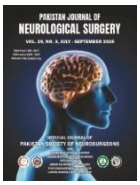

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Original Research

Clinical and Radiological Evaluation of Pediatric Leukodystrophies: A Prospective Study from a Tertiary Care Center in Pakistan

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ABSTRACT

Objective: To evaluate the clinical and magnetic resonance imaging (MRI) characteristics of pediatric patients with leukodystrophies and assess the diagnostic value of MRI in a low-resource setting.

Materials & Methods: This prospective observational study was conducted at the Department of Radiology, Lady Reading Hospital, Peshawar, Pakistan, between January and November 2024. A total of 165 children under 14 years of age with clinically suspected leukodystrophies were included. MRI was performed using a 1.5 Tesla scanner and interpreted independently by two experienced radiologists. Radiological patterns were analyzed and correlated with clinical presentations. Statistical analysis assessed associations between imaging findings and specific symptoms.

Results: Of the 165 patients, the mean age was 5.8 years, with a slight male predominance. Spasticity (74%), developmental delay or regression (65%), and seizures (42%) were the most common clinical presentations. MRI revealed bilateral symmetrical white matter abnormalities in 80% of cases. Metachromatic leukodystrophy showed frontal white matter involvement with U-fiber sparing; adrenoleukodystrophy demonstrated occipital changes with contrast enhancement; and Krabbe disease exhibited a tigroid pattern with thalamic and cerebellar involvement. Contrast enhancement was significantly associated with neuroregression ($p = 0.01$), while cerebellar atrophy correlated with seizures ($p = 0.03$).

Conclusion: MRI provides critical diagnostic value for leukodystrophies in pediatric populations, especially in resource-limited environments. Recognizing characteristic imaging patterns facilitates early diagnosis, aiding timely intervention and improving outcomes.

Keywords: Leukodystrophies, MRI, Pediatric neuroimaging, Metachromatic leukodystrophy, Adrenoleukodystrophy, Krabbe disease.

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INTRODUCTION

Leukodystrophies are a group of inherited, progressive neurodegenerative disorders primarily affecting the white matter of the central nervous system (CNS).[1] These disorders are characterized by defects in the formation, maintenance, or degradation of myelin, a critical component in the efficient transmission of electrical signals along nerve fibers. Disruption of myelin integrity leads to impaired neural function, manifesting in a broad range of clinical symptoms. Leukodystrophies commonly present in infancy or early childhood and usually follow a progressive course that results in significant neurological disability and early mortality.[2]

Although individually rare, the collective incidence of leukodystrophies is approximately one in seventy-six hundred live births. This burden is likely underestimated, especially in low- and middle-income countries where diagnostic resources are limited.[3] Among the most recognized leukodystrophies are metachromatic leukodystrophy (MLD), adrenoleukodystrophy (ALD), and Krabbe disease. These disorders are relatively well-characterized in both clinical and radiological contexts, making them useful prototypes for the broader group of leukodystrophies.[4]

Clinically, leukodystrophies can present with a wide array of symptoms that vary based on age of onset, disease subtype, and rate of progression. Common manifestations in the pediatric population include global developmental delay, regression of acquired milestones, spasticity, seizures, behavioral disturbances, and deficits in vision or hearing. The disease trajectory may be insidious or rapid, often culminating in profound neurocognitive and motor impairments.[5] A detailed clinical history including consanguinity, family history of similar illnesses, and the age of symptom onset is essential but rarely sufficient for a definitive diagnosis.[6]

Magnetic resonance imaging (MRI) plays a pivotal role in the early identification and characterization of leukodystrophies. Compared to computed tomography, MRI provides superior resolution of white matter changes and is more sensitive to early demyelination. Characteristic MRI findings may help in narrowing the differential diagnosis and can, in certain cases, be pathognomonic.[7] For instance, MLD typically presents with symmetrical T2-weighted hyperintensities in the periventricular white matter, beginning in the frontal lobes with sparing of subcortical U fibers in early stages. In ALD, especially the childhood cerebral form, early changes appear in the parieto-occipital white matter, often with contrast enhancement at the leading edge of the lesion, reflecting active demyelination.[8] Krabbe disease is identified by a distinctive tigroid pattern due to patchy myelin loss, along with thalamic and cerebellar involvement.

