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Case Report

Hypomyelinating leukodystrophy-10 presenting with an additional atypical feature of increased body hair and Mongolian spots

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ABSTRACT

Hypomyelinating leukodystrophies (HLDs) are genetically heterogeneous disorders. We present the case of a 3.5-year-old male child with global developmental delay, unsteadiness without seizures, episodes of acute encephalopathy, neuroregression, short stature, and microcephaly accompanied by facial dysmorphism and increased hair growth on the forehead, back, and arms. The female sibling of the proband exhibited similar clinical features, excluding the hypertrichosis, but with additional findings of increased Mongolian spots on the back. MRI of the brain revealed bilateral white matter hyperintensities in the frontal and parietal regions of the cerebral hemispheres. Additional findings in the sibling included a diffusely hypoplastic corpus callosum and prominent lateral ventricles. Whole-exome sequencing identified a likely pathogenic homozygous variant in exon 6 of the PYCR2 gene, which is associated with HLD10. This case presents findings of a rare subtype of HLD and highlights the role of exome sequencing in shortening diagnostic odyssey of previously undiagnosed childhood HLDs, including those with atypical clinical presentations.

Keywords: Leukodystrophy, Hypomyelination, Demyelination, Whole exome sequencing

INTRODUCTION

Hypomyelinating leukodystrophies (HLDs) are characterized by a paucity in myelin development. These genetically heterogeneous disorders typically present during the infantile period but exhibit a spectrum of severity ranging from severe, rapidly progressive infantile forms to mild, slowly deteriorating adult-onset cases. Pelizaeus-Merzbacher disease (PMD) is the most common congenital HLD. The diagnosis of specific HLDs relies on differentiating neurological and non-neurological symptoms, brain MRI findings, and genetic testing.[1,2]

The concept of hypomyelinating disorders was introduced by Schiffmann, van der Knaap, and colleagues, who identified their characteristic magnetic resonance imaging (MRI) appearance: the absence of T2 hypointensity without significant loss of T1 hyperintensity.[3] Associated findings can include cerebellar atrophy and a hypoplastic corpus callosum, although their presence varies among cases. A HLD diagnosis is confirmed when two MRIs performed at least six months apart after the age of one year show no significant improvement in myelination. These disorders may result from a primary defect in myelin formation or from primary neuronal diseases leading to secondary hypomyelination.

CASE REPORT

A 3.5-year-old male child, the firstborn of a third-degree consanguineous couple, was referred from the department

of pediatrics for evaluation of global developmental delay and unsteadiness. He was delivered vaginally with a birth weight of 2.5 kg following an uneventful immediate postnatal period. According to the parents, there were no reported seizures, episodes of acute encephalopathy, neuroregression, or hearing and visual disturbances. However, the child lacked awareness of bladder and bowel habits. On examination, his length was at -4 SD, weight at -2.5 SD**,** and head circumference at -4 SD. Facial dysmorphism was observed, characterized by increased hair over the small ears with anteverted earlobes, prominent eyebrows, down-slanting prominent eyes, a bulbous nasal tip, a smooth philtrum, and a prominent chin (Figures 1 A-C). Additionally, there was increased hair over the forehead, back and arms. Examination of the neck, chest, spine, and extremities was normal. Systemic examination revealed a conscious but restless child with involuntary movements. Eye contact and responsiveness to sounds were intact. Muscle tone and reflexes were normal. Other systems examination was normal.

The female sibling exhibited similar facial features, although slightly less coarse than those of the proband (Figures 1 D and E). She did not have increased hair but had additional findings of increased Mongolian spots over her back (Figure 1 F). On anthropometric measurements, her length was at -3.5 SD, weight at -4 to -4.5 SD, and head circumference at -2 SD.

MRI brain of both siblings showed bilateral white matter hyperintensities in the frontal and parietal regions of the cerebral hemispheres (Figure 2 A), diffusely hypoplastic corpus callosum and prominent lateral ventricles in younger (female) sibling (Figures 2 B and C). They had normal hearing and eye evaluations. A skeletal survey was normal except for decreased bone age in both. Abdominal ultrasound and 2D echocardiogram were also normal for both. Based on the history, clinical findings, and investigative results, a presumptive diagnosis of an autosomal recessive neurodevelopmental genetic disorder was made.

