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GENETIC SPECTRUM AND PHENOTYPIC VARIABILITY OF PEDIATRIC LEUKOENCEPHALOPATHIES: A CASE SERIES OF TEN CHILDREN

Neuro Science

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ABSTRACT

Background: Pediatric leukoencephalopathies are a heterogeneous group of disorders characterized by abnormalities of cerebral white matter resulting from genetic, metabolic, or mitochondrial defects. Advances in genomic technologies, particularly whole exome sequencing (WES), have significantly improved the identification of underlying genetic etiologies. **Purpose:** To describe the clinical, neuroimaging, and genetic spectrum of children presenting with suspected genetic leukoencephalopathy evaluated by WES at a tertiary pediatric neurology center. **Methods:** This retrospective case series included ten children presenting with developmental delay, seizures, or neurological deficits accompanied by white matter abnormalities on brain magnetic resonance imaging. Clinical characteristics, neuroimaging findings, and genomic data were reviewed. Genetic variants were interpreted according to the American College of Medical Genetics and Genomics guidelines. **Results:** The cohort included ten children aged 7 months to 6 years. Global developmental delay was the most common presenting feature (80%), followed by seizures (60%) and motor abnormalities including hypotonia or spasticity (50%). Neuroimaging demonstrated diverse patterns such as hypomyelination, megalencephalic leukodystrophy with subcortical cysts, periventricular white matter abnormalities, and structural brain malformations. Whole exome sequencing identified pathogenic or likely pathogenic variants in genes including MLC1, ARSA, PYCR2, GJC2, NFIA, and AARS2, while variants of uncertain significance were detected in POLR1A, VPS51, and DIAPH1. Autosomal recessive inheritance predominated in the cohort. **Conclusion:** This series highlights the marked clinical and genetic heterogeneity of pediatric leukodystrophies and emphasizes the diagnostic value of whole exome sequencing in children with unexplained white matter disorders. Early genetic diagnosis facilitates accurate prognostication, genetic counseling, and improved multidisciplinary management.

KEYWORDS

INTRODUCTION

Leukoencephalopathies are a diverse group of neurological disorders characterized by abnormalities of cerebral white matter and may result from genetic, metabolic, or inflammatory etiologies. Advances in neuroimaging and genomic technologies have significantly expanded the understanding of these conditions and improved diagnostic precision.[1]

Genetic leukodystrophies commonly present in childhood with developmental delay, seizures, motor dysfunction, or progressive neurological deterioration. The clinical presentation may overlap among different etiologies, making diagnosis challenging.[2]

Hypomyelinating leukodystrophies represent an important subset of these disorders and include conditions caused by mutations in genes such as POLR1A, PYCR2, and GJC2, among others.[3] The clinical spectrum may include hypotonia, spasticity, intellectual disability, seizures, and cerebellar dysfunction.

Certain genes implicated in mitochondrial and metabolic pathways have also been associated with leukodystrophy phenotypes. For example, mutations in AARS2 have been linked to progressive leukodystrophy with neurological decline and ovarian failure.[4]

Similarly, variants affecting myelin-related proteins such as TUBB4A have been described in patients with hypomyelination mimicking Pelizaeus–Merzbacher disease.[5]

Given the substantial genetic heterogeneity of these disorders, next-generation sequencing techniques, particularly whole exome sequencing, have become essential diagnostic tools.[6] These approaches have facilitated the identification of rare and novel variants responsible for white matter diseases.

In addition to classical leukodystrophies, several rare syndromes including leukoencephalopathy with calcifications and cysts have been described, further expanding the phenotypic spectrum of white matter disorders.[7]

Recent research has also highlighted molecular mechanisms underlying neuronal injury and plasticity in related disorders, including pathways involving aminoacyl-tRNA synthetases.[8]

The clinical presentation of leukodystrophies may also include seizures, endocrine abnormalities, or movement disorders, emphasizing the need for multidisciplinary diagnostic approaches.[9]

Early recognition of genetic white matter disorders is essential for appropriate management, prognostication, and genetic counseling.[10]

This study describes the clinical, radiological, and genetic characteristics of ten children with suspected leukodystrophy evaluated using whole exome sequencing at a tertiary pediatric neurology center.

METHODS

Study Design: A retrospective case series of children evaluated for suspected genetic leukoencephalopathy between 2023 and 2026.

Patient

Children were included if they met the following criteria:

- Developmental delay, seizures, or neurological deficits
- Brain MRI showing white matter abnormalities
- Whole exome sequencing performed for diagnostic evaluation

Clinical Data Collection

Clinical information collected included:

- Age at presentation
- Sex
- Consanguinity
- Neurological symptoms
- Developmental milestones
- Seizure history

Neuroimaging

MRI scans were reviewed for patterns suggestive of leukodystrophy including:

- Hypomyelination
- Demyelination
- White matter volume loss
- Structural brain abnormalities

Genetic Testing

Whole exome sequencing was performed using next-generation sequencing platforms. Variants were interpreted according to ACMG guidelines, and pathogenicity classification was assigned as:

- Pathogenic
- Likely pathogenic
- Variant of uncertain significance

RESULTS

Demographic Characteristics

- Ten children were included in the study. The age at evaluation ranged from 7 months to 6 years, with a predominance of males.
- Consanguinity was reported in several cases, suggesting autosomal recessive inheritance in many patients.

