Case Report

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Paediatrics Section

A Rare Co-existence of POLR1C-related Hypomyelinating Leukodystrophy and Congenital Pulmonary Adenomatoid Malformation in a Child: A Case Report

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ABSTRACT

Hypomyelinating Leukodystrophy 11 (HL-11) and Congenital Pulmonary Adenomatoid Malformation (CPAM) are rare conditions, and their co-occurrence is exceptionally uncommon. The co-occurrence of HL-11 and CPAM in a single patient has not been previously reported in the literature. A seven-year-old boy presented with progressive weakness, tremors, and developmental delay since the age of four and a half years. Developmental milestones, such as independent walking and fine motor skills, like grasping objects, were achieved later than expected for his age. Physically, the child exhibited a lean build, with height and weight in the 25th percentile for his age, and no dysmorphic features. Neuroimaging studies conducted at seven years of age revealed periventricular white matter abnormalities consistent with leukodystrophy. Genetic analysis using whole-exome sequencing identified a heterozygous mutation in the POLR1C gene, confirming HL-11. Due to recurrent pneumonia, High-Resolution Computed Tomography (HRCT) of the chest revealed a CPAM in the right lung. The index case was managed with levetiracetam, pacitane, baclofen, propranolol, occupational therapy, and supportive care. This case underscores the need to consider coexisting diagnoses in children with complex neurological symptoms and atypical respiratory findings, even when a neurological condition has been established, emphasising the importance of comprehensive evaluation for optimised patient management.

Keywords: Lung cysts, Mitochondrial dysfunction, Paediatric neurology, White matter disease

CASE REPORT

A seven-year-old boy presented to the paediatric department with a four-and-a-half-year history of progressive left-sided body weakness. Initial clumsiness progressed to pronounced weakness, which limited activities such as running and playing. By six years of age, assistance was required for tasks like climbing stairs and buttoning clothes. Frequent falls over the past one and a half years, initially attributed to clumsiness, increase in frequency and severity, indicating a balance disturbance. Right-hand tremors emerged over the past year, particularly evident during fine motor tasks. A single generalised tonic-clonic seizure occurred at 1.5 years of age, lasting approximately two minutes.

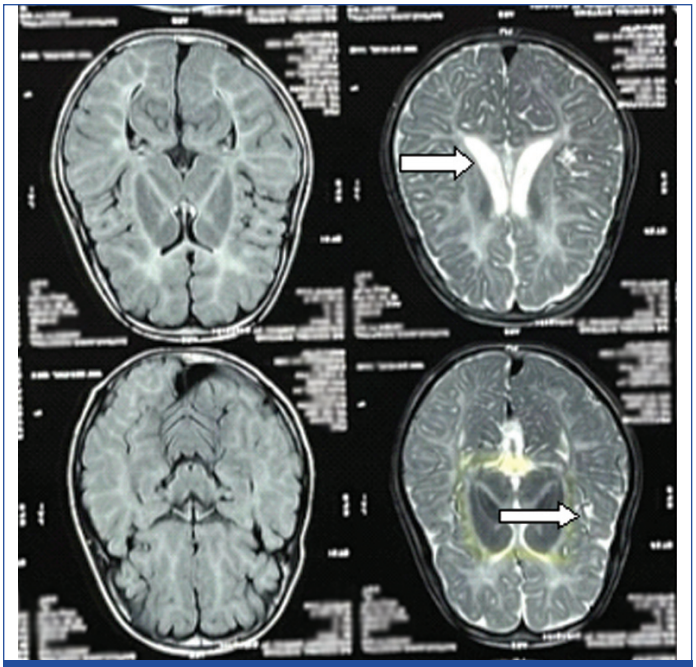
The antenatal history was unremarkable, with no reported maternal comorbidities such as diabetes, hypertension, or infections. Delivery was full-term via spontaneous vaginal mode at 39 weeks' gestation, with no complications. The child's birth history was otherwise uneventful. Developmental milestones were delayed: independent walking began between 2 and 2.5 years (delayed from the typical 12-18 months), the first words were spoken around four years (delayed from the typical 12-18 months), and fine motor skills, such as grasping objects, were achieved later than expected for his age. The child, currently seven years old, was enrolled in nursery school but required additional teacher support due to balance and coordination challenges. Physically, he exhibited a lean built, with height and weight in the 25th percentile for his age, and no dysmorphic features.

