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Clinical and MRI Evaluation of Children with Leukodystrophies

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Abstract

Introduction: Leukodystrophies are a diverse group of rare, inherited neurodegenerative disorders affecting the brain's white matter, leading to progressive neurological impairment. Magnetic Resonance Imaging (MRI) plays a crucial role in diagnosing these conditions, offering detailed insight into white matter abnormalities and aiding in distinguishing various leukodystrophies.

Objective: This study aims to evaluate children with leukodystrophies using MRI, establish accurate diagnoses, assess the severity and extent of white matter lesions, and demonstrate the different patterns of abnormal myelination.

Methods: This prospective observational study was conducted in the Department of Radiodiagnosis and Imaging at Sher-I-Kashmir Institute of Medical Sciences, Srinagar, from June 2022 to June 2024. All children suspected of having white matter disorders based on clinical features and biochemical tests were included. MRI was performed to identify patterns of white matter involvement, and findings were correlated with clinical data.

Results: A total of 29 children (age range: 2 months to 18 years) were evaluated. MRI findings revealed that demyelinating leukodystrophies were the most common, with symmetrical white matter involvement. Hypomyelinating disorders showed diffuse white matter changes with sparing of the U-fibers. Specific patterns, such as tigroid appearance in metachromatic leukodystrophy and posterior fossa involvement in Alexander disease, were identified. MRI was instrumental in narrowing down differential diagnoses and identifying characteristic patterns for various leukodystrophies.

Conclusion: MRI is an invaluable tool in the diagnosis and management of leukodystrophies in children. It allows for early identification of disease patterns, which is critical for appropriate clinical management and potential therapeutic interventions. Further research is needed to explore the genetic basis of these disorders in the Kashmiri population.

Keywords: Leukodystrophies, Magnetic Resonance Imaging (MRI), White Matter Disorders, Demyelination, Hypomyelination

Introduction

Leukodystrophies are a heterogeneous group of inherited disorders primarily characterized by the abnormal development or degeneration of white matter in the brain.[1] These conditions affect the protective myelin sheath surrounding nerve fibers, which leads to progressive neurological deterioration.[2] According to the Global Leukodystrophy Initiative (GLIA), leukodystrophies are defined as heritable disorders

impacting the central nervous system's white matter, sometimes involving the peripheral nervous system as well. [3] They are typically diagnosed in childhood and manifest with symptoms such as motor dysfunction, developmental delay, seizures, spasticity, and cognitive impairment. [4]

The etiology of leukodystrophies is primarily genetic, with several gene mutations affecting the production, maintenance, or repair of myelin. Advances in molecular genetics, including whole-exome and whole-genome sequencing, have facilitated the identification of many genes associated with these disorders. [5] Genetic testing has become integral in diagnosing leukodystrophies, helping to pinpoint specific mutations and guide treatment strategies. For instance, Metachromatic Leukodystrophy (MLD) is linked to a deficiency in arylsulfatase A, while Adrenoleukodystrophy (ALD) is caused by mutations in the ABCD1 gene. [6] Other examples include Krabbe Disease, caused by a deficiency in galactocerebrosidase, and Pelizaeus-Merzbacher Disease (PMD), linked to mutations in the PLP1 gene. [7]

Magnetic resonance imaging (MRI) plays a pivotal role in diagnosing and managing leukodystrophies. The distinct MRI patterns associated with different leukodystrophies are invaluable in differentiating these conditions. T1-weighted imaging, T2-weighted imaging, and Fluid-Attenuated Inversion Recovery (FLAIR) imaging are among the most frequently employed techniques to assess myelin integrity and detect areas of demyelination.[8] Additionally, advanced techniques such as Diffusion-Weighted Imaging (DWI) and Magnetic Resonance Spectroscopy (MRS) provide insights into microstructural changes and biochemical disturbances in white matter. These imaging patterns vary among different leukodystrophies, helping to classify the disease and monitor its progression.[9] For instance, hypomyelinating leukodystrophies exhibit mild hyperintensity on T2-weighted images, while demyelinating leukodystrophies display prominent hyperintensity in the white matter on T2-weighted images and hypointensity on T1-weighted sequences.[10]

The clinical presentation of leukodystrophies is highly variable, depending on the specific disorder and the extent of white matter involvement. Developmental delays, motor dysfunction, seizures, and cognitive decline are common features. The age at which symptoms first appear and the rate of progression can vary significantly, from early infancy to later childhood or adolescence. Some leukodystrophies are rapidly progressive and can lead to early death, while others may have a slower course, allowing for longer periods of preserved function.[11]