Clinical Features

The most common presenting symptoms included:

- Global developmental delay – 80%
- Seizures – 60%
- Motor abnormalities (hypotonia or spasticity) – 50%
- Language delay – 40%
- Autism spectrum features – 20%

Additional findings included microcephaly, macrocephaly, nystagmus, and movement disorders.

Neuroimaging Findings

MRI demonstrated diverse patterns including:

- Hypomyelinating leukodystrophy
- Megalencephalic leukodystrophy with cysts
- Periventricular white matter abnormalities
- Cerebellar hypoplasia
- Basal ganglia calcifications
- Structural brain malformations

Genetic Findings

Whole exome sequencing identified variants in several genes associated with leukodystrophy and neurodevelopmental disorders.

Pathogenic or likely pathogenic variants were detected in genes including:

- MLC1
- ARSA
- PYCR2
- GJC2
- NFIA
- AARS2

Variants of uncertain significance were observed in genes such as:

- POLR1A
- VPS51
- DIAPH1

Most disorders followed autosomal recessive inheritance, reflecting the high prevalence of consanguinity in the cohort.

DISCUSSION

This case series highlights the clinical and genetic heterogeneity of pediatric leukodystrophies. White matter disorders encompass a broad spectrum of conditions with overlapping clinical features, making diagnosis challenging.[11]

Global developmental delay and seizures were the most common presenting features in our cohort, consistent with previous reports describing similar phenotypic patterns in children with leukodystrophies.[1]

Hypomyelinating leukodystrophies accounted for a substantial proportion of cases in this series, particularly those associated with PYCR2 and GJC2 mutations. These disorders are characterized by defective myelin formation and often present with hypotonia, developmental delay, and progressive neurological impairment.[3]

The identification of MLC1 mutations in one patient with macrocephaly and subcortical cysts aligns with previously described cases of megalencephalic leukodystrophy.

Similarly, the presence of ARSA mutations highlights the importance of considering metachromatic leukodystrophy in children presenting with progressive neurological symptoms.

Variants in AARS2 have been associated with mitochondrial dysfunction and leukodystrophy, reflecting the growing recognition of mitochondrial mechanisms in white matter disorders.[4]

The detection of variants of uncertain significance underscores the limitations of current genomic interpretation and emphasizes the need for further functional studies and genotype–phenotype correlation.

Despite advances in genetic testing, a subset of patients with leukodystrophy remains genetically undiagnosed, suggesting the existence of additional yet-unidentified genes or regulatory variants.

Multidisciplinary collaboration between neurologists, geneticists, and radiologists is essential to improve diagnostic accuracy and patient care.[2]

Key Messages

What is already known on this topic

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

What this study adds

- This case series demonstrates the wide genetic spectrum of leukodystrophies identified using whole exome sequencing.
- Multiple genes including MLC1, PYCR2, ARSA, GJC2, NFIA, and AARS2 were identified in children with diverse neuroimaging patterns.

Clinical implications.

- Early use of genomic sequencing in children with unexplained white matter abnormalities can significantly improve diagnostic yield.
- Identification of genetic etiology allows accurate counseling, prognosis assessment, and targeted management strategies.

LIMITATIONS

Several limitations should be considered when interpreting the findings of this study. First, the sample size was relatively small, reflecting the rarity of pediatric leukodystrophies and limiting the ability to draw broader epidemiological conclusions. Second, the retrospective design may have introduced incomplete clinical documentation in some cases. Third, functional validation of variants of uncertain significance was not performed, and segregation analysis was not available for all families. Additionally, whole exome sequencing may not detect certain structural variants, deep intronic variants, or epigenetic abnormalities, which may contribute to undiag-nosed cases.

Future Directions

Future research should focus on multicenter collaborative studies to better characterize the clinical and genetic spectrum of pediatric leukodystrophies. Integration of advanced genomic approaches such as whole genome sequencing, transcriptomic analysis, and functional studies may help clarify the pathogenicity of variants of uncertain significance. Longitudinal studies are also required to better understand disease progression, genotype–phenotype correlations, and potential therapeutic targets in these rare disorders.

CONCLUSION

Pediatric leukodystrophies represent a highly heterogeneous group of disorders with diverse clinical and genetic etiologies. Whole exome sequencing provides a powerful diagnostic tool for identifying the underlying genetic causes of white matter diseases in children. Early genetic diagnosis facilitates targeted management, informs prognosis, and enables appropriate genetic counseling for affected families.

Further research is needed to expand the understanding of genotype –phenotype relationships and to identify novel therapeutic targets in these disorders.