Whole-exome sequencing from peripheral blood leukocyte DNA of the elder sibling identified a likely pathogenic homozygous variant, c.751C>T (p.Arg251Cys)**,** in exon 6 of the PYCR2 gene [NM_013328], which is associated with HLDs10. The variant is not present in population databases like 1000 genome (https://www.internationalgenome.org/1000-genomes-browsers/), and genome aggregation database (gnomAD) (https://gnomad.broadinstitute.org/). It is reported as pathogenic in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), human gene mutation database (HGMD) http://www.hgmd.cf.ac.uk/ac/index.php). It has a CADD score of 31, and its pathogenicity is supported by ACMG criteria: PM1, PP3, and PP5. The same homozygous variant was identified in the sister by sanger sequencing.

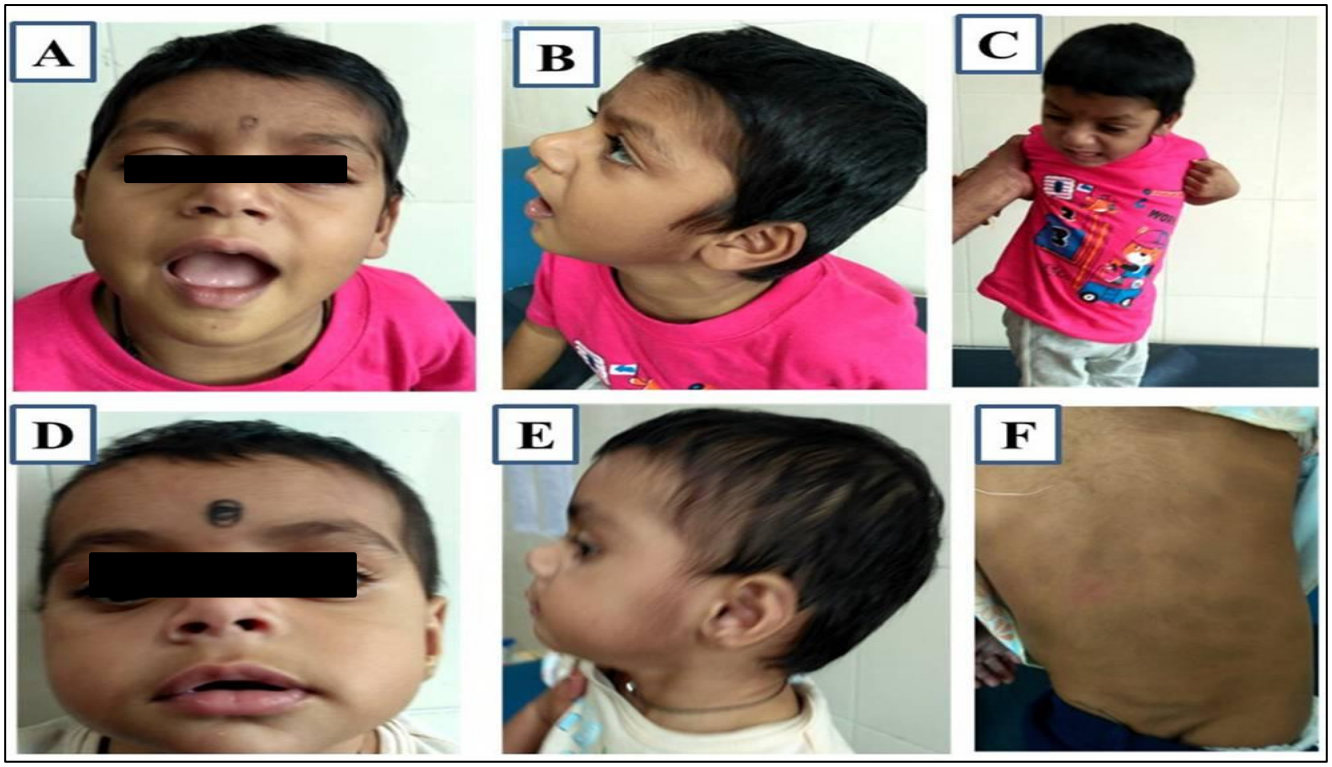

Figure 1 (A-F): Depicts clinical features of siblings. Facial dysmorphism of the 1st child in the form of increased hair over forehead, small ears and anteverted ear lobules, prominent eyebrows and down slanting prominent eyes, bulbous nasal tip, smooth philtrum and prominent chin. Female sibling with similar facial features but slightly less coarse. Female sibling with increased Mongolian spots over the back.