There are no definitive cures for most leukodystrophies, but several treatment strategies aim to slow disease progression and manage symptoms. Hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) are options for certain leukodystrophies, such as MLD and Krabbe disease.[12] Gene therapy is an emerging area of research and holds promise for correcting genetic defects in leukodystrophies like ALD.[13] Supportive care, including physical therapy, occupational therapy, speech therapy, and nutritional support, plays an essential role in improving the quality of life for affected individuals.[14]

Despite advancements in understanding leukodystrophies, significant gaps remain, particularly regarding their prevalence, clinical presentation, and MRI characteristics in specific populations. Most of the existing literature focuses on Western populations, with limited data on children from diverse ethnic backgrounds, including Kashmiri children. The unique genetic and environmental factors in the Kashmiri population may influence the manifestation and progression of leukodystrophies. Additionally, there is a paucity of studies addressing the early diagnosis and management strategies tailored to this group. Conducting this study on Kashmiri children is crucial to bridge these gaps, providing insights into the regional prevalence, specific MRI patterns, and clinical features of leukodystrophies in this population.

This research aims to enhance understanding, improve diagnostic accuracy, and inform better clinical practices and interventions, ultimately contributing to improved outcomes for affected children in the Kashmir region.

Materials and methods

Study Design and setting

This prospective observational study was conducted in the Department of Radiodiagnosis and Imaging at Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar.

Study period

The present study was conducted from June 2022 to June 2024.

Study Population and inclusion criteria

The study included all children suspected of having white matter disorders on history and clinical examination and on biochemical lab tests.

Exclusion Criteria

Patients were excluded if they had:

1. Implantable metallic devices
2. Surgical clips and magnetic foreign bodies
3. Cochlear implants
4. Claustrophobia

Sample size and sampling technique

A complete enumeration sampling technique was utilized, with all patients presenting to the study institution and meeting the inclusion criteria and not excluded as per the exclusion criteria being recruited into the study sample.

Data collection methodology and observation

The researchers retrospectively reviewed cases with confirmed diagnoses and described their clinical presentation and neuroimaging findings in detail. Informed written consent was obtained from all study participants before their inclusion in the study. Each patient underwent a comprehensive MRI of the brain before the final diagnosis. The diagnosis was further refined using additional biochemical tests and genetic studies. For children who were non-cooperative during the imaging process, sedation was necessary. The researchers utilized either oral or parenteral sedation agents, depending on the individual needs of the patients. Oral sedation was achieved using Triclofos at a dose of 50 mg/kg, while intravenous sedation was administered using ketamine at doses ranging from 0.5 to 2 mg/kg. To ensure patient safety, resuscitative equipment, including an Ambu bag, was prepared in advance and readily available. The imaging examinations were conducted using a 1.5 Tesla MRI scanner, specifically the Magnetom Avanto from Siemens, located in Erlangen, Germany. The imaging protocols included T1-weighted, T2-weighted, FLAIR (Fluid-Attenuated Inversion Recovery), DWI (Diffusion-Weighted Imaging), and MR spectroscopy sequences. These imaging techniques provided comprehensive data for evaluating the patients' brain structures.

The first discriminator in the imaging analysis was the presence or absence of hypomyelination, which is a crucial factor in diagnosing various neurodevelopmental disorders. T1-weighted sequences played a particularly important role in assessing hypomyelination. Hypomyelination was identified by its characteristic imaging features on T1 sequences, which provided detailed information about the myelination status of the patients' brains. The study population consisted of children who were suspected

of having neurodevelopmental disorders. Their clinical presentations varied widely, and the neuroimaging findings provided valuable insights into the underlying pathologies. Some patients presented with developmental delays, while others exhibited more specific neurological symptoms such as seizures, hypotonia, or spasticity. In cases where hypomyelination was identified, the T1-weighted images revealed diffuse or focal areas of reduced signal intensity, indicating delayed or abnormal myelination. These findings were correlated with the patients' clinical presentations and other diagnostic tests to arrive at a final diagnosis. The T2-weighted and FLAIR sequences complemented the T1-weighted images by providing additional information about the brain's structural and pathological changes. Diffusion-Weighted Imaging (DWI) was particularly useful in identifying acute or subacute ischemic events and other abnormalities affecting the brain's white matter. MR spectroscopy further contributed to the diagnostic process by allowing the researchers to assess the brain's metabolic profile. This technique provided information about the concentrations of various metabolites, which could indicate specific metabolic or genetic disorders. The retrospective review of confirmed cases allowed the researchers to compile a comprehensive database of neuroimaging findings associated with different clinical presentations. This database served as a valuable reference for the prospective component of the study, where newly diagnosed patients were assessed using the same imaging protocols and diagnostic criteria. Throughout the study, the collaboration between the Department of Radiodiagnosis and Imaging and the Department of Pediatrics and Pediatric neurology ensured a multidisciplinary approach to patient care. The integration of clinical and imaging data, along with biochemical and genetic studies, provided a holistic view of each patient's condition and facilitated accurate diagnoses.

