ARTICLE

Clinico-Radiological Correlation of Pediatric Leukodystrophies: MRI Pattern Recognition and Its Association with Clinical Phenotype and Biochemical Findings

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ABSTRACT

Background:

Pediatric leukodystrophies are inherited white-matter disorders with overlapping neurological features. Structured magnetic resonance imaging (MRI) pattern recognition can narrow the differential diagnosis and direct targeted biochemical and molecular testing, particularly where resources are limited.

Methods:

This multicenter cross-sectional study included 92 children from three tertiary-care hospitals in Multan, Pakistan. Clinical phenotype, head circumference, biochemical results and brain MRI findings were recorded. Each MRI was assigned a dominant pattern by anatomical distribution and tissue response, with diagnostic modifiers documented separately, and compared with the final multidisciplinary diagnosis.

Results:

Mean age was 5.7 ± 3.3 years and 58 (63.0%) were boys. Metachromatic leukodystrophy was the commonest diagnosis (21.7%), followed by X-linked adrenoleukodystrophy (17.4%) and Krabbe disease (12.0%). Symmetrical confluent abnormalities occurred in 80.4%. The MRI pattern matched the final diagnostic category in 78 children (84.8%). Biochemical testing in 74 children supported the diagnosis in 60. A characteristic MRI pattern, a supportive biochemical result and a discriminating MRI modifier independently predicted etiological confirmation.

Conclusion:

Combining dominant MRI patterns with clinical and imaging modifiers agreed closely with the final diagnosis and can guide selective investigation in resource-limited hospitals.

Keywords: Leukodystrophy, Magnetic resonance imaging, Pattern recognition, Pediatric neuroradiology

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INTRODUCTION

Leukodystrophies are genetic disorders that mainly affect the formation or maintenance of cerebral white matter. Each is rare, but together they cause substantial progressive motor, cognitive, visual and behavioral disability in children.[1] Current classifications recognize that the primary defect may lie in oligodendrocytes, astrocytes, microglia, axons or specific metabolic pathways, not in myelin alone.[2]

Presentation depends on mechanism, age at onset and pace of progression. Regression, spasticity, hypotonia, ataxia, seizures and visual loss are common but non-specific.[3] Macrocephaly, neuropathy, adrenal dysfunction, deterioration after minor illness or trauma, and the inheritance pattern are more informative.[4] Even so, a confident diagnosis usually requires radiological and laboratory correlation.

MRI is central because the distribution and behavior of white-matter change often reflect the underlying pathology.[5] Review begins by deciding whether myelin was never adequately formed (hypomyelination) or has been lost.[5] Symmetry, confluence, location, anterior–posterior gradient and U-fiber involvement are then assessed, together with the corpus callosum, internal capsules, corticospinal tracts, brainstem, cerebellum, spinal cord and deep gray nuclei.[6]

Metachromatic leukodystrophy typically causes symmetrical periventricular and deep white-matter change with early U-fiber sparing and a tigroid pattern.[7] Cerebral X-linked adrenoleukodystrophy usually starts in the splenium and parieto-occipital white matter, with an enhancing or diffusion-restricting leading edge.[8] Krabbe disease may mimic metachromatic leukodystrophy but more often involves the corticospinal tracts, internal capsules, cerebellum and brainstem.[9] Vanishing white matter disease shows progressive rarefaction and cystic breakdown.[10]

In subcortical-onset disease, head size, deep gray structures and spectroscopy become important. Canavan disease combines macrocephaly, diffuse spongiform change and a high N-acetylaspartate (NAA) peak.[11] Alexander disease shows frontal predominance, a periventricular rim, brainstem involvement and enhancement,[12] while megalencephalic leukoencephalopathy with subcortical cysts (MLC) causes swollen white matter with anterior temporal and frontoparietal cysts.[13]

Mitochondrial leukodystrophies may be tract-selective, rarefying or cavitating.[14] Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) selectively affects the dorsal columns, corticospinal tracts, medullary pathways and cerebellar peduncles.[15,16] Other respiratory-chain disorders show well-defined cavities, middle-layer callosal involvement and marginal diffusion restriction.[14]

Because patterns evolve and overlap, MRI alone cannot establish every diagnosis. A tiered pathway of phenotype, structured MRI, targeted biochemistry and selective molecular testing may be more practical than universal genomic testing in low-resource settings. This study examined dominant MRI patterns and modifiers in children with suspected leukodystrophy and their relationship with phenotype, biochemistry and final diagnosis.