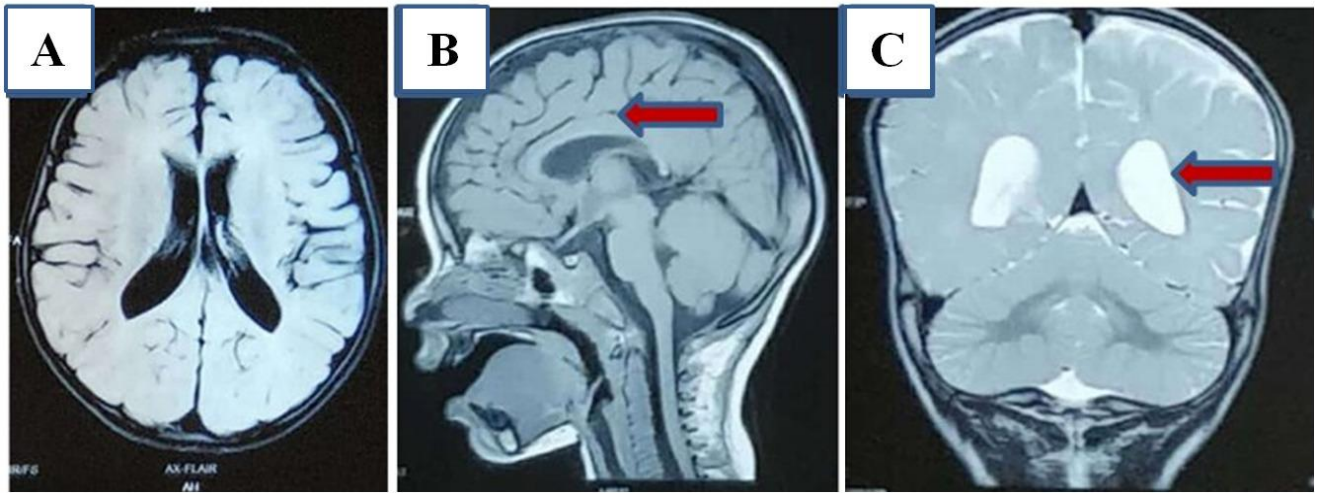

Figure 2 (A-C): MRI brain findings in two siblings. Bilateral white matter hyperintensity in fronto-parietal regions in both children on T1 weighted MRI brain. MRI brain showing diffuse hypoplastic corpus callosum in the female sibling. Prominent lateral ventricles on T2 weighted MRI brain in the female sibling.

Table 1: The comparable and differentiating clinical features of previously reported PYCR2 associated HLD and our case.

Clinical features	Previously reported cases	Our case
Symptoms		
Developmental delay	+	+
Intellectual disability	+	+
Seizures	+/-	-
Hyperkinetic movements	+/-	+
Hearing loss	+/-	-
Signs		
Facial dysmorphism	+	+
Nystagmus/strabismus	+/-	-
Dental abnormalities	+/-	-
Increased body hair	-	+
Increased Mongolian spots	-	+
Arachnodactyly	+/-	-
Hyperextensible distal joints	+/-	-
Pectus carinatum	+/-	-
Muscle atrophy/wasting	+	-
Systemic examination		
Hypertonia	+	-
Brisk reflexes	+	-
MRI brain		
Hypomyelination	+	+
Cerebral atrophy	+/-	-
Thin corpus callosum	+	+
Prominent lateral ventricles	-	+
Other findings		
Congenital heart disease	+/-	-
Undescended testis	+/-	-

DISCUSSION

Leukodystrophies are a group of rare neurodevelopmental genetic disorders that are either static or progressive. They primarily affect the myelination of the central nervous system, regardless of the structural white matter component involved, the molecular processes affected, or the presence or absence of peripheral nervous system

involvement.[4] These disorders exhibit genetic heterogeneity, with autosomal, X-linked, and mitochondrial patterns of inheritance.

Recently, the term "genetic leukoencephalopathy" was introduced by the Global Leukodystrophy Initiative Consortium. This term describes heritable neuronal disorders characterized by secondary hypomyelination but that do not necessarily meet the strict diagnostic criteria for leukodystrophies.[5]

Based on the pathological changes and pathogenetic mechanisms in the white matter components, leukodystrophies are classified into the following categories:[6] a) Disorders due to a primary defect in oligodendrocytes or myelin (e.g., hypomyelinating, demyelinating, and dysmyelinating disorders), b) Astrocytopathies, c) Leuko-axonopathies, d) Microgliopathies, and e) Leukovasculopathies. A common pathogenetic mechanism across these categories is the predominant involvement of oligodendrocytes.

HLDs are a clinically and genetically heterogeneous group of disorders characterized by a deficit in myelin formation. Diagnosis is supported by MRI findings where brain scans, performed at least six months apart in a child aged 1-2 years, show no significant progression in myelination.[3] HLDs represent the largest category of undiagnosed childhood leukodystrophies.