Data management and statistical analysis

The collected data were checked for consistency, completeness and entered into Microsoft Excel (MS-EXCEL, Microsoft Corp.) data sheet. Analyzed with the statistical program Statistical Package for the Social Sciences (IBM SPSS, version 22). Data were organized and presented using the principles of descriptive and inferential statistics. The data were categorized and expressed in proportions. The continuous data were expressed as mean±SD. The data were graphically presented in the form of tables, vertical bars, horizontal bar, pie diagram. Where analytical statistics were performed, a p-value of <0.05 was considered to be statistically significant for the purpose of the study. For analytical statistics, Chi-square test was used for categorical data and student’s t-test was used for continuous data.

Ethical consideration

The Institutional Ethics Committee of study institution reviewed and approved the project before it was carried out.

All of the participants were informed in their own language about the study and their rights for participation before providing data for the researcher-administered questionnaire. They were informed about the participant’s role and rights, to clarify that their participation was voluntary, the information was treated confidentially, and they could withdraw from the study at any time. After the collection of data, the data was cleaned, anonymized and stored in a password protected spreadsheet for data analysis.

Results

The present study assessed 29 patients. The majority of the patients (44.8%) were older than 10 years, followed by 41.4% who were between 1 to 5 years old. Only a small proportion (10.4%) were less than 1

year old, and 3.4% were aged between 5 to 10 years. The sex distribution was relatively balanced, with 51.7% being female and 48.3% being male. The most common presenting complaints included seizures (55.2%) and developmental delays (41.4%), with other symptoms such as difficulty in walking, cognitive impairment, ataxia, and hypotonia appearing less frequently.

MRI findings showed that 93.1% of the patients had T2/FLAIR hyperintensities in the white matter, with 82.8% displaying symmetrical lesions. The involvement of periventricular white matter was observed in 62.1% of the cases, while the centrum semiovale was involved in 51.7%. Subcortical regions and brainstem involvement were noted in 34.5% and 20.7% of patients, respectively. Basal ganglia involvement was observed in 34.4 % with frontal white matter and cerebellar involvement noted in 31 % of patients. Bilateral thalami and occipital white matter involvement was noted in 24.1 and 13.8 % respectively. Gliotic areas and encephalomalacia were observed in 17.2% of the patients, and tigroid stripe appearance was noted in 6.9%. Elevated choline and reduced NAA on MR spectroscopy were also found in 6.9% of patients.

Genetic testing supported the diagnosis in several cases, with Vanishing White Matter Disease (10.3%), Metachromatic Leukodystrophy (6.9%), and Juvenile Alexander's Disease (6.9%) being the most common. Krabbe Disease and Leigh's Syndrome were each present in 3.4% of the patients. Laboratory findings further confirmed conditions like Adrenoleukodystrophy and Propionic Acidemia, revealing metabolic abnormalities unique to specific leukodystrophies.

MRI, combined with genetic and laboratory testing, enabled accurate diagnosis in 79.3% of cases, underscoring its role in evaluating children with suspected leukodystrophies. The final diagnosis distribution showed that Leigh's syndrome, vanishing white matter disease and Metachromatic Leukodystrophy were the most prevalent, each accounting for 10.3% of the cases. Adrenoleukodystrophy, Juvenile Alexander's Disease, and Krabbe Disease were each diagnosed in 6.9% of the patients. Less common diagnoses included Canavan's Disease, L2 Hydroxyglutaric Aciduria, Biotin Thiamine disease, Maple Syrup Urine Disease, Merosin-Negative Congenital Muscular Dystrophy, and others. The sex-based analysis revealed that certain leukodystrophies had a significant gender distribution. Adrenoleukodystrophy and Leigh's Syndrome were exclusively found in males ($p < 0.001$), whereas Krabbe Disease, Canavan's Disease, Central Hypothyroidism, and L2 Hydroxyglutaric Aciduria were only observed in females. However, other conditions like Biotin-Thiamine Responsive Basal Ganglia Disease, Juvenile Alexander's Disease, Metachromatic Leukodystrophy, and Vanishing White Matter Disease were present in both sexes.