Imaging not only aids in diagnosis but may also offer prognostic information. Contrast enhancement on MRI indicates disruption of the blood-brain barrier and active inflammation, which may correlate with rapid clinical progression.[9] Involvement of infratentorial structures, such as the brainstem and cerebellum, is associated with more severe motor dysfunction. Advanced MRI techniques, including diffusion-weighted imaging, spectroscopy, and diffusion tensor imaging, may offer additional insights, although they are not always accessible in routine clinical settings.[10]

While imaging is invaluable, genetic and biochemical tests remain the gold standard for diagnosis. These include enzyme assays, very long chain fatty acid levels, and molecular genetic testing through next-generation sequencing. However, the cost and limited availability of these tests in many public-sector hospitals restrict their use. As a result, clinical and radiological correlation becomes essential in resource-limited environments.

Therapeutic options for leukodystrophies remain limited. Most forms lack a definitive cure,

and treatment is primarily supportive, focusing on managing symptoms, preventing complications, and improving quality of life. Selected cases of ALD and MLD may benefit from hematopoietic stem cell transplantation if performed at a presymptomatic or early symptomatic stage. Gene therapy is a developing modality but is still experimental and largely restricted to research settings in developed countries. Consequently, timely diagnosis is crucial for optimizing the effectiveness of the limited therapeutic options available.[11]

In countries like Pakistan, where consanguineous marriages are common, the prevalence of autosomal recessive disorders including leukodystrophies may be relatively higher. Unfortunately, lack of awareness and limited access to diagnostic and genetic facilities often result in misdiagnosis or delayed diagnosis. Many children are mistakenly diagnosed with cerebral palsy, epilepsy, or metabolic encephalopathy. In such settings, MRI serves as a critical diagnostic tool, offering early evidence of disease that may not be clinically apparent.[12]

This prospective observational study was conducted at Lady Reading Hospital, a tertiary care center in Peshawar, Pakistan. The aim of the study was to assess the clinical features and MRI findings in children under the age of fourteen years diagnosed with leukodystrophies. The study focused on well-characterized subtypes, including MLD, ALD, and Krabbe disease. Through a systematic approach combining clinical examination and MRI analysis, the study sought to identify characteristic imaging patterns, evaluate associations with clinical presentations, and develop a framework for early recognition and classification of leukodystrophies.

This research also aimed to highlight the diagnostic challenges in low-resource settings and advocate for the use of pattern-based imaging interpretation in the absence of molecular testing. The inclusion of MRI feature comparison tables and diagnostic pattern summaries is intended to assist clinicians and radiologists in making timely and accurate diagnoses. By promoting structured imaging evaluation and increasing awareness of leukodystrophies, this study aspires to contribute to improved diagnostic accuracy and patient outcomes.

In conclusion, leukodystrophies are a significant category of pediatric neurological disorders with serious implications for diagnosis and long-term care. MRI plays a crucial role in their early identification, particularly in regions with limited access to genetic testing. This study provides a clinical-radiological perspective on leukodystrophies in a pediatric population, with the goal of advancing local diagnostic strategies and contributing to the broader understanding of these complex disorders.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational study was conducted at the Department of Radiology, Lady Reading Hospital, Peshawar, a major tertiary care center in Khyber Pakhtunkhwa, Pakistan. The study period extended from January 2024 to November 2024. Ethical approval was obtained from the Institutional Review Board of Lady Reading Hospital (IRB Approval No 4/LRH/MTI) Written informed consent was obtained from the guardians of all enrolled patients in accordance with institutional and ethical guidelines.