MATERIALS AND METHODS

This multicenter cross-sectional study was conducted in the radiology and pediatric neurology departments of three tertiary-care hospitals in Multan, Pakistan, from July 2024 to December 2025. Institutional review boards of all participating hospitals approved the study, and parents or guardians gave written informed consent. Children aged one month to 16 years with clinical and MRI features suggesting an inherited leukodystrophy were enrolled consecutively; all eligible children during the study period were included, so no formal sample-size calculation was performed. Children with acquired (hypoxic-ischemic, infectious, inflammatory, vascular, toxic, nutritional or neoplastic) white-matter disease, inadequate MRI or incomplete records were excluded, leaving 92 children.

Demographics, head circumference, macrocephaly, consanguinity, family history, age at onset and neurological features were recorded. MRI was performed at 1.5 T with T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted and susceptibility-weighted sequences, with contrast and proton MR spectroscopy when indicated. Two experienced radiologists, blinded to biochemical results, reviewed anonymized studies independently and resolved disagreements by consensus.

Assessment covered myelination, symmetry, confluence, distribution, anterior–posterior predominance, U-fibers, corpus callosum, internal capsules, corticospinal tracts, brainstem, cerebellum, spinal cord (where imaged), deep gray matter, diffusion restriction, swelling, rarefaction, cavitation and enhancement. Rarefaction was FLAIR signal between that of white matter and cerebrospinal fluid (CSF); cavitation was a sharply marginated area of CSF-like signal suppressed on FLAIR. Each case received one dominant pattern, while head size, U-fibers, deep gray disease, callosal pattern, diffusion, enhancement, rarefaction, cavitation and spectroscopy were recorded as modifiers (Table 1).

Operational MRI pattern classification

MRI pattern	Principal MRI features	Main diagnostic correlates
Posterior demyelinating	Confluent parieto-occipital disease with splenial involvement; margin may enhance or restrict diffusion	X-linked adrenoleukodystrophy
Periventricular/tigroid	Symmetrical periventricular and deep disease with early U-fiber sparing; tigroid pattern	Metachromatic leukodystrophy; Krabbe disease
Subcortical/U-fiber predominant	Early subcortical disease; head size, regional predominance, cysts and spectroscopy as modifiers	Canavan disease, Alexander disease, MLC
Tract-selective brainstem/spinal	Symmetrical involvement of long tracts, brainstem pathways or spinal columns	LBSL
Rarefying/cavitating	FLAIR rarefaction or CSF-like cavitation	Vanishing white matter; mitochondrial leukodystrophies
Hypomyelinating	Persistently high T2 signal with near-normal T1 signal	Pelizaeus–Merzbacher spectrum
Indeterminate/mixed	No single dominant pattern	Further metabolic and molecular work-up