Discussion

Leukodystrophies are a diverse group of inherited disorders characterized by abnormal development or degeneration of the brain's white matter. These disorders affect the protective myelin sheath surrounding nerve fibers, leading to progressive motor and cognitive decline. Typically diagnosed in childhood, leukodystrophies result in severe neurological impairments. Magnetic Resonance Imaging (MRI) plays a crucial role in diagnosing and managing these conditions by providing detailed images of white matter, enabling differentiation among the various leukodystrophy types.[5] The clinical presentations of leukodystrophies vary depending on the specific disorder and the extent of white matter involvement. Common symptoms include developmental delay, motor dysfunction, spasticity, seizures, and cognitive decline. MRI is invaluable in revealing characteristic patterns of white matter abnormalities, which are critical for differentiating between leukodystrophies.[6]

In this study, the age distribution of patients diagnosed with leukodystrophies provides important insights into the sociodemographic factors influencing the prevalence of these disorders. The majority of patients were over 10 years old (44.8%), followed by those aged 1 to 5 years (41.4%). These findings align with Bonkowsky et al., who reported a higher incidence of leukodystrophies in older children, with significant developmental regression and morbidity by age 8.2 years.[4] Additionally, this study found a slight predominance of females (51.7%) over males (48.3%), consistent with Gulati et al.'s findings that hypomyelinating disorders often show a balanced gender distribution.[15] Zhang et al. also reported that while some leukodystrophies, such as Alexander disease, have a higher incidence in males, others, like Canavan disease, exhibit a more balanced distribution.[16] These sociodemographic patterns underscore the importance of diagnostic vigilance across all age groups and genders.

The presenting complaints in this study, particularly seizures (55.2%) and developmental delay (41.4%), mirror the clinical manifestations commonly reported in leukodystrophies. Zhang et al. found seizures to be a frequent symptom, especially in children with Alexander disease, where 77.3% of patients developed epilepsy.[16] Similarly, Madieh et al. noted that Metachromatic Leukodystrophy (MLD) is often associated with seizures, present in 13% of their study population.[17] Gulati et al. also observed developmental delays as a prevalent symptom in their cohort, particularly in patients with hypomyelinating disorders, which is consistent with this study's findings.[15] Other symptoms, such as difficulty in walking (24.1%), cognitive impairment (20.7%), and ataxia (13.8%), highlight the diverse and progressive nature of leukodystrophies, as noted by Alfadhel et al. who emphasized the variability in clinical presentations depending on the specific disorder.[18]

MRI findings in this study revealed typical patterns of white matter abnormalities, with 93.1% of patients displaying T2/FLAIR hyperintensities. This aligns with Groeschel et al., who reported that MRI shows a characteristic spatial progression in leukodystrophies, particularly in MLD cases.[19] Periventricular white matter involvement, seen in 62.1% of this study’s patients, corresponds with observations by Bonkowsky et al., who noted that hypoplastic cerebellum often accompanies periventricular white matter changes in leukodystrophies.[4] The presence of symmetrical lesions in 82.8% of patients resonates with findings from Groeschel et al. and Cousyn et al., who identified symmetrical U-fiber involvement as indicative of severe motor dysfunction in late-infantile MLD.[20] Additionally, less common MRI findings such as gliotic areas and encephalomalacia (17.2%) align with Zhang et al., who observed a correlation between cerebellar changes and severe motor dysfunction in MLD patients.[16] The involvement of basal ganglia in 34.4% of patients and the detection of elevated choline and reduced NAA in 6.9% of cases further reinforce Ashrafi et al.'s findings on the utility of MR spectroscopy in identifying specific metabolic abnormalities in leukodystrophies.[21]

Genetic and laboratory findings in this study underscore the diverse genetic landscape of leukodystrophies, with Vanishing White Matter Disease, MLD, and Leigh’s Disease being the most prevalent, each accounting for 10.3% of cases. Kristjánsdóttir et al. identified significant neurochemical markers reflecting white matter damage, which supports the findings in this study.[22] The identification of MLD in 10.3% of patients mirrors Malgotra et al.’s study, which highlighted MRI’s critical role in diagnosing white matter diseases.[23] The prevalence of Leigh’s Syndrome (10.3%) corresponds with Nowell et al.'s observations on the significance of MRI in detecting idiopathic white matter abnormalities.[24] Additionally, the presence of Krabbe Disease in 6.9% of patients demonstrates the importance of genetic and biochemical markers in diagnosing and managing leukodystrophies.