Study Population

A total of 165 pediatric patients were enrolled in the study. All patients were under the age of 14 years and were referred to the radiology department with clinical suspicion of leukodystrophy. Both male and female patients were included. The decision to include a case was based on clinical indicators such as developmental regression, spasticity, seizures,

and family history of similar disorders.

Inclusion criteria were age less than 14 years, clinical suspicion of leukodystrophy, MRI performed at Lady Reading Hospital, and guardian-provided informed consent. Patients were excluded if they had acquired demyelinating disorders such as acute disseminated encephalomyelitis, history of significant perinatal hypoxic injury, infective or traumatic white matter lesions, or incomplete or poor-quality MRI data.

MRI Protocol and Image Review

All MRI examinations were performed using a 1.5 Tesla scanner. The imaging protocol included axial and sagittal T1-weighted images, axial T2-weighted images, fluid-attenuated inversion recovery (FLAIR) sequences, diffusion-weighted imaging (DWI), and post-contrast T1-weighted sequences when indicated.

Each MRI scan was reviewed independently by two consultant radiologists with more than five years of experience in pediatric neuroimaging. In cases of disagreement, a consensus was reached through joint review. Radiologists were blinded to the clinical details during the imaging assessment to reduce bias.

Data Collection

Demographic data including patient age and gender were recorded. Clinical features such as global developmental delay, neurodevelopmental regression, seizures, spasticity, and family history were systematically collected using a structured data sheet. Radiological parameters assessed included symmetry and extent of white matter involvement, predominant lobar involvement (frontal, parietal, temporal, occipital), involvement of deep structures (thalamus, brainstem, cerebellum), presence or absence of contrast enhancement, subcortical U-fiber sparing or involvement, atrophy (cortical or cerebellar), and specific imaging signs such as tigroid pattern.

Statistical Analysis

The data were compiled and analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.0. Descriptive statistics including means, frequencies, and percentages were used to summarize patient demographics and imaging findings. Chi-square test was applied to assess associations between categorical variables. Logistic regression analysis was used to identify potential predictors of specific imaging features. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Clinical Characteristics of Patients with Leukodystrophies

A total of 165 pediatric patients under the age of 14 years were included in this prospective study. The majority of patients were male, with a male-to-female ratio of approximately 1.2 to 1. The mean age at presentation was 5.8 years. The clinical characteristics of the study population are summarized in Table 1. The most frequent presenting complaint was spasticity, observed in 122 patients (74 percent). Developmental delay or regression was reported in 107 patients (65 percent), while 69 patients (42 percent) presented with seizures. A positive family history of similar illness was documented in 47 patients (28 percent).

Table 1: *Clinical Characteristics of Patients with Leukodystrophies.*

Clinical Feature	Number of Patients	Percentage (%)
Developmental Delay/ Regression	107	65
Spasticity	122	74
Seizures	69	42
Family History of Similar Illness	47	28

Comparative MRI Features in MLD, ALD, and Krabbe Disease

MRI findings revealed that bilateral symmetrical white matter involvement was present in 132 patients (80 percent). Specific MRI patterns varied across the different leukodystrophy subtypes. Among the 46 cases diagnosed as metachromatic leukodystrophy (MLD), the predominant finding was frontal white matter involvement with sparing of the subcortical U fibers. Adrenoleukodystrophy (ALD), identified in 23 patients, predominantly involved the occipital white matter with periventricular sparing and frequent contrast enhancement. In Krabbe disease, diagnosed in 13 patients, a characteristic tigroid pattern was observed along with involvement of the thalami and cerebellar structures. These radiological features are detailed in Table 2.