Physical examination revealed a head circumference within the normal range for age. Neurological examination demonstrated right upper limb spasticity with cogwheel rigidity, brisk deep tendon reflexes bilaterally (more pronounced on the right), intentional right-hand tremors, left-sided weakness {Medical Research Council (MRC) grade 3/5}, gaze-evoked nystagmus, dysmetria, oculomotor apraxia, and a wide-based, unsteady gait, suggesting cerebellar and motor pathway involvement [1]. On a detailed examination of various systems, only the chest examination had positive findings in the form of decreased air entry on the right side of the chest.

Laboratory investigations, including complete blood count, electrolytes, serum inflammatory markers, and total immunoglobulins, were normal. The electroencephalogram and cerebrospinal fluid analysis showed no abnormalities. Given the progressive weakness, spasticity, tremors, developmental delay, and seizure history, leukodystrophy was suspected. Differential diagnoses included other leukodystrophies (e.g., Pelizaeus-Merzbacher disease, metachromatic leukodystrophy), mitochondrial disorders, and cerebral palsy. These were ruled out by the absence of sulfatide accumulation (metachromatic leukodystrophy), specific PLP1 gene mutations (Pelizaeus-Merzbacher disease), or perinatal hypoxic injury (cerebral palsy), and were confirmed by genetic testing.

Magnetic Resonance Imaging (MRI) of the brain, performed at seven years of age, showed periventricular T2-FLAIR hyperintensities, white matter paucity, cerebellar atrophy, and white matter cysts [Table/Fig-1], consistent with leukodystrophy. Whole-exome sequencing identified a heterozygous mutation in exon 6 of the POLR1C gene, confirming HL-11 [Table/Fig-2]. The child was managed with levetiracetam (30 mg/kg/day) for seizures, pacitane (1 mg tid), and baclofen (2.5 mg BD) for spasticity, propranolol (10 mg HS) for tremors, and physical, occupational, and speech therapy for supportive care, as no cure exists for HL-11.

During the examination, decreased right-sided air entry prompted a chest X-ray, which revealed a radiopaque mass in the right hemithorax. The mass was initially treated as pneumonia with broad-spectrum antibiotics, but it persisted after four weeks. HRCT of the chest demonstrated multiple cystic lesions with bronchiectatic changes in the right lung [Table/Fig-3], consistent with CPAM. The cardiothoracic and vascular surgery department recommended surgical resection, but the family declined due to the child's overall



[Table/Fig-1]: MRI brain showed periventricular T2-FLAIR hyperintensities with white matter paucity, cerebellar atrophy and white matter cyst.

CLINICAL DETAILS

Spasticity and tremors. Suspicion of White matter disorder/Leukodystrophy

FAMILY HISTORY AND PEDIGREE ANALYSIS

- No relevant family history.