The distribution of final diagnoses in this study reflects the complexity and diversity of leukodystrophies, with Leigh's disease and MLD each accounting for 10.3% of cases. These findings align with Groeschel et al., who reported distinct MRI severity patterns in MLD patients.[23] Krabbe Disease and Juvenile Alexander's Disease were each found in 6.9% of patients, which is consistent with Bonkowsky et al.'s findings on the morbidity associated with Krabbe Disease.[4] The diverse diagnoses, including Canavan's Disease (3.4%) and Vanishing White Matter Disease (10.3%), emphasize the need for comprehensive diagnostic approaches that integrate clinical, genetic, and imaging data.

Conclusion

With a diagnostic accuracy of 79.6%, the study demonstrated that MRI, when combined with genetic and biochemical testing, is crucial for diagnosing various leukodystrophies, including Vanishing White Matter Disease, Metachromatic Leukodystrophy, and Juvenile Alexander's Disease. The findings highlighted the importance of early diagnosis for better management of these progressive conditions. The age distribution suggested that leukodystrophies are often diagnosed in older children, likely due to more pronounced clinical symptoms over time. Additionally, the study explored potential gender differences, indicating that certain leukodystrophies may have sex-linked genetic predispositions.

Tables and figures

Table 1. clinic-demographic characteristics of study participants (N=29)

Parameters	**Frequency**	**Percentage**
Age groups		
<1 year	3	10.4
1-5 years	12	41.4
5-10 years	1	3.4
>10 years	13	44.8
Sex		
Male	14	48.3
Female	15	51.7
Presenting complaints		
Developmental delay	12	41.4
Seizures	16	55.2
Difficulty in waking	7	24.1
Cognitive impairment	6	20.7
Hypotonia	3	10.3
Ataxia	4	13.8

Table 2. Distribution of patient according to their MRI findings (N=29)

Findings*	**Frequency**	**Percentage**
Involvement of Periventricular White Matter	18	62.1
Involvement of Centrum Semiovale	15	51.7

Involvement of Subcortical Regions	10	34.5
Involvement of Brainstem	6	20.7
Symmetrical Lesions	24	82.8
Gliotic Areas and Encephalomalacia	5	17.2
Tigroid Stripe Appearance	2	6.9
Elevated Choline and Reduced NAA on MR Spectroscopy	2	6.9
Frontal white matter involvement	9	31
Involvement of basal ganglia	10	34.4
Cerebellar involvement	9	31
Occipital white matter involvement	4	13.8
Bilateral thalami involvement	7	24.1

*Multiple findings possible in a single patient

Table 3. Distribution of patient according to their genetic findings (N=29)

Findings*	Findings	Frequency	Percentage
Krabbe Disease	Gene mutation in GALC gene encoding galactocerebrosidase	1	3.4
Vanishing White Matter Disease	Compound heterozygous variants in EIF2B1 gene	3	10.3
MerosinNegative Congenital Muscular Dystrophy	Homozygous mutation in LAMA2 gene	1	3.4
Metachromatic Leukodystrophy	Homozygous Gly99Asp gene mutation	2	6.9
Leigh's Syndrome	Mutant mt DNA gene (MTND-59)	1	3.4
Juvenile Alexander's disease	Mutation in gene encoding GFAP	2	6.9

*Multiple findings possible in a single patient

Table 4. Distribution of patient according to their laboratory findings (N=29)

Findings*	Findings	Frequency	Percentage
Propionic Acidemia	Increased 3-hydroxypropionic acid, propionate glycine	1	3.4
L2 Hydroxyglutaric Aciduria	Elevated 2-hydroxyglutaric acid in urine	1	3.4
Canavan's Disease	Increased concentration of NAA in urine	1	3.4

Leigh's Syndrome	Elevated levels of lactate in serum	2	6.9
Infantile onset Krabbes disease	Elevated psychosine levels in blood	1	3.4
Adrenoleukodystrophy	Elevated levels of VLCFAS in blood	2	6.9
Maple syrup urine disease	TMS revealed elevated leucine 2905 U and valine 720 U.	1	3.4
Metachromatic leukodystrophy	Arylsulfatase A enzyme activity decreased down to 7.3 % of control value	2	6.9
Other diseases	Various findings across different biomarkers	8	27.6

*Multiple findings possible in a single patient

Table 5. Distribution of patient according to their final diagnosis (N=29)

