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ORIGINAL ARTICLE

Spectrum of Magnetic Resonance Spectroscopy (MRS) in Differentiating Paediatric Leukodystrophies in Pakistani Population

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ABSTRACT

Aim: To determine the frequency of findings of MRS in differentiating paediatric leukodystrophies in Pakistani population.
Study design: Cross sectional descriptive study.
Place and duration of study: Armed Forces Institute of Radiology and Imaging, Military Hospital Rawalpindi from 25th August 2018 to 24th February 2019.
Methodology: A total of 110 individuals who were coming in for an MRI test and were either male or female, older than one month of age, and younger than 12 years of age, were chosen. A 3.0T MRI scanner equipped with MRS techniques was used for each scan. Axial T1 and T2 Weighted spin-echo, FLAIR, coronal, and sagittal T2 Weighted spin-echo images were all part of the MRI imaging protocol. During the same session, a single section multivoxel 2D chemical shift spectroscopy sequence was also carried out. In MRS, the metabolites that were detected in each of our patients were choline, creatine, lactate, N-acetyl aspartate, and myo-inositol. Data were examined utilizing SPSS 21.
Results: The average age was 5.24±1.89 year. 56 (50.91%) of the 110 patients were male children, compared to 54 (49.09%) female children, for a male to female ratio of 1.1:1. The following paediatric leukodystrophies were more often found with MRS in this study: Krabbes disease in 13 (11.82%), Canavan's disease in 19 (17.27%), Adrenoleukodystrophy in 41 (37.27%), Leigh disease in 25 (22.73%), and Metachromatic leukodystrophy in 12 (10.91%).
Practical Implication: The underlying issue has recently been linked to mutations in the DARS2 gene, which codes for mitochondrial aspartyl-tRNA synthetase.
Conclusion: MRS, which is more affordable than other existing tests, should be utilized in every patient with clinical leukodystrophies.
Keywords: Leukodystrophies, Magnetic resonance spectroscopy, MRS

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 manifestation, imaging results, and pathology vary for each type of leukodystrophy. Symptoms can appear as early as 6 months after birth, with earlier onset leading to greater impairment[1,2].

MRI is the preferred method for diagnosing white matter illnesses, including leukodystrophies. Abnormalities in myelin often appear as high signal intensities on T2WI and low signal intensities on T1WI on MRI. A consistent pattern of inadequate myelination on two subsequent MRIs taken six months apart is used as the diagnostic threshold for hypomyelination or demyelination[3]. 1H-MRS is used to analyze the resonance frequencies of various metabolites[4] in the aberrant signal locations, including choline, creatine, and N-acetyl aspartate[1]. Lactate and myo-inositol can also be identified using MRS as markers for glial activity[1]. 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[5-7].

The most common leukodystrophies in Pakistan include Krabbes disease (11.5%), Canavan's disease (15%), Adrenoleukodystrophy (31%), Leigh disease (23%) and Metachromatic leukodystrophy (11.5%)[1]. These illnesses are more prevalent in Pakistan due to consanguineous marriages. UK research has found that 13% of identified cases were of Pakistani ethnicity[8]. There is no cure for leukodystrophies, but a diagnosis can aid with family genetic testing. Using MRI and MRS together is effective in diagnosing suspected leukodystrophies and can distinguish between different types of leukodystrophies and pathological vs normal demyelination. This method is also relatively affordable compared to other available tests[1]. A paediatric patient showing increasing signs of encephalopathies and inability to achieve developmental milestones may have leukodystrophy, as indicated by MRI & MRS results.

The study aims to understand the use of MRS in identifying paediatric leukodystrophies in the Pakistani population, with a focus on accuracy and cost-effectiveness. The high prevalence of leukodystrophies in this population, due to consanguineous marriages, and the sensitivity of MRS in distinguishing between different types of leukodystrophies and pathological vs normal demyelination make it a valuable tool for diagnosis. The study aims to contribute to the development of better diagnostic and treatment methods for these debilitating illnesses.

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MATERIALS AND METHODS

This cross-sectional descriptive study was done at the Armed Forces Institute of Radiology and Imaging, Military Hospital Rawalpindi from August 25, 2018, to February 24, 2019. Using the WHO sample size calculator, the sample size was determined to be 110 patients with a confidence interval of 95%, projected population of 11.5%, and absolute precision of 6%.[1] Consecutive sampling without regard to probability was used to choose the patients. Patients having a leukodystrophy diagnosis or cases referred from other institutions with clinical signs and symptoms of leukodystrophies were included. Patients were included if they were older than 01 month and younger than 12 years of age, and they might be of either sex. Patients with internal cardiac pacemakers, cochlear implants, non-titanium aneurysm clips, or any other metallic foreign body were excluded from the research owing to MRI contraindications, as well as patients whose focal lesion is a mass or tumor (found on CT/MRI).