RESULT SUMMARY

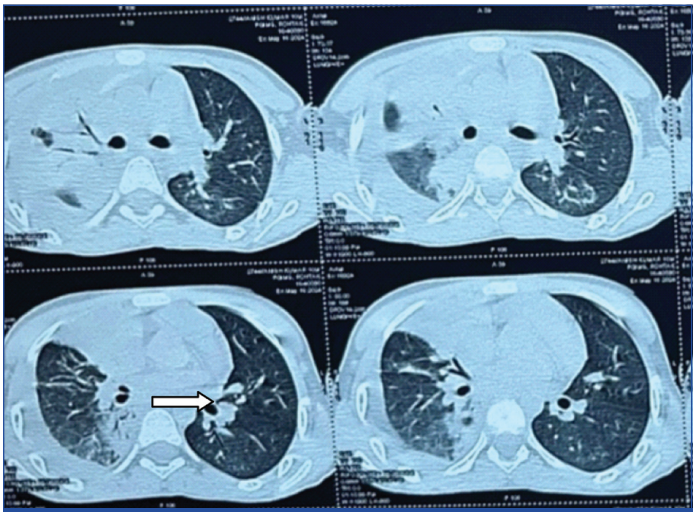
'Variant of Uncertain Significance' (VUS) and 'Likely pathogenic' variant was detected in *POLR1C* gene. (suspected to be compound heterozygous)

VARIANT TABLE

GENE	Genomic location	VARIANT*	EXON	TYPE	ZYGOSITY	CONDITION/ PHENOTYPE GROUP	CLASSIFICATION*
POLR1C	chr6:43487462	NM_203290.3: c.268G>T; p.Glu90*	6	Stop gained	Heterozygous	Leukodystrophy, hypomyelinating, 11	Variant of Uncertain Significance (VUS)
POLR1C	chr6:43488772	NM_203290.3: c.908G>A; p.Arg303Gln	6	Missense	Heterozygous	Leukodystrophy, hypomyelinating, 11	Likely pathogenic

*Clinical correlation recommended

[Table/Fig-2]: Whole exome sequencing revealed a heterozygous mutation in exon 6 of the POLR1C gene.



[Table/Fig-3]: HRCT chest revealed multiple cystic lesions with bronchiectatic changes in the right lung.

health and HL-11 diagnosis. The patient returned six months later with no change in neurological symptoms but with worsening respiratory symptoms and was advised admission; however, the attendants refused this recommendation. Subsequently, during a telephonic follow-up, the father informed that the child had unfortunately succumbed to the illness at home during the night.

DISCUSSION

The HL-11 is a specific subtype of leukodystrophy caused by mutations in the POLR1C gene. This gene encodes the catalytic subunit of mitochondrial RNA polymerase, an essential enzyme for mitochondrial DNA transcription [2]. Disruptions in mitochondrial function due to POLR1C mutations have a significant impact on myelinogenesis, leading to the characteristic neurological decline observed in HL-11 patients. Clinical manifestations of HL-11 typically begin in childhood and include progressive weakness, spasticity, ataxia, seizures, and cognitive decline [3]. While the primary focus of leukodystrophies is on the central nervous system, some rare cases may present with additional organ system involvement.

The CPAM is the most common congenital lung malformation in children. Although CPAM is not directly related to the nervous system, it is another rare congenital disorder affecting approximately 1 in 25,000 births [4]. CPAM arises from abnormal development of the bronchial airways, resulting in cyst formation within lung tissue [5]. While it typically presents with respiratory symptoms in infancy, some cases of CPAM may remain asymptomatic until later childhood, further complicating diagnosis.

This case describes a unique presentation of a child diagnosed with both HL-11 and CPAM. HL-11 is an autosomal recessive leukodystrophy caused by mutations in the POLR1C gene, which encodes a key enzyme involved in mitochondrial DNA (mtDNA) replication [6]. Mitochondrial dysfunction and impaired mtDNA maintenance lead to progressive white matter damage, resulting in the characteristic neurological features observed in our patient. Mutations in the POLR1C gene have been reported to cause a spectrum of clinical presentations, including HL-11, Alpers syndrome, and Mitochondrial Recessive Ataxia with Seizures (MT-RAS). The phenotypic variability is likely due to the specific mutations and the resulting degree of POLR1C enzyme dysfunction [7]. Further research is needed to understand the genotype-phenotype correlations in POLR1C-related disorders.