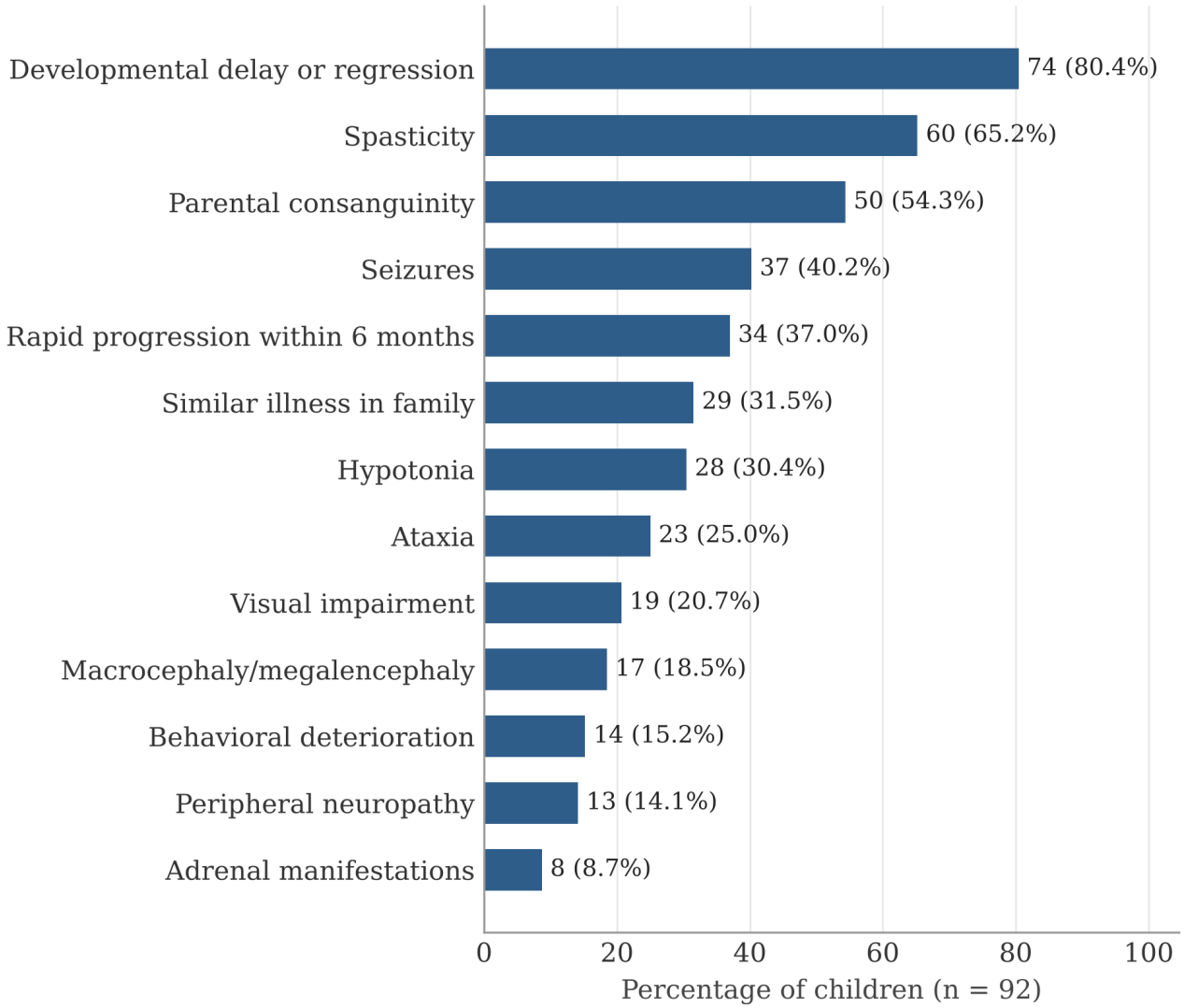
CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; LBSL, leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; MLC, megalencephalic leukoencephalopathy with subcortical cysts; NAA, N-acetylaspartate.

Biochemical tests included arylsulfatase A activity, plasma very-long-chain fatty acids (VLCFA), galactocerebrosidase activity and urinary N-acetylaspartic acid, with serum or CSF lactate when mitochondrial disease was suspected. Available molecular results covered *ARSA*, *ABCD1*, *GALC*, *ASPA*, *GFAP*, *MLC1*, *GLIALCAM*, *DARS2*, *EIF2B1–5* and mitochondrial genes. The final diagnosis was agreed at a multidisciplinary meeting; MRI guided testing but was not treated as confirmation. Etiological confirmation was defined as a disease-specific biochemical and/or molecular result consistent with the final diagnosis.

Data were analyzed in SPSS 26.0. Chi-square or Fisher's exact tests, Cohen's kappa (κ) for inter-reader agreement and multivariable logistic regression were used. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) are reported; $p < 0.05$ was significant.