These disorders primarily affect the central nervous system, but other organs may also be involved.[7,8] This group includes Pelizaeus-Merzbacher disease PMD, the prototype of hypomyelinating disorders, and PMD like diseases.

HLD-10 is caused by biallelic pathogenic variants in the PYCR2 gene, which encodes the mitochondrial enzyme pyrroline-5-carboxylate reductase 2. There are three PYCR isozymes, with PYCR1 and PYCR2 being associated with human diseases. This enzyme plays a key role in proline synthesis, an essential amino acid for the central nervous system.[9,10] HLD-10 is characterized by progressive microcephaly, which results from increased apoptosis due to oxidative stress in PYCR2-deficient neuronal cells. Additionally, reduced oligodendroglial differentiation occurs due to impaired activity of enlarged mitochondria.[11]

The differential diagnosis for HLD-10 includes PMD, HLD 6**,** and phosphoglycerate dehydrogenase deficiency.[12,13] Notably, the genes responsible for other HLDs do not share the same biological pathway as the PYCR2 gene.[14]

To date, only 27 cases of HLD-10 have been reported, with the youngest patient being 1 year old and the oldest at 21 years. Among these cases, 15 had nonsense variants and 12 had missense variants**.** A total of 14 pathogenic and likely pathogenic variants (8 missense and 6 nonsense) has been identified, with most of these located in exons 4 and 6.[15,16]

Genotype-phenotype correlations in hypomyelinating disorders are well established only for a few conditions. In HLD-10, hyperkinetic movements were notably more common in patients with protein-truncating variants compared to those with missense variants.[17] Most mutations in PYCR2 associated with HLD-10 are clustered in the dimerization domain of the protein, impairing multimerization. Interestingly, these mutations do not result in proline depletion in the serum. Therefore, PYCR2-associated HLD is a clinically recognizable neuronal disorder that does not involve biochemical alterations.[18]

As per Escande-Beillard et al loss of PYCR2 upregulates serine hydroxymethyltranferase 2 (SHMT2), an enzyme that breaks down serine to glycine and hyperglycinemia has significant role in the pathogenesis of HLD-10. Depletion of SHMT2 to reverse the neuronal injury in these cases is the hope of future.[19]

None of the previously reported cases of PYCR2-associated HLD have survived beyond the first decade of life. Notably, increased body hair and Mongolian spots were not reported in earlier cases of this disorder. Additionally, while spasticity and muscle wasting were observed in previous reports, these features were not present in our case. A comparison of the clinical features of previously reported PYCR2-associated HLD cases and our case is provided in Table 1, highlighting both common and differentiating characteristics.

Leukodystrophies affecting the central nervous system typically present with nonspecific and overlapping symptoms. MRI features characteristic of a specific disorder may not always be present in every patient. MRI scans obtained during childhood are more informative than those obtained in adolescents or adults with hypomyelination disorders, as pattern recognition is more challenging in older individuals.[2]

Magnetic resonance spectroscopy (MRS) is not applicable for diagnosing HLDs, as it does not allow for myelin quantification. According to Steffi F, Dreha-Kulaczewski et al quantitative MRI offers better delineation of undiagnosed or undefined hypomyelinating disorders.[2,20] Ultimately, the definitive diagnosis of hypomyelinating disorders is achieved through molecular genetic testing**.**

CONCLUSION

While MRI brain pattern recognition can be suggestive of certain disorders, the imaging findings often overlap in the advanced stages of disease. With the advent of NGS-based exome sequencing**,** the definitive diagnosis of many previously undiagnosed childhood HLDs has been made and is expected to increase in the near future, even

in cases with atypical features. The candidate gene approach**,** combined with robust tagging, aids in identifying novel variants and genes associated with these disorders, thereby enhancing the diagnostic yield.