Diagnosis	Frequency	Percentage
Adrenoleukodystrophy	2	6.9
Biotin-Thiamine Responsive Basal Ganglia Disease(BRBGD)	2	6.9
Canavan's Disease	1	3.4
Central Hypothyroidism	1	3.4
Hereditary Spastic Paraplegia	2	6.9
Infantile Vanishing White Matter Disease	1	3.4
Juvenile Alexander's Disease	2	6.9
Krabbe Disease	2	6.9
L2 Hydroxyglutaric Aciduria	1	3.4
Leigh's Syndrome	3	10.3
Maple Syrup Urine Disease	1	3.4
Merosin-Negative Congenital Muscular Dystrophy	1	3.4
Metachromatic Leukodystrophy	3	10.3
Phenylketonuria	1	3.4
Propionic Acidemia	1	3.4
Seizure Disorder	2	6.9
Type 1 Glutaric Aciduria	1	3.4
Vanishing White Matter Disease	2	6.9

Table 6. Distribution of patient according to their final diagnosis as per the sex (N=29)

Diagnosis	Female	Male	p-value
Adrenoleukodystrophy	0 (0)	2 (100)	<0.001*
Biotin-Thiamine Responsive Basal Ganglia Disease	0 (0)	2 (100)	

Canavan's Disease	1 (100)	0 (0)	
Central Hypothyroidism	1 (100)	0 (0)	
Hereditary Spastic Paraplegia	2 (100)	0 (0)	
Infantile Vanishing White Matter Disease	1 (100)	0 (0)	
Juvenile Alexander's Disease	1 (50)	1 (50)	
Krabbe Disease	2 (100)	0 (0)	
L2 Hydroxyglutaric Aciduria	1 (100)	0 (0)	
Leigh's Syndrome	1 (33.3)	2 (66.7)	
Maple Syrup Urine Disease	0 (0)	1 (100)	
Merosin-Negative Congenital Muscular Dystrophy	0 (0)	1 (100)	
Metachromatic Leukodystrophy	1 (33.3)	2 (66.7)	
Phenylketonuria	1 (100)	0 (0)	
Propionic Acidemia	0 (0)	1 (100)	
Seizure Disorder	1 (50)	1 (50)	
Type 1 Glutaric Aciduria	0 (0)	1 (100)	
Vanishing White Matter Disease	2 (100)	0 (0)	

*Statistically significant

Figure 1. Leigh's disease (Patient 5)

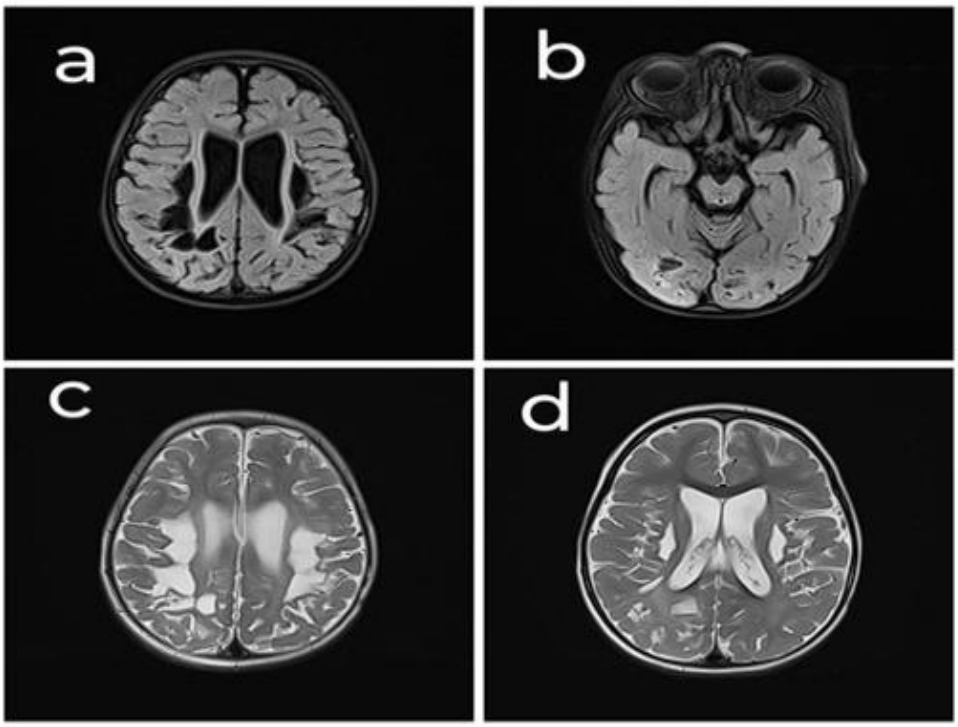

Image a & b Axial FLAIR images showing symmetric large gliotic areas with encephalomalacia in bilateral parietal lobes and cerebellum. c & d Axial T2W images showing encephalomalacia in bilateral parietal lobes and bilateral basal ganglia