Table 2: *Comparative MRI Features in MLD, ALD, and Krabbe Disease.*

MRI Feature	MLD (n=46)	ALD (n=23)	Krabbe (n=13)
Frontal Predominance	Yes	No	No
Occipital Predominance	No	Yes	No
Periventricular Sparing	No	Yes	No
Tigroid Pattern	No	No	Yes
Brainstem Involvement	Occasional	Occasional	Frequent
Cerebellar Atrophy	Rare	Mild	Common
Contrast Enhancement	Rare	Common	Rare
U-fiber Sparing	Sparing Present	Lost	Sparing Lost

Infratentorial and Enhancement Patterns

Brainstem signal changes were noted in 29 percent of patients, while cerebellar atrophy was seen in 35 percent. Contrast enhancement was documented in 31 cases (19 percent), indicating active demyelination. Subcortical U-fiber sparing was preserved in 18 patients (11 percent), predominantly in early-stage MLD cases, and was lost in advanced ALD and Krabbe disease.

Pattern-Based Diagnostic Summary for Common Leukodystrophies

Table 3 provides a concise diagnostic summary comparing the key clinical and MRI features across the three most common leukodystrophy subtypes. Metachromatic leukodystrophy typically presented between two to five years of age, with frontal white matter hyperintensities and behavioral regression. Adrenoleukodystrophy had a later onset, with adrenal insufficiency and posterior brain involvement. Krabbe disease, presenting in infancy, was associated with rapid progression, feeding difficulties, and thalamic and cerebellar abnormalities on imaging.

Statistical Correlation Between Clinical and Imaging Features

Statistical analysis demonstrated significant associations between clinical symptoms and specific imaging features. Brainstem involvement was significantly associated with the presence of spasticity ($p = 0.02$), while cerebellar atrophy correlated with a higher frequency of seizures

Table 3: *Pattern-Based Diagnostic Summary for Common Leukodystrophies.*

Leukodystrophy	Typical Onset Age	Key MRI Features	Clinical Hallmarks
Metachromatic Leukodystrophy	2–5 years	Frontal white matter hyperintensities, sparing of U-fibers	Regression of milestones, hypotonia, behavioral changes
Adrenoleukodystrophy	4–10 years	Parieto-occipital involvement, contrast enhancement, periventricular sparing	Adrenal insufficiency, vision loss, rapid deterioration
Krabbe Disease	0–6 months	Tigroid pattern, thalamic involvement, cerebellar atrophy	Irritability, stiffness, feeding difficulties

(p = 0.03). Contrast enhancement was significantly linked to patients presenting with acute neurodevelopmental regression (p = 0.01).

These findings underscore the importance of correlating imaging patterns with clinical presentation for early and accurate diagnosis of leukodystrophies in pediatric patients. The compiled data also suggest that distinct radiological features can reliably differentiate between subtypes, even in settings where genetic testing is unavailable.

DISCUSSION

Leukodystrophies represent a heterogenous group of inherited disorders characterized by progressive degeneration of the white matter in the central nervous system due to abnormalities in myelin formation or maintenance. Numerous studies have attempted to classify and describe their clinical and radiological features to enable early diagnosis and targeted management.[13] This study, conducted in a tertiary care center in Pakistan, provides prospective data from a developing country context and offers comparisons with international literature to better understand the diagnostic role of MRI in resource-limited settings.[14]

Internationally, several studies have described the characteristic imaging patterns associated with leukodystrophies. Van der Knaap et al, were among the first to systematically describe disease-specific MRI patterns, establishing the utility of radiological criteria in narrowing diagnostic differentials.[1] In their extensive review, metachromatic leukodystrophy (MLD) was noted for its frontal predominant white matter changes and U-fiber sparing in early stages, consistent with the findings in this study. Similarly, Krabbe disease exhibited the typical tigroid appearance and involvement of the thalami and cerebellum, features also frequently reported in Asian cohorts.

In contrast, a study by Abdelrahman et al, involving pediatric patients from North Africa reported a higher proportion of atypical imaging patterns and mixed white matter involvement, particularly in late-presenting cases.[15] This suggests regional variability in disease presentation and possibly a broader genetic heterogeneity in populations with higher consanguinity rates, such as Pakistan. The relatively high frequency of adrenoleukodystrophy (ALD) cases in the current study also parallels findings from Middle Eastern registries, where X-linked inheritance patterns and male predominance are emphasized.