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REFERENCES

1. Pouwels PJ, Vanderver A, Bernard G, Wolf NI, Dreha-Kulczewksi SF, Deoni SCL, et al. Hypomyelinating leukodystrophies: translational research progress and prospects. Ann Neurol. 2014;76(1):5-19.
2. Numata Y, Gotoh L, Iwaki A, Kurosawa K, Takanashi J, Deguchi K, et al. Epidemiological, clinical, and genetic landscapes of hypomyelinating leukodystrophies. J Neurol. 2014;261(4):752-8.
3. Schiffmann R, van der Knaap MS. Invited article: An MRI-based approach to the diagnosis of white matter disorders. Neurology. 2009;72(8):750-9.
4. Kevelam SH, Steenweg ME, Srivastava S, Helman G, Naidu S, Schiffmann R, et al. Update on leukodystrophies: a historical perspective and adapted definition. Neuropediatrics. 2016;47(6):349-54.
5. Vanderver A, Prust M, Tonduti D, Mochel F, Hussey HM, Helman G, et al. Case Definition and Classification of Leukodystrophies and Leukoencephalopathies. Mol Genet Metab. 2015;114(4):494-500.
6. Van der Knaap MS, Bugiani M. Leukodystrophies: a proposed classification system based on pathological changes and pathogenetic mechanisms. Acta Neuropathol. 2017;134(3):351-82.
7. Barkovich AJ, Deon S. Reprint of Hypomyelinating disorders: An MRI approach. Neurobiol Dis. 2016;92(A):46-54.
8. Arai-Ichinoi N, Uematsu M, Sato R, Suzuki T, Kudo H, Kikuchi A, et al. Genetic heterogeneity in 26 infants with a hypomyelinating leukodystrophy. Hum Genet. 2016;135(1):89-98.
9. Perez-Arellano I, Carmona-Alvarez F, Martinez AI, Rodríguez-Díaz J, Cervera J, et al. Pyrroline5-carboxylate synthase and proline biosynthesis: from osmotolerance to rare metabolic disease. Protein Sci. 2010;19(3):372-82.
10. Rakotomamonjy J, Rylaarsdam L, Guemez-Gamboa A. PYRC2-Related Hypomyelinating Leukodystrophy: More to This Than Meets the Eye. Neuron. 2020;107(1):3-5.
11. Torii T, Shirai R, Kiminami R, Nishino S, Sato T, Sawaguchi S, et al. Hypomyelinating Leukodystrophy 10 (HLD10)-Associated Mutations of PYCR2 Form Large Size Mitochondria, Inhibiting Oligodendroglial Cell Morphological Differentiation. Neurol Int. 2022;14(4):1062-80.
12. Simons C, Wolf NI, McNeil N, Caldovic L, Devaney JM, Takanohashi A, et al. A de novo mutation in the b-tubulin gene TUBB4A results in the leukoencephalopathy hypomyelination with atrophy of the basal ganglia and cerebellum. Am J Hum Genet. 2013;92(5):767-73.
13. De Koning TJ, Jaeken J, Pineda M, Van Maldergem L, Poll-The BT, van der Knaap MS. Hypomyelination and reversible white matter attenuation in 3-phosphoglycerate dehydrogenase deficiency. Neuropediatrics. 2000;31(6):287-92.
14. Nakayama T, Al-Maawali A, El-Quessny M, Rajab A, Khalil S, Stoler JM, et al. Mutations in PYCR2, Encoding Pyrroline-5-Carboxylate Reductase 2, Cause Microcephaly and Hypomyelination. Am J Hum Genet. 2015;96(5):709-19.
15. Akbari M, Ebrahimi Tapeh Z, Zaersabet M, Rahimi H, Ganji M. Novel pyrroline-5-carboxylate reductase 2 (PYCR2) mutation in an Iranian patient with hypomyelinating leukodystrophy: findings of molecular and in silico investigations. Egypt J Med Hum Genet. 2023;24:12.
16. Hosseini SA, Ghelichi-Ghojogh M. Mutation in PYCR2 gene and hypomyelinating leukodystrophy in children: a case report study. Ann Med Surg (Lond). 2023;85(5):2177-9.
17. Afroze B, Mercimek-Andrews S. Pyrroline-5-Carboxylate Reductase 2 Deficiency: A New Case and Review of the Literature. Can J Neurol Sci. 2020;47(2):280-2.
18. Zaki MS, Bhat G, Sultan T, Issa M, Jung HJ, Dikoglu E, et al. PYCR2 Mutations cause a lethal syndrome of microcephaly and failure to thrive. Ann Neurol. 2016;80(1):59-70.
19. Escande-Beillard N, Loh A, Saleem SN, Hiroshi H, Hidetaka S, Bruno R. Loss of PYCR2 Causes Neurodegeneration by Increasing Cerebral Glycine Levels via SHMT2. Neuron. 2020;107(1):82-94.e6.
20. Dreha-Kulaczewski SF, Brockmann K, Henneke M, Dechent P, Wilken B, Gärtner J, Helms G. Assessment of myelination in hypomyelinating disorders by quantitative MRI. J Magn Reson Imaging. 2012;36(6):1329-38.

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