After approval from Institutional Ethical Board we started obtaining informed agreement, all patients receiving an MRI of the brain who met our inclusion criteria were recruited in the

acquisition study. By including them in the exclusion criteria, all confounding variables were eliminated. A 3.0T MRI scanner equipped with MRS techniques was used to capture each scan. Axial T1 and T2 Weighted spin-echo, FLAIR, coronal, and sagittal T2 Weighted spin-echo sequences are all part of the MRI imaging routine. During the same session, a single section multivoxel 2D chemical shift spectroscopy sequence was also carried out. In MRS, the metabolites that were detected in each of our patients were choline, creatine, lactate, N-acetyl aspartate, and myo-inositol. One radiologist, who was unaware of the ultimate diagnosis, evaluated the study for each patient. SPSS version 21 was used to analyze the data.By frequency and proportion, qualitative factors including gender and the different kinds of leukodystrophies were assessed. Age-related quantitative data were calculated using the mean±SD. Through stratification, effect modifiers like age and gender were managed. To determine their influence on the result, post-stratification chi square was used, and a p-value of ≤0.05 was taken as significant.

RESULTS

The mean age was 5.24±1.89 years. The majority of the 81 patients (73.64%) ranged in age from 1 month to 6 years. 56 (50.91%) of the 110 patients were men, compared to 54(49.09%) women, for a ratio of males to females 1.1:1. The following paediatric leukodystrophies were more often found with MRS in this study: Krabbes disease in 13(11.82%), Canavan's disease in 19(17.27%), adrenoleukodystrophy in 41(37.27%), Leigh disease in 25 (22.73%) and metachromatic leukodystrophy in 12(10.91%) [Tables 1-3].

Table 1: Frequency of paediatric leukodystrohies (n=110)

Leukodystrophies	No.	%
Krabbes disease	13	11.82
Canavan's disease	19	17.27
Adrenoleukodystrophy	41	37.27
Leigh	25	22.73
Metachromatic leukodystrophy	12	10.91

Table 2: Stratification of the findings of MRS with respect to age

Findings of MRS		1 month 6 years (n=81)	7-11 years (n=29)	P-value
Krabbes disease	Yes	11	2	0.339
	No	70	27	
Canavan's disease	Yes	11	8	0.087
	No	70	21	
Adrenoleuko-dystrophy	Yes	31	10	0.717
	No	50	19	
Leigh disease	Yes	18	7	0.833
	No	63	22	
Metachromatic leukodystrophy	Yes	10	2	0.419
	No	71	27	

Table 3: Stratification of the findings of MRS with respect to gender

Findings of MRS		Male (n=56)	Female (n=54)	P-value
Krabbes disease	Yes	9	4	0.159
	No	47	50	
Canavan's disease	Yes	7	12	0.177
	No	49	42	
Adrenoleuko-dystrophy	Yes	19	22	0.460
	No	37	32	
Leigh disease	Yes	14	11	0.562
	No	42	43	
Metachromatic leukodystrophy	Yes	7	5	0.586
	No	49	49	

DISCUSSION

The most crucial and readily available test for a patient presenting with signs and symptoms of a leukodystrophyis a brain MRI. Images that are T1- and T2-weighted and fluid-attenuated inversion-recovery (FLAIR) are the absolute minimum needed for a typical inquiry. The relationship between MRI findings and clinical findings might be quite variable. In order to distinguish between solely inflammatory, tumorous, or vascular etiologies and disorders with metabolic/degenerative features, specific patterns and localizations of lesions must be evaluated. The rapid changes in myelination throughout infancy must be considered. White matter abnormalities may now be diagnosed using a thorough MRI-based method that was just published.[9]

Several various leukodystrophies have certain common MRI patterns, such as the sparing of the subcortical U-fibers in conditions like X-linked adrenoleukodystrophy (X-ALD) and MLD, or the central white matter's streaky or "tigroid" look characteristic of metachromatic leukodystrophy. The structure of the Virchow-Robin spaces in the brain and the buildup of storage material or fluid surrounding blood arteries both contribute to streaky patterns. Other patterns are almost diagnostic because they are so distinctive. In conditions like juvenile Alexander disease (AD) and vanishing white matter illness, this could be the case. A rising variety of hereditary illnesses that have typically been categorised by identification of their distinctive MRI pattern exhibit hypomyelination[10].

In leukodystrophies with an inflammatory component, notably in X-ALD, contrast enhancement is seen. FLAIR studies are the most effective way to find cystic lesions. For example, leukoencephalopathy with damage of the brainstem and spinal cord and increased lactate[11] may be detected using magnetic resonance spectroscopy (MRS), as can Canavan disease and other mitochondrial illnesses. A lower NAA peak implies primary white matter illness with neuronal involvement. Infantile globoid cell leukodystrophy can cause severe enlargement of the optic nerves[12].

The following paediatric leukodystrophies were more often found using MRS in my study: Krabbes disease in 13(11.82%), Canavan's disease in 19(17.27%), Adrenoleukodystrophy in 41(37.27%), Leigh disease in 25 (22.73%), and Metachromatic leukodystrophy in 12(10.91%). According to research, Krabbes disease, Canavan's disease, Adrenoleukodystrophy, Leigh disease and Metachromatic leukodystrophy are the most prevalent leukodystrophies (11.5%)[1].