Multiple studies have corroborated the utility of contrast enhancement in differentiating active from chronic lesions. For instance, Eichler et al, demonstrated that gadolinium enhancement in ALD correlates strongly with active demyelination and predicts rapid neurological decline.[10] This finding supports the use of contrast-enhanced sequences in routine MRI protocols, especially in patients with rapidly progressing symptoms. The inclusion of contrast sequences in this study highlights its diagnostic and prognostic relevance.

A meta-analysis by Sharma et al. emphasized that cerebellar atrophy, though not pathognomonic, is often a marker of advanced disease and poor prognosis in leukodystrophies.[16] The presence of such features in our cohort underscores the importance of early imaging before irreversible structural damage occurs.

While our findings are consistent with global patterns, the identification of brainstem involvement as significantly associated with motor symptoms mirrors the conclusions drawn by Kassem et al, in their retrospective cohort study, which found brainstem changes to be common in leukodystrophies with pyramidal tract involvement.[17]

Moreover, in resource-rich countries, confirmatory diagnosis of leukodystrophies often involves genetic and enzymatic testing. However, in developing countries, such investigations are rarely available due to cost and infrastructural limitations. As a result, several authors have

advocated for a pattern-recognition approach based on imaging.[18]

The findings of this study have several clinical applications. Firstly, they affirm the diagnostic reliability of MRI in the absence of genetic confirmation. Secondly, the identification of subtype-specific patterns enables clinicians to prioritize cases for referral to genetic counseling or specialized care centers. Thirdly, the recognition of active demyelination through contrast enhancement offers a window of opportunity for emerging treatments, such as hematopoietic stem cell transplantation in early-stage ALD and MLD. Several clinical trials, including those led by Lund et al, have shown that outcomes are significantly improved when intervention is initiated during the contrast-enhancing phase.[19]

This study also highlights the potential for public health integration. Recognizing leukodystrophies as a significant burden in pediatric neurology can support advocacy for neonatal screening programs.[20] Although newborn screening for X-linked ALD has been implemented in several U.S. states, it remains absent in countries like Pakistan. Regional data such as this can serve as a basis for cost-benefit analyses and policy development aimed at early detection.

Furthermore, establishing national or regional leukodystrophy registries can consolidate cases, promote research collaboration, and facilitate access to clinical trials. Initiatives like the Global Leukodystrophy Initiative Clinical Trials Network (GLIA-CTN) have underscored the need for multi-institutional collaboration to develop effective therapeutic strategies.[21] Incorporating imaging criteria as part of such registries can be an efficient first step in developing unified diagnostic pathways.[22]

The benefits of this research extend to medical education and training. The compilation of well-characterized radiological patterns allows for the development of standardized teaching modules, which can enhance diagnostic confidence among radiology residents and neurologists.[23] This is especially relevant in institutions without access to advanced neurogenetic laboratories.

Despite these valuable insights, the study has several limitations. The lack of genetic or biochemical confirmation in most cases limits the ability to definitively categorize all subtypes.[24] While MRI patterns are often suggestive, overlapping features can pose diagnostic challenges. This limitation has been acknowledged in prior literature, where atypical or mixed-pattern leukodystrophies are frequently reported in genetically diverse populations.

Additionally, the study was limited to a single tertiary care center. As a result, the sample may not be representative of the broader population, particularly rural areas with reduced access to MRI. A multicenter design would allow for greater generalizability of findings. Moreover, the study did not assess interobserver variability in MRI interpretation, which is an important factor in real-world radiological practice.

Another limitation is the lack of long-term follow-up data. Since leukodystrophies are progressive, serial imaging and clinical evaluations over time would offer deeper insights into disease trajectory and radiological progression. Longitudinal studies would also enable assessment of treatment response, especially in patients receiving supportive or emerging therapies.

