervous system (CNS) and Peripheral nervous system PNS. These disorders often worsen with time.[1, 2] These are the result of irregularities in the development of myelin, which might be due to a lack in enzymes or a storage issue. Each kind of leukodystrophy has distinct clinical manifestations, imaging findings, and pathological characteristics. The symptoms may manifest 6 months after birth and an earlier beginning is associated with more significant impairment.[3]
Inherited LD are a collection of disorders that impact the myelin and result in substantial health issues and mortality in 33% of individuals before they reach 8 years of age.[4] Typically, there are more than thirty disorders that are classified as main learning disabilities. Heritable illnesses known as primary LD mostly impact glial cells in the white matter.[5] Individually, they are seldom, yet as a

whole, they are prevalent. Their exact incidence is uncertain because to difficulties in diagnosis; nonetheless, it is expected to fall within the range of 7,663 to 50,000.[6]

Both clinical and radiological evidence may provide valuable guidance for investigating a youngster who is thought to have leukodystrophy. Nevertheless, around 50% of leukodystrophy patients remain undetected despite recent advancements.[7] The majority of LD illnesses may be dysfunction of cellular organelles. Every LD has unique clinical, chemically, pathological, and radiologic characteristics.[8]

MRI is the ideal imaging technique for diagnosis of white matter diseases. LD frequently manifest as regions with aberrant signal intensity that look brighter than normal on T2-weighted images and darker than normal on T1-weighted images. The diagnostic criterion for hypomyelination/demyelination on MRI is the presence of a consistent pattern of insufficient myelination on two consecutive MRI scans performed six months apart. Proton Magnetic Resource Spectroscopy (1H-MRS) is a precise method used to identify and measure the levels of metabolite peaks found inside regions of aberrant signal. The instrument quantifies the resonance frequencies of various metabolites, providing us with amplitude values shown in a line graph.[7] The primary metabolites often identified in leukodystrophies are N-acetyl aspartate, creatine, and choline.[3] In addition, MRS is also valuable for identifying the presence of lactate and myo-inositol (mI), which are markers for glial activity, at frequent intervals. When a voxel is put on lesions of various LD, distinct metabolite peaks will be seen.[8]

1H-MRS is a quantitative method that may provide a deeper understanding of the pathological alterations occurring in the white matter.[3] MRS is a well-recognized analytical technique in the field of chemistry that is used to identify compounds and assess their bio-physical properties.[9] MRS enables the identification of relatively tiny compounds at concentrations ranging from 0.5 to 10 millimoles, both inside cells and in the extracellular spaces. 1H-MRS identifies three primary metabolite peaks: N-acetylaspartate (NAA), which serves as an indicator of neuronal integrity; choline (Cho), which acts as a marker for cell membranes; and creatine (Cr), which indicates energy reserves.[10]

A research observed that Krabbe's disease, Canavan's disease, adrenoleukodystrophy LD, Leigh disease, and Metachromatic LD occurred in 11.5%, 15%, 31%, 23%, and 11.5% of children, respectively.[8] Quantifying metabolites precisely using MRS is not often done as part of standard practice in children who have aberrant signal intensity on MRI. Based on my understanding, there is currently no accessible local data on this particular issue. The purpose of our research was to evaluate the many forms of leukodystrophies using MRS in order to provide early therapy tailored to each individual type, with the goal of minimizing the related morbidity and death.

MATERIAL AND METHODS

This case series was conducted at the Radiology department of Allied Hospital in Faisalabad from July 2022 to December 2022.The sample size of 130 was determined using the WHO sample size calculator, taking into account the prevalence of distinct kinds of leukodystrophy in children as 11.5%, an absolute precision requirement of 5.5%, and a confidence level of 95%.[8]

Children of both genders, ranging in age from 2 months to 15 years, who had leukodystrophy, were included. The diagnosis of leukodystrophy was made based on symptoms including macrocephaly, spasticity, hyperreflexia, and ataxia. This diagnosis was further validated using a brain MRI, which revealed dysmyelination and anomalies (hypodense region) in the white matter signal intensity. Children who had other neurological conditions or trauma, and who showed hypo-myelination on their first MRI scan and had a history of headaches with less than four punctate white matter hyperintensities were not included in the study.

Following permission from the hospital's ethical committee, patients who met the inclusion criteria and came via OPD were included and provided with informed consent. 1H-MRS was conducted on all patients using a single-section multivoxel 2D chemical shift spectroscopy sequence. The sequence had a

nominal planar resolution and a section thickness of 15 mm. After automated shimming and gradient tweaking, water suppression was achieved using a selected inversion pulse. The spectra were obtained from a specific region of interest inside the damaged white matter, with a volume of 4-6 mL. The raw data from the 1H-MRS was uploaded to the Workstation, namely the Extended MR workspace version 2.6.3.4, located in the Netherlands. Numeric integration was used to determine the peak areas of Cho, Cr and NAA after baseline adjustment. Additionally, ratios of white matter intravoxel (NAA/Cr, Cho/Cr, and Cho/NAA) were computed. All forms of leukoencephalopathies showed preservation of spectra in the cortical gray matter and CSF. The data was examined using SPSS version 16. Descriptive statistics, such as the mean and standard deviation, provide information on numerical quantities, such as age. Frequency and percentage were computed for all categorical factors such as gender and kinds of leukodystrophy. A p-value less than or equal to 0.05 was deemed statistically significant.

