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CLINICAL HETEROGENEITY OF PEDIATRIC LEUKOENCEPHALOPATHIES: A TEN-CASE SERIES

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ABSTRACT **Background:** Leukoencephalopathies represent a heterogeneous group of disorders characterized by abnormalities of cerebral white matter. Clinical manifestations vary widely and include developmental delay, seizures, movement disorders, and motor impairment. Early recognition of phenotypic patterns is essential for timely diagnosis and management.[1] **Purpose:** To describe the clinical phenotypic spectrum of children presenting with suspected leukoencephalopathy at a tertiary pediatric neurology center. **Methods:** This retrospective case series included ten children presenting with neurological symptoms and neuroimaging evidence of white matter abnormalities. Clinical data including age at presentation, developmental profile, seizure history, neurological examination findings, and neuroimaging patterns were reviewed. **Results:** Ten children aged 7 months to 6 years were included. Global developmental delay was the most common presenting feature (80%), followed by seizures (60%), motor abnormalities including hypotonia or spasticity (50%), and language delay (40%). Additional clinical manifestations included macrocephaly, microcephaly, dystonia, ataxia, and nystagmus. Neuroimaging revealed diverse patterns including hypomyelination, periventricular white matter abnormalities, megalencephalic leukodystrophy with cysts, cerebellar hypoplasia, and structural brain malformations. **Conclusion:** Pediatric leukoencephalopathies demonstrate considerable phenotypic variability. Recognition of characteristic clinical patterns can facilitate early suspicion of white matter disorders and guide further diagnostic evaluation.

KEYWORDS : Leukoencephalopathy, leukodystrophy, pediatric neurology, white matter disorders, clinical spectrum

INTRODUCTION

Leukoencephalopathies comprise a diverse group of neurological disorders characterized by abnormalities affecting cerebral white matter. These conditions may arise from genetic, metabolic, mitochondrial, or inflammatory causes and frequently present during childhood.[1]

The clinical manifestations of leukodystrophies are often heterogeneous and may include developmental delay, seizures, hypotonia, spasticity, movement disorders, and cognitive impairment.[2]

Advances in neuroimaging have significantly improved the ability to identify white matter abnormalities in children with neurological symptoms. Magnetic resonance imaging (MRI) plays a central role in the diagnostic evaluation of suspected leukodystrophies.[3]

Several inherited disorders affecting myelin formation have been described, including hypomyelinating leukodystrophies and demyelinating conditions. These disorders often present with early developmental delay and progressive neurological deterioration.[3]

Some leukodystrophies may also present with additional neurological features such as movement disorders, ataxia, and visual disturbances.[4]

Rare syndromes such as leukoencephalopathy with brain calcifications and cysts illustrate the expanding phenotypic spectrum of white matter diseases.[7]

Certain leukodystrophies may also be associated with systemic manifestations including endocrine abnormalities or epilepsy syndromes.[9]

Despite advances in diagnostic techniques, the phenotypic variability of leukodystrophies often delays recognition and diagnosis. Early identification of characteristic clinical patterns is therefore essential for timely management.[10]

This study aims to describe the phenotypic spectrum of children presenting with suspected leukodystrophy at a tertiary pediatric neurology center.

METHODS

Study Design

A retrospective case series of pediatric patients presenting with suspected leukodystrophy.

Inclusion Criteria

Children were included if they had:

- Neurological symptoms suggestive of white matter disease
- MRI findings demonstrating white matter abnormalities
- Clinical evaluation performed at the pediatric neurology center

Data Collection

Clinical data collected included:

- Age at presentation
- Sex
- Developmental history
- Seizure history
- Neurological examination findings
- Neuroimaging findings

Neuroimaging

Brain MRI findings were reviewed for patterns suggestive of leukodystrophy including hypomyelination, demyelination, white matter volume loss, and structural abnormalities.

RESULTS

Demographic Characteristics

Ten children were included in the study. Age at presentation ranged from 7 months to 6 years, with a predominance of male patients.

Clinical Phenotypes

The most frequent clinical manifestations were:

- Global developmental delay – 80%
- Seizures – 60%
- Motor abnormalities (hypotonia or spasticity) – 50%
- Language delay – 40%
- Additional clinical features included:
- Macrocephaly
- Microcephaly
- Dystonia
- Ataxia
- Nystagmus
- Drooling and bulbar dysfunction

Some children presented with early infantile seizures, while others developed progressive motor impairment and movement disorders.