The absence of newborn or sibling screening is also a missed opportunity for early detection. As shown in studies from Western countries, pre-symptomatic diagnosis can dramatically alter outcomes, particularly in conditions like ALD. Incorporating family-based screening protocols could significantly improve prognostic outcomes in future local cohorts.

In conclusion, this study provides valuable comparative data on the imaging patterns of leukodystrophies in children under 14 years in a

resource-limited setting. By correlating radiological features with clinical presentation, it reinforces the utility of MRI as a frontline diagnostic tool in the absence of molecular confirmation. The findings are largely consistent with international literature, affirming the global applicability of imaging-based diagnosis. Future studies should aim for multicenter collaboration, integration of genetic testing, and development of national registries. The ultimate goal is to establish early diagnostic protocols and treatment strategies tailored to the needs and constraints of local healthcare systems.

REFERENCES

1. Wolf NI, Ffrench-Constant C, van der Knaap MS. Hypomyelinating leukodystrophies—Unravelling myelin biology. Nature Reviews Neurology. 2021;17(2):88–103. Doi: 10.1038/s41582-020-00432-1
2. van de Stadt SI, Huffnagel IC, Turk BR, van der Knaap MS, Engelen M. Imaging in X-linked adrenoleukodystrophy. Neuropediatrics. 2021;52(4):252–260. Doi: 10.1055/s-0041-1730937
3. Kundu GK, Islam R, Noor E, Mukib AB. Clinical Spectrum and Neuroimaging Changes in Neurodegenerative Disorder—Experiences in Tertiary Care Hospital of Bangladesh. European Journal of Clinical Medicine. 2021;2(6):10–14. Doi: 10.24018/ejclinicmed.2021.2.6.143
4. Amarnath C, Patel H, Kesvadas C, Thomas B, Jayadevan ER, editors. Comprehensive Textbook of Clinical Radiology Volume II: Central Nervous System. Elsevier Health Sciences; 2023.
5. Malgotra S, Kumar A, Mahajan M. Evaluation of Pediatric Leukodystrophies using Magnetic Resonance Imaging: A Prospective Study from North India. Medical Journal of Dr. DY Patil University. 2023;16(6):962–967.
6. Muthusamy K, Sivadasan A, Dixon L, Sudhakar S, Thomas M, Danda S, Wszolek ZK, Wierenga K, Dhamija R, Gavrilova R. Adult-onset leukodystrophies: a practical guide, recent treatment updates, and future directions. Frontiers in Neurology. 2023;14:1219324.
7. Poursalehi N, Movahedinia M, Mohammadi MH, Ghanei ME, Vahidi Mehrjerdi MY, Kalantar SM. From Clinical Presentation to Genetic Confirmation: A Case of L2HGDH-Related Leukodystrophy in an 11-Year-Old. Neurology Letters. 2025;4(1):53–57. Doi: 10.61186/nl.4.1.53
8. de Vasconcelos P, Lacerda JF. Hematopoietic stem cell transplantation for neurological disorders: a focus on inborn errors of metabolism. Frontiers in Cellular Neuroscience. 2022;16:895511. Doi: 10.3389/fncel.2022.895511
9. Helman G, Orthmann-Murphy JL, Vanderver A. Approaches to diagnosis for individuals with a suspected inherited white matter disorder. Handbook of Clinical Neurology. 2024;204:21–35.
10. Eichler FS, Kuehl JS. Hematopoietic stem cell therapy and ex vivo gene therapy for X-linked adrenoleukodystrophy. Handbook of Clinical Neurology. 2024;202:265–278.
11. Thakkar RN, Patel D, Kioutchoukova IP, Al-Bahou R, Reddy P, Foster DT, Lucke-Wold B. Leukodystrophy imaging: insights for diagnostic dilemmas. Medical Sciences. 2024;12(1):7.
12. Bradbury AM, Ream MA. Recent advancements in the diagnosis and treatment of leukodystrophies. In: Seminars in Pediatric Neurology. 2021;37:100876. Doi: 10.1016/j.spen.2021.100876
13. Mahdieh N, Soveizi M, Tavasoli AR, Rabbani A, Ashrafi MR, Kohlschütter A, Rabbani B. Genetic testing of leukodystrophies… Scientific Reports. 2021;11(1):3231. Doi: 10.1038/s41598-021-82804-7
14. Bonkowsky JL, Keller S, Capal JK, Lotze T, Shellhaas RA, Urion DK, Chen E, Trotter TL, Berry SA, Burke LW, Geleske TA. Leukodystrophies in children: diagnosis, care, and treatment. Pediatrics. 2021;148(3). Doi: 10.1542/peds.2021-060121
15. Baldi C, Bertoli-Avella AM, Al-Sannaa N, Alfadhel M, Al-Thihli K, Alameer S, Elmonairy AA, Al Shamsi AM, Abdelrahman HA, Al-Gazali L, Shawli A, Al-Hakami F, Yavuz H, Kandaswamy KK, Rolfs A, Brandau O, Bauer P.Expanding the clinical and genetic spectra of NKX6-2-related disorder. Clin Genet. 2018;93(5):1087–1092. Doi: 10.1111/cge.13221
16. Sharma S, Sundaram S, Kesavadas C, Thomas B.An algorithmic approach to MR imaging of hypomyelinating leukodystrophies. *J* Magn Reson