MRS may be helpful in the differential diagnosis of leukodystrophies, however alterations in metabolite ratios or levels are not always indicative of a specific disease. Alexander illness has been associated with elevated mI and lactate levels as well as decreased NAA levels[13,14]. Canavan illness has been associated with elevated NAA levels[15], although other investigations have not detected any appreciable alterations.16However, it is believed that elevated NAA is a biomarker for illnesses of the white matter, including Pelizaeus-Merzbacher disease and Canavan disease.[17]In Pelizaeus-Merzbacher disease, higher levels of NAA, higher levels of mI and Cr, as well as lower levels of Cho, were discovered.[18]In Krabbe disease, lactate and NAA levels were also decreased. In Gaucher disease, there were elevated Cho-Cr ratios that were inversely linked with the impairment[19].

In their assessment of the MRI-based method for diagnosing white matter diseases, Schiffman and van der Knaap[20] discussed this method. A hypomyelinating condition must first be distinguished from other white matter illnesses. Diagnosis of a hypomyelinating condition will be aided further by the presence or absence of peripheral nerve involvement. Determination of pattern of white matter disorders either confluent, patchy, or multifocal white matter alterations as the following step. Although there are certain exceptions, patchy or multifocal signal anomalies suggest the diagnosis of an acquired white matter disorder. It's important to understand the observed pattern of involvement in the white matter diseases, if they are confluent (frontal, parieto-occipital, diffuse, periventricular, or sub-cortical).Additionally, the involvement of other structures (grey matter, basal ganglia, spinal cord) and the presence of other abnormalities including cysts, calcifications, microbleeds, and other features may aid in the diagnosis[21].

Reduced NAA/Cr and elevated Cho/Cr, MI/Cr, and Glx/Cr are seen in X-ALD. Patients with X-ALD show spectroscopic

abnormalities in their normal-appearing white matter (NAWM) that occur before the illness progresses.[22] Choline levels have increased, but NAA levels have decreased. They only arise in those regions of the brain where future lesion development is seen. These regions can be a demyelination zone that is about to happen or has already started.

The adult version of X-ALD is adrenomyeloneuropathy (AMN). The pathophysiology of the illness often only affects the spinal cord and peripheral nerves ("pure AMN"), although histology reveals brain involvement. Global NAA/Cho and NAA/Cr levels were lower in MRS trials compared to controls. The internal capsule and parieto-occipital white matter show these alterations the greatest. Reduced NAA ratios without an increase in Cho/Cr imply significant axonal involvement.[23]Additionally, Dubey et al. showed that the Expanded Impairment Status Scale (EDSS) score had an inverse relationship with the global NAA/Cr, which raised the possibility that axonal damage contributed to clinical disability in pure AMN. In female participants heterozygous for X-ALD, even individuals who exhibit clinical indications of spinal cord involvement, brain involvement detectable by MRI is uncommon. However, in female participants with normal MRI results, NAA levels are decreased in the corticospinal projection fibers, indicating axonal malfunction.[24]

Aspartoacylase (ASPA), an enzyme involved in the conversion of NAA to aspartate and acetate, is lacking in people with Canavan disease. Lack of Aspartoacylasecauses NAA to build up, which interferes with proper myelination and causes spongiform degeneration of the brain.[25]By using MR spectroscopy in vivo, it is possible to identify the increases in NAA, which may subsequently be verified by measuring NAA in the urine.

Pyramidal, cerebellar, and dorsal column dysfunction are progressively progressing symptoms that define LBSL (Leukoencephalopathy with Brainstem and Spinal Cord) as a clinical condition. While U-fibers are spared, LBSL has a highly specific MRI pattern characterized by specific involvement of cerebral and cerebellar white matter, as well as brainstem and spinal pathways.The white matter in LBSL often exhibits reduced NAA and elevated lactate, Cho, and MI by MR spectroscopy, which suggests axonal degeneration and gliosis. The underlying issue has recently been linked to mutations in the DARS2 gene, which codes for mitochondrial aspartyl-tRNA synthetase. Medical resources, diagnosis, and treatment must improve in developing countries. There are limited resources: access to medical and health resources; knowledge about disease; awareness, trainings, and awareness about health. The heath literacy is mandatory for any disease and facilitates the patients with resources, databases, and trainings about disease. [26-32]

CONCLUSION

Krabbes disease accounts for 11.82% of MRS findings in juvenile leukodystrophies, Canavan's disease for 17.27%, Adrenoleukodystrophy for 37.27%, Leigh disease for 22.73% and Metachromatic leukodystrophy for 10.91%. We suggest that MRS be utilized in every patient with clinical signs and symptoms of leukodystrophies since it is more affordable than other tests and because its usage will allow us to distinguish between pathological and healthy demyelination.

Limitations of study: Some of the limitations of this study were the exclusion of children with other physical co-existent genetic deformities; children with space occupying lesions as well as some children having MRI incompatible hearing aids or other prosthesis. One of the limitations faced by this study was patient's loss to follow up.

Conflict of interest: Nil

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