Neuroimaging Patterns

Brain MRI findings demonstrated diverse patterns including:

- Hypomyelinating leukodystrophy
- Megalencephalic leukodystrophy with subcortical cysts
- Periventricular white matter abnormalities
- Cerebellar hypoplasia
- Ventriculomegaly
- Structural brain malformations including corpus callosum abnormalities

DISCUSSION

Clinical heterogeneity of pediatric leukoencephalopathy

The present series demonstrates that pediatric leukoencephalopathy should not be regarded as a single clinical syndrome. Rather, it encompasses a continuum ranging from developmental and epileptic encephalopathy to predominantly motor, cerebellar, ocular motor, behavioral, and structural brain phenotypes. This clinical heterogeneity is consistent with the expanding recognition of genetic and metabolic disorders presenting as pediatric white-matter disease.[1,2]

Developmental delay was the dominant phenotype in our cohort, occurring in seven of ten children. Developmental impairment is one of the most frequent entry points into the diagnostic pathway for childhood leukodystrophy, although its severity and associated neurological manifestations vary considerably.[1,2]

Seizures were documented in five children. The electroclinical spectrum ranged from focal tonic seizures and recurrent infantile seizures to frequent focal epileptiform abnormalities and modified hypsarrhythmia. This supports the observation that epilepsy can be an important presenting manifestation of inherited white-matter disorders rather than merely a late complication.[1,11]

Motor phenotype and white-matter involvement

Motor dysfunction was heterogeneous, encompassing hypotonia, variable tone, spasticity, motor delay, and ataxia. The coexistence of hypotonia and later pyramidal signs is clinically relevant because different white matter disorders may preferentially or sequentially involve corticospinal and cerebellar pathways.

The child with lower-limb hypotonia and developmental delay demonstrated periventricular/deep white-matter abnormalities accompanied by cerebral atrophy and corpus-callosum thinning. Conversely, the child with appendicular spasticity and opisthotonic posturing demonstrated a more complex structural malformation pattern, including polymicrogyria and dysplastic corpus callosum. Thus, the MRI phenotype may provide an important clue to the anatomical substrate underlying the motor phenotype.

Macrocephaly and megalencephalic leukodystrophy

One of the clearest phenotype–MRI correlations in the cohort was observed in the child with macrocephaly/megalencephaly, mild predominantly motor developmental delay, and seizures. MRI demonstrated megalencephalic leukodystrophy with temporal cystic changes.

This combination illustrates the diagnostic value of integrating head circumference, developmental trajectory, seizure phenotype, and characteristic MRI morphology, rather than interpreting the white-matter abnormality in isolation. Such pattern-based approaches are increasingly emphasized in the evaluation of inherited white-matter disorders.[1,3]

Cerebral atrophy as a major imaging phenotype

Cerebral atrophy was another recurring imaging feature. Frontotemporal atrophy was observed in the two children with developmental delay, language impairment, autism, variable tone, and cortical thumb abnormalities. Mild frontotemporal atrophy was also noted in the child with recurrent seizures.

This finding is important because cerebral atrophy can sometimes be overlooked when evaluating a child for leukodystrophy, particularly when the MRI does not show a classic confluent white-matter pattern. The literature on unclassified white-matter disorders emphasizes that some children initially present with nonspecific or atypical imaging patterns, making longitudinal clinical–radiological correlation particularly important.[2]

Corpus callosum abnormalities

Corpus-callosum abnormalities occurred across several phenotypically different patients, including thinning in children with developmental delay and white-matter abnormalities and dysplasia in the child with polymicrogyria and ventriculomegaly.

Corpus-callosum involvement therefore appeared to be a recurring structural marker rather than a phenotype-specific finding. Its presence alongside white-matter abnormalities, developmental delay, epilepsy, or congenital brain malformations should increase suspicion for an underlying genetic disorder.

Cerebellar and ocular motor phenotype

The most clinically distinct phenotype was observed in the child with nonprogressive cerebellar ataxia, nystagmus, square-wave jerks, head nodding, and mild speech impairment, despite relatively preserved cognition and motor development.