RESULTS

The age of participants in this research ranged from 2 months to 15 years, with a mean age of 5.68 ± 2.56 years. The majority of patients, namely 116 individuals (89.23%), were between the age range of 2 months to 8 years. Among the 130 patients, there were an equal number of men and females, with 65 (50.0%) of each gender, resulting in a male to female ratio of 1:1. The study utilized proton magnetic resonance spectroscopy to determine the prevalence of various types of leukodystrophy in children. The frequencies of each type were as follows Krabbe disease in 15 cases (11.54%), Canavan's disease in 23 cases (17.69%), adrenoleukodystrophy in 48 cases (36.92%), Leigh disease in 30 cases (23.08%), and metachromatic leukodystrophy in 14 cases (10.77%).

Table-I: Baseline Characters of patients (n = 130)

Variables		N	%age
Age	2 months to 8 years	116	89.23
	9-15 years	14	10.77
Gender	Male	65	50
	Female	65	50
Findings of MRS	Krabbe disease	15	11.54
	Canavan's disease	23	17.69
	Adrenoleukodystrophy	48	36.92
	Leigh disease	30	23.08
	Metachromatic Leukodystrophy	14	10.77
Total		130	100

Table II: Association of MRS with respect to age (n = 130).

	2 months-8 yrs	**9-15 year**
	(n = 116)	**(n = 14)**
Krabbe disease	11	4
	-9.50%	-28.60%
Canavan's disease	22	1
	-19%	-7.10%
Adreno LD	43	5
	-37.10%	-35.70%
Leigh disease	27	3
	-21.40%	-21.40%
Metachromatic LD	13	1
	-7.10%	-7.10%

p-value = 0.272

Table III: Association of MRS with gender (n = 130)

	Male	Female
	(n = 65)	(n = 65)
Krabbe disease	11	4
	-16.90%	-6.20%
Canavan's disease	9	14
	-13.80%	-21.50%
Adreno LD	21	27
	-32.30%	-41.50%
Leigh disease	16	14
	-24.60%	-21.50%
Metachromatic LD	8	6
	-12.30%	-9.20%

p-value = 0.238

DISCUSSION:

LD with an inflammatory component, especially X-ALD, exhibit contrast enhancement. FLAIR investigations are the most effective method for detecting cystic lesions. MRS is useful in identifying increased levels of NAA in Canavan disease, or lactate in LD with brainstem and spinal cord involvement and high lactate, as well as other mitochondrial illnesses.[11] A reduction in the NAA peak suggests that there is neuronal damage happening in the main white matter disorder. Infantile globoid cell LD may result in substantial expansion of the optic nerves.[12] In our study, frequency of different types of LD were as follows; Krabbe disease in 15 (11.54%), Canavan's disease in 23 (17.69%), adrenoleukodystrophy LD in 48 (36.92%), Leigh disease in 30 (23.08%) and metachromatic leukodystrophy in 14 (10.77%). In a study, Krabbe's disease, Canavan's disease, Adreno LD, Leigh disease and Metachromatic LD was noted in 11.5%, 15%, 31%, 23% and 11.5% children respectively.[8] When considering the possible causes of leukodystrophies, MRS may provide some assistance. However, it is important to note that changes in the ratios of metabolites are not suggestive of a particular illness.[5] Elevated concentrations of NAA have been seen in individuals with Canavan illness,[13] however, other investigations failed to see any substantial alterations.[14] However, elevated levels of NAA are considered to be a biomarker for white matter illnesses such as Pelizaeus-Merzbacher disease (PMD) and Canavan disease.[15] Elevated levels of NAA and elevated mI and Cr, together with a decrease in Cho, were seen in patients with PMD. The levels of both NAA and lactate were decreased in individuals with Krabbe disease. Higher Cho-Cr ratios were seen in Gaucher disease, which showed a negative correlation with the degree of impairment.[16] Schiffman and van der Knaap [17] conducted a comprehensive evaluation for diagnosing white matter abnormalities. To begin, it is necessary to distinguish a hypomyelinating illness from other conditions affecting the white matter of the brain. If a hypomyelinating condition is present, the diagnosis might be further aided by determining whether there is involvement of the peripheral nerves. Next, we need to ascertain if the white matter alterations in other white matter disorders are continuous, scattered, or occurring in many locations. The presence of patchy or multifocal signal abnormalities suggests the likelihood of an acquired white matter pathology, however there may be some exceptions. When the white matter alterations are merged together, it is crucial to observe their main location. Ultimately, the identification of supplementary characteristics such cysts, calcifications, microbleeds, and the inclusion of other structures can aid in the determination of the diagnosis.[18] Dubey et al. provided evidence that the Expanded impairment Status Scale (EDSS) score showed an inverse correlation with global NAA/Cr, indicating a possible involvement of axonal damage in clinical impairment in pure AMN.[19] Brain involvement, as seen by MRI, is infrequent in female participants with X-ALD who have one copy of the mutated gene, even if they show clinical signs of spinal cord involvement. However, levels of NAA are decreased in the corticospinal projection fibers in female participants who have normal findings on MRI,

indicating the presence of axonal malfunction.[20]

CONCLUSION

The study determined the prevalence of various types of LD in children through the use of magnetic resonance spectroscopy. Therefore, we suggest utilizing MRS in all patients with clinical leukodystrophies due to its cost-effectiveness compared to other tests. Additionally, the implementation of MRS will aid in distinguishing between healthy demyelination and pathological demyelination

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Author's Contribution

AR: Conception, discussion and literature review
ZS: Data analysis and results evaluation
IJ: Manuscript writing, search and interpretation of data Literature**.**
IS: Analysis, Design
TK: Acquisition of data
HR: Statistical analysis of result

All the authors have approved the final manuscript draft and accept the responsibility of research integrity.