Imaging. 2025;61(4):1531–1551. Doi:10.1002/jmri.29558.
17. Kassem H, Wafaie A, Abdelfattah S, Farid T**.** Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL): assessment of the involved white matter tracts by MRI. Eur J Radiol. 2014;83(1):191–6. Doi: 10.1016/j.ejrad.2013.09.023.
18. Alfadhel M, Almuqbil M, Al Mutairi F, et al. The leukodystrophy spectrum in Saudi Arabia… Frontiers in Pediatrics. 2021;9:633385. Doi: 10.3389/fped.2021.633385
19. Miller WP, Mantovani LF, Muzic J, Rykken JB, Gawande RS, Lund TC, et al. Intensity of MRI Gadolinium Enhancement in Cerebral Adrenoleukodystrophy: A Biomarker for Inflammation and Predictor of Outcome following Transplantation in Higher Risk Patients. AJNR Am J Neuroradiol. 2016;37(2):367–372. Doi: 10.3174/ajnr.A4500.
20. Grønbæk-Thygesen M, Hartmann-Petersen R. Cellular and molecular mechanisms of aspartoacylase and its role in Canavan disease. Cell & Bioscience. 2024;14(1):45.
21. Moser AB, Seeger E, Raymond GV. Newborn screening for X-linked adrenoleukodystrophy: past, present, and future. International Journal of Neonatal Screening. 2022;8(1):16. Doi: 10.3390/ijns8010016
22. Biswas A, Malhotra M, Mankad K, Carney O, D'Arco F, Muthusamy K, Sudhakar SV. Clinico-radiological phenotyping and diagnostic pathways in childhood neurometabolic disorders—a practical introductory guide. Translational Pediatrics. 2021;10(4):1201. Doi: 10.21037/tp-21-143
23. Mehmood S. Genetic Studies in Pakistani Families with Hereditary Neurological Disorders.
24. Schoenmakers DH, Beerepoot S, van den Berg S, et al. Expert consensus on endpoints for… Metachromatic Leukodystrophy registry. Orphanet Journal of Rare Diseases. 2022;17(1):48. Doi: 10.1186/s13023-022-02225-y

Additional Information

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Data Availability Statement or data sharing, interested researchers can contact the corresponding authors.

AUTHORS CONTRIBUTIONS

Sr.#	Author's Full Name	Intellectual Contribution to Paper in Terms of:
1	Muhammad Islam	Study design and methodology
2	Sana Jamshid	Paper writing
3	Rimsha Farooq	Data collection and calculations
4	Sumaira Noureen	Analysis of data and interpretation of results
5	Zakir Rahman	Literature review and referencing
6	Intikhab Khalil	Editing and quality insurer