This case emphasizes that inherited white-matter disorders may occasionally present with a predominantly cerebellar–oculomotor phenotype rather than severe global developmental impairment. Recog-nition of this broader spectrum is particularly important because such children may initially be evaluated for isolated cerebellar or ocular motor disorders.

Structural Malformations and Leukoencephalopathy

The child with polymicrogyria, ventriculomegaly, dysplastic corpus callosum, white-matter thinning, and bulky thalami represents a particularly important subgroup in which brain malformation and white-matter abnormalities coexist.

This observation supports a developmental rather than purely degenerative concept of some pediatric leukoencephalopathies. In such cases, abnormalities of neuronal migration, axonal development, and myelination may coexist, producing a complex MRI phenotype.

Atypical acute encephalopathic presentation

The youngest child in the series presented with acute clusters of seiz-ures and low-grade fever, with MRI showing basal ganglia, thalamic, and midbrain abnormalities including diffusion restriction and enhancement. This presentation differs substantially from the more typical chronic developmental phenotype observed in the remainder of the cohort.

This case illustrates an important diagnostic principle: not every genetic white-matter disorder presents with a slowly progressive leukodystrophy phenotype. Acute or episodic encephalopathic presentations can also occur, and clinical context, serial imaging, metabolic investigations, and genomic testing may be required to establish the diagnosis.[1,2,6]

Overall phenotype–MRI relationship

Taken together, our findings suggest three broad clinical-radiological patterns within this small cohort:

1. Developmental–epileptic phenotype: developmental delay with seizures and variable cerebral/white-matter abnormalities.
2. Motor–structural phenotype: hypotonia, spasticity or motor delay associated with white-matter loss, corpus-callosum abnormalities, cerebral atrophy, or congenital malformations.
3. Cerebellar–oculomotor phenotype: ataxia, nystagmus, square-wave jerks and relatively preserved cognition/motor function.

These patterns are not mutually exclusive, but they illustrate the broad clinical spectrum encountered in pediatric white-matter disorders. The increasing recognition of atypical and previously unclassified white-matter disorders reinforces the need for close collaboration between pediatric neurologists, neuroradiologists, metabolic specialists, and genomic laboratories.[2,11]

LIMITATIONS

This study has several limitations. The small sample size limits the ability to generalize findings to larger populations. The retrospective design may have resulted in incomplete documentation of certain clinical features. Additionally, longitudinal follow-up data were not available for all patients.

Future Directions

Future studies involving larger multicenter cohorts are required to better characterize the phenotypic spectrum of pediatric leukodystrophies. Long-term follow-up studies may provide further insight into disease progression and clinical outcomes.

Key Messages

What is already known

- Pediatric leukodystrophies represent a heterogeneous group of disorders affecting cerebral white matter.
- Clinical manifestations commonly include developmental delay, seizures, and motor abnormalities.

What this study adds

- This case series highlights the wide phenotypic variability among children with white matter disorders.

- Global developmental delay and seizures were the most frequent presenting features.

Clinical implications

- Early recognition of phenotypic patterns can facilitate prompt neuroimaging and genetic evaluation.
- Understanding clinical variability aids clinicians in identifying potential leukodystrophy cases.

CONCLUSION

Pediatric leukoencephalopathies demonstrate considerable clinical heterogeneity. Global developmental delay, seizures, and motor abnormalities represent common presenting features. Recognition of these phenotypic patterns can facilitate early identification of white matter disorders and guide appropriate diagnostic evaluation.

Table 1. Phenotypic Spectrum of 10 Children with Leukoencephalopathy

Case No.	Age at Presentation	Clinical Features									
		Developmental Delay	Seizures	Motor Abnormality (Hypotonia/ Spasticity)	Language Delay	Movement Disorder (Dystonia/ Ataxia)	Nystagmus	Head Size (Macrocephaly/ Microcephaly)	Visual Impairment	Behavioral Changes (Autism/ Irritability)	Regression
1	1.0 year	+	+	Hypotonia	+	–	–	Microcephaly	–	+ (Irritability)	+
2	1.5 years	+	+	Hypotonia	+	+ (Dystonia)	+	Normal	–	+ (Irritability)	+
3	2.0 years	+	+	Spasticity	+	+ (Ataxia)	+	Microcephaly	+	+ (Autistic features)	+
4	3.0 years	+	+	Spasticity	+	+ (Dystonia)	–	Normal	+	+ (Irritability)	+
5	1.2 years	+	+	Hypotonia	+	–	+	Macrocephaly	–	–	+
6	0.8 year	+	+	Spasticity	+	+ (Ataxia)	–	Normal	+	+ (Autistic features)	+
7	2.5 years	+	–	Hypotonia	–	–	–	Microcephaly	–	–	–
8	4.0 years	+	+	Spasticity	+	+ (Dystonia)	+	Macrocephaly	+	+ (Irritability)	+
9	2.0 years	+	–	Hypotonia	–	+ (Ataxia)	+	Normal	–	–	–
10	6.0 years	+	–	Spasticity	+	+ (Dystonia)	+	Normal	+	+ (Autistic features)	+