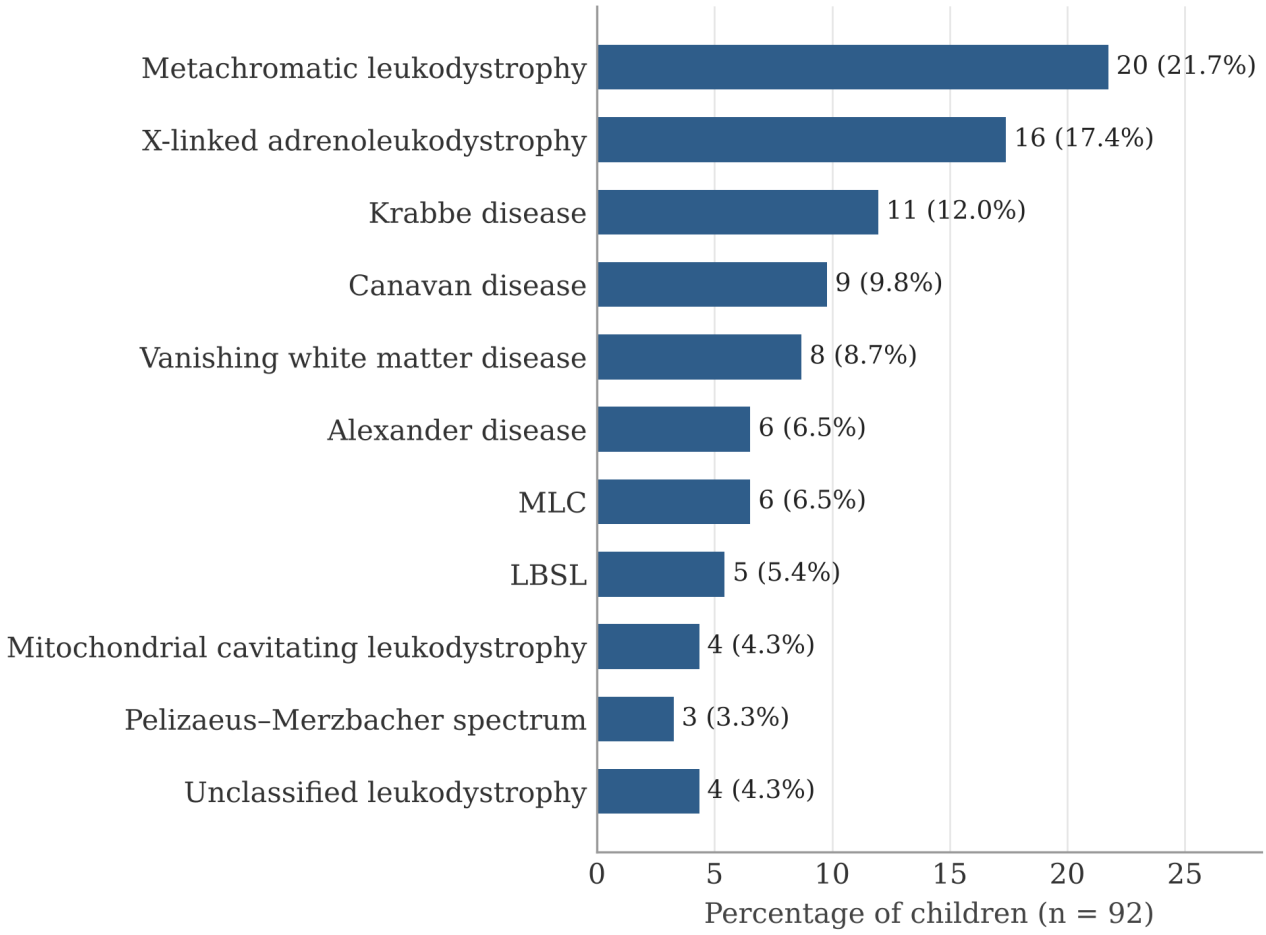
RESULTS

Of 119 children screened, 27 were excluded for acquired injury, poor MRI quality or incomplete data, leaving 92. Mean age was 5.7 ± 3.3 years and mean age at onset 3.2 ± 2.6 years; 63.0% were boys and 57.6% lived in rural areas. Developmental delay or regression (80.4%) and spasticity (65.2%) predominated. Consanguinity was present in 54.3%, an affected relative in 31.5% and macrocephaly in 18.5% (Figure 1).