The co-occurrence of HL-11 and CPAM in this case suggests the possibility of a shared genetic or environmental trigger. CPAM is a congenital malformation of the airways, and the underlying genetic causes are not fully understood. However, several genes have been implicated in CPAM development, including NKX2, SOX2, HOXB5, YY1, FABP7, FGFR2, SPOCK2, and STX11 [8-10]. It is possible that mutations in these genes, or others yet to be identified, could also increase susceptibility to HL-11 or other mitochondrial disorders. While the exact cause of co-occurrence in this case remains unknown, whole-exome sequencing of the patient and their family members could be helpful in elucidating the genetic underpinnings of this complex case. This approach could identify mutations in POLR1C and CPAM-associated genes, as well as any potential modifier genes that influence the phenotypic presentation.

The management of HL-11 remains primarily supportive, focussing on symptomatic relief and optimising quality of life. Antiepileptic medications can be used to control seizures, while physiotherapy and occupational therapy can help manage muscle weakness and improve motor function. Surgical intervention is the mainstay of treatment for CPAM, particularly when it causes significant respiratory symptoms or complications like recurrent infections [11].

CONCLUSION(S)

This case illustrates the importance of evaluating co-existing conditions in children with complex presentations. Neurological symptoms suggested leukodystrophy, while atypical respiratory findings led to the CPAM diagnosis. A thorough workup—including history, examination, imaging, genetic testing, and, when indicated, whole-exome sequencing—is essential for accurate diagnosis and effective management.

REFERENCES

[1] Ciesla N, Dinglas V, Fan E, Kho M, Kuramoto J, Needham D. Manual muscle testing: A method of measuring extremity muscle strength applied to critically ill patients. J Vis Exp. 2011;(50):2632.

[2] Yadav N, Saini J, Nagappa M. Novel mutation in the POLR1C gene causing hypomyelinating leukodystrophy in an adult. Neurol Clin Pract. 2021;11(3):e3670e369.
[3] Charzewska A, Wierzba J, Iżycka-Świeszewska E, Bekiesińska-Figatowska M, Jurek M, Gintowt A, et al. Hypomyelinating leukodystrophies- a molecular insight into the white matter pathology. Clin Genet. 2016;90(4):293-304.
[4] Mehta PA, Sharma G. Congenital pulmonary airway malformation. StatPearls Publishing; 2023.
[5] Sime H, Abera G, Mengistu A, Lamessa S. Congenital pulmonary airway malformation (CPAM): A case report, Jimma University Medical Center, Southwest Ethiopia. Ethiop J Health Sci. 2021;31(4):907-10.
[6] Kraoua I, Karkar A, Drissi C, Benrhouma H, Klaa H, Samaan S, et al. Novel POLR1C mutation in RNA polymerase III-related leukodystrophy with severe myoclonus and dystonia. Mol Genet Genomic Med. 2019;7(9):e914.
[7] Saneto RP, Cohen BH, Copeland WC, Naviaux RK. Alpers-Huttenlocher syndrome. Pediatr Neurol. 2013;48(3):167-78.
[8] Hsu JS, Zhang R, Yeung F, Tang CSM, Wong JKL, So M-T, et al. Cancer gene mutations in congenital pulmonary airway malformation patients. ERJ Open Res. 2019;5(1):00196-2018.
[9] Zhang G, Cai C, Li X, Lou L, Zhou B, Zeng H, et al. Application of second-generation sequencing in congenital pulmonary airway malformations. Sci Rep. 2022;12(1):01-07.
[10] Zhang G, Lou L, Shen L, Zeng H, Cai C, Wu R, et al. The underlying molecular mechanism of ciliated epithelium dysfunction and TGF-β signaling in children with congenital pulmonary airway malformations. Sci Rep. 2024;14(1):01-10.
[11] Singh S, Mishra A, Murthy C, Inban P, Abdefatah Ali M, Yadav AS, et al. Rare case of hypomyelinating leukodystrophy and its management. A case report and literature review. Cureus. 2023;15(3):e36471. Doi: 10.7759/cureus.36471.

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