+ = Present ; – = Absent

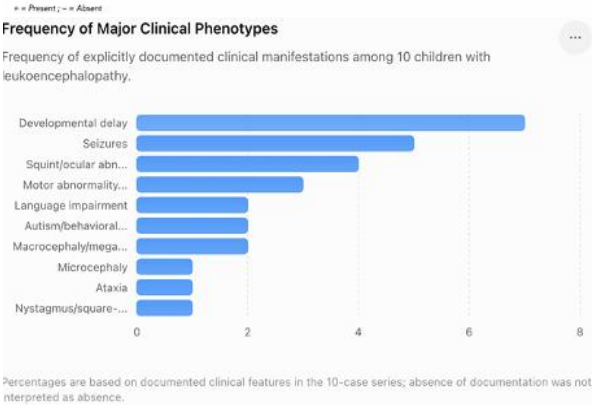

Figure 1. Frequency distribution of major clinical phenotypes in the 10-case leukoencephalopathy series.

REFERENCES

1. Radhakrishnan R, Kralik S, Class J, Sivam S, Sivam I, Patel R. Genetic and metabolic conditions presenting as pediatric leukodystrophies. Semin Ultrasound CT MR. 2025;46(2):92-116.
2. Stutterd CA, Vanderver A, Lockhart PJ, Helman G, Pope K, Uebergang E, et al. Unclassified white matter disorders: a diagnostic journey requiring close collaboration between clinical and laboratory services. Eur J Med Genet. 2022;65(9):104551.
3. Sasaki M. Inherited white matter disorders in Japan: focusing on demyelinating leukodystrophy. Brain Dev. 2025;47(5):104404.
4. Perez Parra S, Heckers SH, Wilcox WR, McKnight CD, Jinnah HA. The emerging neurological spectrum of AARS2-associated disorders. Parkinsonism Relat Disord. 2021;93:50-54.
5. Shimojima K, Okumura A, Ikeno M, Nishimura A, Saito A, Saitsu H, et al. A de novo TUBB4A mutation in a patient with hypomyelination mimicking Pelizaeus–Merzbacher disease. Brain Dev. 2015;37(3):281-285.
6. Elitt CM, Volpe JJ. Degenerative disorders of the newborn. In: Volpe's Neurology of the Newborn. Philadelphia: Elsevier; p.967-1007.
7. Grafstein J, Aoyama Y, Godfrey R, Howe C, Stephen J, Malicdan MC, et al. Leukoencephalopathy, brain calcifications, and cysts (LCC): two unique cases. Rare. 2025;3:100112.
8. Luo S, Lyu Z, Huang H, Zhao J, Li Y, Luo Y. Targeting AARS1-dependent lactylation improves neuronal process plasticity and mitigates cognitive deficits in sepsis-associated encephalopathy. Brain Behav Immun. 2026;135:106493.
9. Herrera-García JD, Guillen-Martínez V, Creus-Fernández C, Mínguez-Castellanos A, Carnero-Pardo C. Epilepsy and ovarian failure: two cases of adolescent-onset ovario-leukodystrophy. Clin Neurol Neurosurg. 2018;165:94-95.
10. Klingelhoefer L, Misbahuddin A, Jawad T, Mellers J, Jarosz J, Weeks R, Chaudhuri KR. Vanishing white matter disease presenting as opsoclonus myoclonus syndrome in childhood. Pediatr Neurol. 2014;51(1):157-164.
11. Gasca Saldaña D, Enríquez Peregrino K, Dávila-Ortiz De Montellano D, Boll Woehrlen M. Genetic leukodystrophies and leukoencephalopathies in a referral center. J Neurol Sci. 2023;455:121845.