Clinical characteristics of the participants (n = 92); labels give n (%).

Metachromatic leukodystrophy was the commonest diagnosis, followed by X-linked adrenoleukodystrophy and Krabbe disease (Figure 2). Subcortical disorders included Canavan disease, Alexander disease and MLC. Nine children had mitochondrial phenotypes: five LBSL and four other respiratory-chain leukodystrophies. All children with X-linked adrenoleukodystrophy or Pelizaeus–Merzbacher disease were boys. Four children remained unclassified because no disease-specific diagnosis could be established.



Final multidisciplinary diagnoses (n = 92); labels give n (%). Abbreviations as in Table 1.

Symmetrical confluent abnormalities were present in 74 children (80.4%). The posterior pattern was closely linked to X-linked adrenoleukodystrophy, and the periventricular/tigroid pattern to metachromatic leukodystrophy and some Krabbe cases. Among subcortical disorders, head size, regional predominance, cysts and spectroscopy separated the diagnoses. Tract-selective involvement characterized LBSL, while rarefaction or cavitation occurred in vanishing white matter and respiratory-chain disease. Overall concordance was 84.8% (Table 2).

Dominant MRI patterns, concordance and key modifiers

Final diagnosis	Dominant MRI pattern	Concordant, n/N (%)	Key modifier, n/N
Metachromatic leukodystrophy	Periventricular/tigroid	18/20 (90.0)	U-fiber sparing, 16/20
X-linked adrenoleukodystrophy	Posterior demyelinating	15/16 (93.8)	Marginal enhancement, 9/16
Krabbe disease	Periventricular/tigroid with corticospinal involvement	8/11 (72.7)	Internal capsule/corticospinal involvement, 8/11
Canavan disease	Subcortical/U-fiber predominant	8/9 (88.9)	Macrocephaly or elevated NAA, 8/9
Vanishing white matter disease	Rarefying/cavitating	7/8 (87.5)	Residual radiating strands, 6/8
Alexander disease	Subcortical/U-fiber predominant (frontal)	5/6 (83.3)	Periventricular rim or enhancement, 4/6
MLC	Subcortical/U-fiber predominant	6/6 (100)	Anterior temporal/frontoparietal cysts, 6/6
LBSL	Tract-selective brainstem/spinal	5/5 (100)	Dorsal column/corticospinal involvement, 5/5
Mitochondrial cavitating leukodystrophy	Rarefying/cavitating	3/4 (75.0)	Callosal middle layer or lactate peak, 3/4
Pelizaeus–Merzbacher spectrum	Hypomyelinating	3/3 (100)	Persistent deficient myelination, 3/3
Unclassified leukodystrophy	Indeterminate/mixed	0/4 (0)	Non-specific findings
Overall		78/92 (84.8)	

Biochemical testing in 74 children supported the diagnosis in 60 (81.1%), most often in X-linked adrenoleukodystrophy and Canavan disease. Molecular testing in 31 supported it in 27 (87.1%). Spectroscopy in 19 children showed high NAA in seven of eight with Canavan disease and a lactate peak in four with mitochondrial or LBSL phenotypes (Table 3).

Biochemical and molecular findings by diagnostic group

Diagnostic group	Biochemical testing, n	Supportive biochemical result, n/N (%)	Molecular testing, n	Supportive molecular result, n/N
Metachromatic leukodystrophy	18	15/18 (83.3)	5	4/5
X-linked adrenoleukodystrophy	16	15/16 (93.8)	5	5/5
Krabbe disease	9	6/9 (66.7)	3	2/3
Canavan disease	8	7/8 (87.5)	4	4/4
Vanishing white matter diseasea	4	3/4 (75.0)	3	3/3
Alexander diseasea	4	3/4 (75.0)	3	2/3
MLCa	4	3/4 (75.0)	3	3/3
LBSL	4	3/4 (75.0)	3	3/3
Mitochondrial cavitating leukodystrophy	4	3/4 (75.0)	2	1/2
Pelizaeus–Merzbacher spectruma	3	2/3 (66.7)	0	—
Overall	74	60/74 (81.1)	31	27/31 (87.1)

[a]No disease-specific biochemical marker exists; "supportive" denotes exclusion of competing leukodystrophies on the metabolic panel. Unclassified children received no targeted testing. Abbreviations as in Table 1.