Figure 2. Vanishing white matter disease (patient 14)

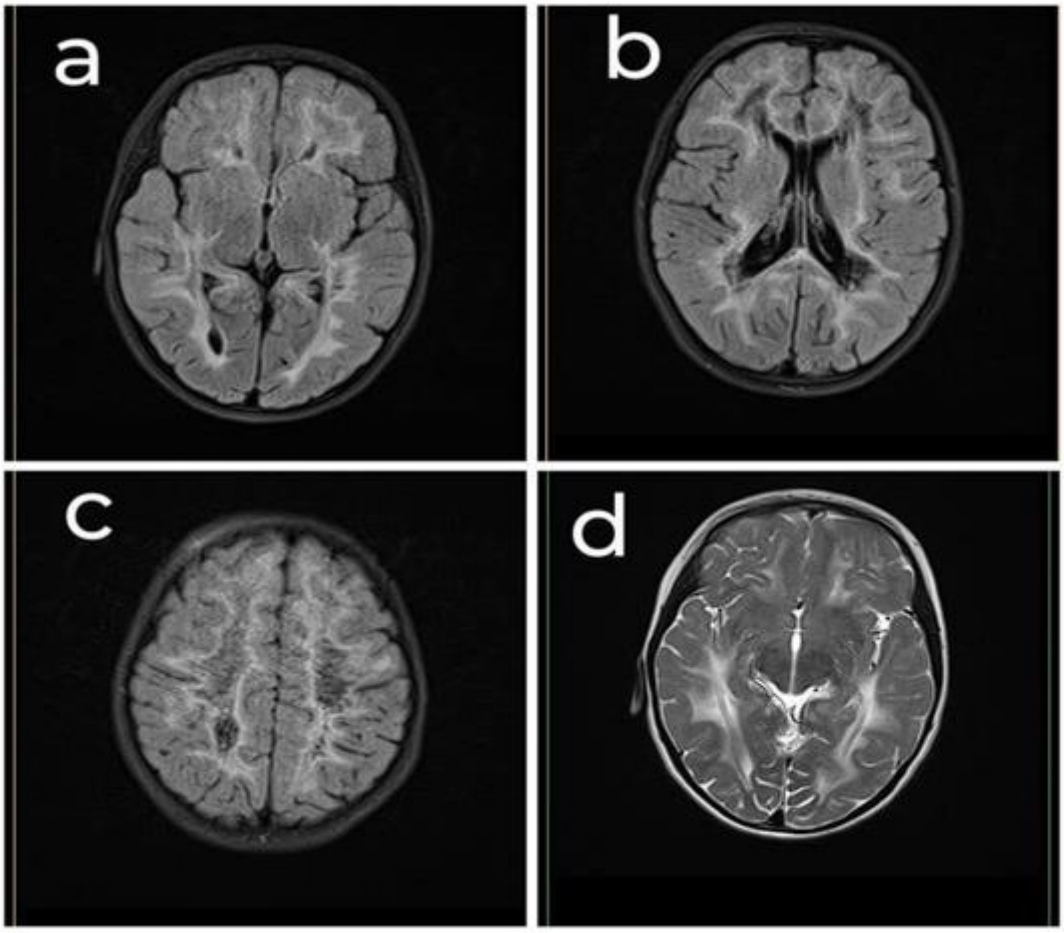

Image a, b & c (Axial FLAIR) showing diffuse symmetric hyperintensities in bilateral cerebral hemispheres with associated cystic degeneration predominantly involving periventricular & bilateral centrum semiovale with sparing of subcortical U-fibers. Image c (Axial T2W) shows hyperintensities along bilateral temporo-occipital regions.

Referenc

1. Köhler W, Curiel J, Vanderver A. Adulthood leukodystrophies. Nature Reviews Neurology. 2018 Feb;14(2):94-105.
2. Vanderver A, Prust M, Tonduti D, Mochel F, Hussey HM, Helman G, et al. Case definition and classification of leukodystrophies and leukoencephalopathies. Molecular Genetics and Metabolism. 2015;114:494-500.
3. Powers JM. The leukodystrophies: overview and classification. Myelin biology and disorders. 2004 Jan 1:663-90.