Table 1. Demographic and Clinical Features of the Cohort (n = 10)

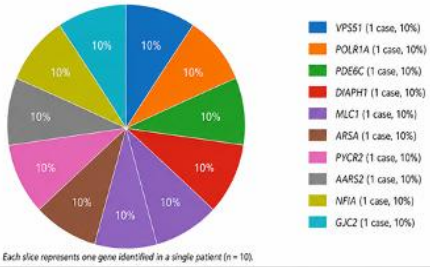
Case	Age at Evaluation	Sex	Consang-uinity	Key Clinical Features	Seizures	Other Neurological Signs	MRI Findings
1	11 months	Male	Present	Developmental delay, jerks	Yes	–	White matter volume loss, ventriculomegaly, thin corpus callosum
2	1 year	Male	Present	Global developmental delay, hypotonia, microcephaly, dysmorphic ears	No	Hypotonia	Periventricular deep white matter hyperintensities, corpus callosum thinning

3	3 years	Female	Not stated	Macrocephaly, mild developmental delay, squint	Yes	–	Megalencephalic leukodystrophy with temporal cysts
4	6 years	Male	Non-consanguineous	Global developmental delay, language impairment, autism, cortical thumb	Yes	Variable tone	Frontotemporal atrophy
5	4 years	Male	Non-consanguineous	Global developmental delay, language impairment, autism	Yes	Cerebellar signs	Cerebellar hypoplasia
6	7 months	Male	Present	Acute cluster seizures, developmental delay	Yes	–	Basal ganglia calcification
7	1 year	Female	Present	Mild developmental delay, tonic seizures	Yes	–	Periventricular white matter demyelination
8	1 year	Male	Non-consanguineous	Recurrent seizures since 5 months	Yes	–	Mild frontotemporal atrophy
9	7 months	Male	Not stated	Developmental delay, drooling, spasticity, dystonia	Yes	Appendicular spasticity	Ventriculomegaly, polymicrogyria, corpus callosum dysplasia
10	7 months	Male	Present	Nystagmus, square wave jerks, ataxia	No	Cerebellar ataxia	Hypomyelinating leukodystrophy

Table 2. Genetic Variants and Inheritance in the Cohort (n = 10)

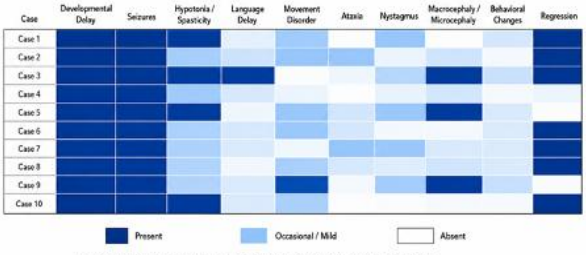
Case	Gene	Variant (HGVS)	Variant Type	Zygosity	ACMG Classification	Associated Disease (OMIM)	Inheritance
1	VPS51	c.2327_2329del (p.Glu776del)	In-frame deletion	Homozygous	VUS	Pontocerebellar hypoplasia type 13	Autosomal recessive
2	POLR1A	c.3754C>G (p.Leu1252Val)	Missense	Homozygous	VUS	Hypomyelinating leukodystrophy 27	Autosomal recessive
3	PDE6C	c.1004+1G>A	Splice-site	Homozygous	Pathogenic	Cone dystrophy 4	Autosomal recessive
4	DIAPH1	c.2855A>G (p.Asn952Ser)	Missense	Homozygous	VUS	Seizures, cortical blindness, microcephaly syndrome	Autosomal recessive
5	MLC1	c.206C>T (p.Ser69Leu)	Missense	Homozygous	Pathogenic	Megalencephalic leukoencephalopathy with subcortical cysts	Autosomal recessive
6	ARSA	c.869G>A (p.Arg290His)	Missense	Homozygous	Pathogenic	Metachromatic leukodystrophy	Autosomal recessive
7	PYCR2	c.751C>T (p.Arg251Cys)	Missense	Homozygous	Likely pathogenic	Hypomyelinating leukodystrophy-10	Autosomal recessive
8	AARS2	c.1571_1579+10del	Splice-site deletion	Heterozygous	Likely pathogenic	Combined oxidative phosphorylation deficiency 8 / progressive leukodystrophy	Autosomal recessive
9	NFIA	c.70C>T (p.Arg24Ter)	Nonsense	Heterozygous	Likely pathogenic	Brain malformations with or without urinary tract defects	Autosomal dominant
10	GJC2	c.392del (p.Pro131fs)	Frameshift deletion	Homozygous	Likely pathogenic	Hypomyelinating leukodystrophy 2 (Pelizaeus-Merzbacher-like disease)	Autosomal recessive

Figure 1. Gene Distribution in 10 Cases of Leukoencephalopathy



Each slice represents one gene identified in a single patient (n = 10).

Figure 2. Phenotypic Spectrum of 10 Leukoencephalopathy Cases



Heatmap represents the presence or absence of major neurological phenotypes in each patient.

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