A characteristic MRI pattern, a supportive biochemical result and a discriminating modifier remained independent predictors of etiological confirmation; confluent abnormalities, family history and consanguinity did not (Table 4).

Factors associated with etiological confirmation

Factor	aOR	95% CI	p-value
Characteristic dominant MRI pattern	7.96	2.04–31.06	0.003
Supportive biochemical result	5.82	1.31–25.86	0.021
Highly discriminating MRI modifier	4.16	1.12–15.45	0.033
Symmetrical confluent abnormality	2.71	0.76–9.68	0.125
Positive family history	2.08	0.46–9.48	0.343
Parental consanguinity	1.43	0.39–5.23	0.588

Inter-reader agreement was 87.0% ($\kappa = 0.83$). Of 14 discordant cases, five had late-stage disease obscuring the original pattern, five showed overlapping patterns and four were unclassified. Two children initially labeled metachromatic leukodystrophy were reclassified as Krabbe disease after enzyme testing.

DISCUSSION

The dominant-pattern and modifier approach agreed with the final diagnosis in 84.8% of children, supporting structured MRI as a first diagnostic filter where genomic sequencing cannot be offered to every child.[17]

Metachromatic leukodystrophy usually showed periventricular disease, tigroid stripes and early U-fiber sparing. MRI change progresses with clinical decline, though not always in step with motor loss in advanced disease.[18] Low arylsulfatase A activity should be interpreted with urinary sulfatides or genetics because of pseudodeficiency,[19] and early confirmation matters because gene therapy works best before major deterioration.[20]

Posterior and splenial involvement was strongly linked to cerebral X-linked adrenoleukodystrophy. Marginal enhancement indicates active inflammation and should prompt urgent treatment assessment.[21] Guidelines recommend serial MRI, adrenal monitoring and biochemical confirmation in boys with raised VLCFA or *ABCD1* variants.[22]

Krabbe disease had the lowest concordance because its pattern changes with stage and overlaps with metachromatic leukodystrophy. Internal capsule, corticospinal, cerebellar and brainstem changes may precede extensive supratentorial disease,[23] so galactocerebrosidase activity should be read alongside psychosine and molecular results.[24]

Separating subcortical distribution from macrocephaly improved discrimination among subcortical disorders. Elevated NAA supported Canavan disease, frontal predominance and enhancement favored Alexander disease,[11,12] and swollen white matter with anterior temporal cysts identified MLC better than head size alone.[25]

The tract-selective pattern reliably identified LBSL and was more specific than lactate, which may be absent.[26] Vanishing white matter disease produced diffuse rarefaction with residual strands, whereas mitochondrial disease produced well-defined cavities and callosal involvement.[10,14]

These findings support a tiered strategy in which routine MRI directs a limited number of targeted tests, reducing unnecessary investigation while identifying children who need early treatment, genetic counseling or follow-up. Multicenter consecutive recruitment, widely available 1.5-T imaging and independent double reading strengthen their practical value. Limitations of this study included potential overestimation of MRI concordance, limited molecular testing, non-universal spectroscopy and spinal imaging, a small regression sample, and assessment at a single disease stage.

CONCLUSION

A dominant MRI pattern refined by clinical, anatomical and spectroscopic modifiers agreed closely with the biochemical and multidisciplinary diagnosis. This tiered approach is practical for tertiary hospitals in Pakistan, directing selective testing and limiting unnecessary investigation. Molecular confirmation remains essential for atypical, overlapping or unclassified cases.

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