4. Bonkowsky JL, Nelson C, Kingston JL, Filloux FM, Mundorff MB, Srivastava R. The burden of inherited leukodystrophies in children. Neurology. 2010 Aug 24;75(8):718-25.
5. Perlman SJ, Mar S. Leukodystrophies. Neurodegenerative Diseases. 2012 Jan 1:154-71.
6. Kohlschütter A, Eichler F. Childhood leukodystrophies: a clinical perspective. Expert review of neurotherapeutics. 2011 Oct 1;11(10):1485-96.
7. Ashrafi MR, Amanat M, Garshasbi M, Kameli R, Nilipour Y, Heidari M, et al. An update on clinical, pathological, diagnostic, and therapeutic perspectives of childhood leukodystrophies. Expert Review of Neurotherapeutics. 2020;20(1):65-84.
8. Orchard PJ, Tolar J. Transplant outcomes in leukodystrophies. In: Seminars in Hematology. WB Saunders; 2010. p. 70-78.
9. Eichler F, Van Haren K. Immune response in leukodystrophies. Pediatric neurology. 2007 Oct 1;37(4):235-44.
10. Waldman AT. Leukodystrophies. CONTINUUM: Lifelong Learning in Neurology. 2018 Feb 1;24(1):130-49.
11. Miranda CO, Brites P, Sousa MM, Teixeira CA. Advances and pitfalls of cell therapy in metabolic leukodystrophies. Cell transplantation. 2013 Feb;22(2):189-204.
12. Matthes F, Andersson C, Stein A, Eistrup C, Fogh J, Gieselmann V, et al. Enzyme replacement therapy of a novel humanized mouse model of globoid cell leukodystrophy. Experimental Neurology. 2015;271:36-45.
13. Biffi A, Aubourg P, Cartier N. Gene therapy for leukodystrophies. Human molecular genetics. 2011 Apr 15;20(R1):R42-53.
14. Aerts-Kaya F, van Til NP. Gene and cellular therapies for leukodystrophies. Pharmaceutics. 2023 Oct 24;15(11):2522.
15. Gulati S, Jain P, Chakrabarty B, Kumar A, Gupta N, Kabra M. The spectrum of leukodystrophies in children: Experience at a tertiary care centre from North India. Annals of Indian Academy of Neurology. 2016 Jul 1;19(3):332-8.
16. Zhang J, Ban T, Zhou L, Ji H, Yan H, Shi Z, et al. Epilepsy in children with leukodystrophies. Journal of Neurology. 2020;267:2612-8.
17. Mahdieh N, Soveizi M, Tavasoli AR, Rabbani A, Ashrafi MR, Kohlschütter A, et al. Genetic testing of leukodystrophies unraveling extensive heterogeneity in a large cohort and report of five common diseases and 38 novel variants. Scientific Reports. 2021;11(1):3231.
18. Alfadhel M, Almuqbil M, Al Mutairi F, Umair M, Almannai M, Alghamdi M, et al. The leukodystrophy spectrum in Saudi Arabia: epidemiological, clinical, radiological, and genetic data. Frontiers in Pediatrics. 2021;9:633385.
19. Groeschel S, Kehrer C, Engel C, í Dali C, Bley A, Steinfeld R, et al. Metachromatic leukodystrophy: natural course of cerebral MRI changes in relation to clinical course. Journal of Inherited Metabolic Disease. 2011;34:1095-102.
20. Cousyn L, Law-Ye B, Pyatigorskaya N, Debs R, Froissart R, Piraud M, et al. Brain MRI features and scoring of leukodystrophy in adult-onset Krabbe disease. Neurology. 2019;93(7)e647-52.
21. Ashrafi MR, Amanat M, Garshasbi M, Kameli R, Nilipour Y, Heidari M, et al. An update on clinical, pathological, diagnostic, and therapeutic perspectives of childhood leukodystrophies. Expert Review of Neurotherapeutics. 2020;20(1):65-84.

22. Kristjánsdóttir R, Uvebrant P, Lekman A, Månsson JE. Cerebrospinal fluid markers in children with cerebral white matter abnormalities. Neuropediatrics. 2001 Aug;32(04):176-82.
23. Groeschel S, Kehrer C, Engel C, í Dali C, Bley A, Steinfeld R, et al. Metachromatic leukodystrophy: natural course of cerebral MRI changes in relation to clinical course. Journal of Inherited Metabolic Disease. 2011;34:1095-102.
24. Nowell AM, Grossman RI, Hackney DB, Zimmerman RA, Goldberg HI, Bilaniuk LT. MR Imaging of White Matter Disease in Children. AJNR American Journal of Neuroradiology. 2004;9(4):503-9.