PYCR2 Mutation Causing Hypomyelination and Microcephaly in an Indian Child

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Abstract

Hypomyelinating leukodystrophy (HLD) represents a group of clinically overlapping but genetically heterogeneous diseases. This group of disorders has the improper formation of myelin sheaths in the central nervous system (CNS), resulting in abnormal white matter, with characteristic MRI findings and clinical presentations of mostly motor dysfunction with variable cognitive and language impairment.

We report a case of a three-year-old boy with global developmental delay, dysmorphic facies, motor signs, progressive microcephaly, and failure to thrive. The child was born of a non-consanguineous marriage. All basic investigations and metabolic tests were normal. Magnetic resonance imaging (MRI) of the brain showed hypomyelination of the deep and subcortical white matter, appearing as hyperintense T2 and iso-intense T1-weighted images, cerebral atrophy with the thinning of the corpus callosum, with normal cerebellum, brainstem, and deep grey nuclei. Further genetic testing in the form of clinical exome sequencing revealed compound heterozygous mutation of the PYCR2 gene and matching the clinical phenotype with the genotype. Therefore, a final diagnosis of hypomyelinating leukodystrophy-10 was made.

There is a wide range of aetiologies for debilitating neurologic disorders, which have common and overlapping clinical presentations. Advances in the field of genetics, growing awareness, and availability of genetic tests help in a better workup of complex neurological cases. A precise diagnosis is useful in outlining the course, treatment (if available), and prognosis of the disease to parents and plays a vital role in planning future pregnancies.

Keywords: Genetics, Neurology, Pediatrics

Introduction

Hypomyelinating leukodystrophy (HLD) represents a group of clinically overlapping but genetically heterogeneous diseases [1]. These patients have an inadequate formation of myelin sheaths in the central nervous system (CNS), resulting in abnormal white matter with characteristic magnetic resonance imaging (MRI) findings and clinical presentations of mostly motor dysfunction with variable cognitive and language impairment [2]. Microcephaly is defined as a head circumference less than 3 SD or Z score < -3. Microcephaly may be observed in 0.1% of the general asymptomatic population but its prevalence is 15%-20% in children with developmental delay [3]. The etiologic spectrum of microcephaly can be wide-ranging from perinatal hypoxic-ischemic injuries, in-utero infections, post-infective sequelae, and structural abnormalities to less common causes like hypomyelinating, metabolic or genetic disorders. Genetic mutations causing these hypomyelination syndromes are being increasingly recognized. Pelizaeus-Merzbacher disease (PMD) due to proteolipid protein 1 (PLP1) gene mutation and hypomyelinating leukodystrophy-6 due to the tubulin beta-4A gene (TUBB4A) mutation are better known genetic syndromes causing hypomyelination and microcephaly. Recently, Nakayama et al., in 2015, for the first time, identified a mutation in the PYCR2 gene causing a similar phenotypic and radiologic presentation [4]. Here, we report a rare case of hypomyelination, microcephaly, reduced white matter volume, and identification of a mutation in the PYCR2 gene in an Indian child.

Case Presentation

A three-year-old boy presented with complaints of not achieving developmental milestones as per age and failure to gain weight. The child was first brought to medical attention at the age of nine months when parents felt that he was not developing like other children his age. There were also some concerns of neuro-regression according to parents as the child had lost the previously acquired milestone (achieved late, around one and half years of age) of sitting without support. At the time of presentation (three years of age), the child could not sit or stand independently and was completely dependent on the caregiver for all activities of daily living. There was no history of seizures. Other associated problems were difficulty in feeding the child, as he had frequent vomiting and suffered from chronic constipation. Birth history revealed that this child was born of a non-consanguineous marriage, born full-term by vaginal delivery with face presentation, with a birth weight of 2.75 kg. There were no ante-natal or peri-natal issues and the baby...
didn’t require neonatal intensive care unit (NICU) admission. There was no family history of any neurological illness and the patient had an older, six-year-old, female sibling who was well and normal. On examination, the child looked severely malnourished with anthropometry showing a weight of 5.7 kg and a head circumference of 42 cm (Figure 1). Previous clinical records revealed that the weight of the child was 4.6 kg at nine months and 6.1 kg at 22 months with the head circumference (HC) being 39 cm at nine months and 40.5 cm at 11 months. All values of weight and HC were below the 3 Z-score, showing severe failure to thrive and microcephaly.

FIGURE 1: Failure to thrive and severe wasting

The child had dysmorphic features in the form of triangular facies, prominent eyebrows and eyelashes, bulbous nose tip, thin vermilion of the upper lip, prominent ears, and his mouth was always open (Figures 2-3).
FIGURE 2: Dysmorphic facies
No fasciculations were noted in the tongue. There was axial hypotonia with partial head lag, appendicular hypertonia, and spasticity of limbs. Deep tendon reflexes were brisk, the plantars were bilateral extensor, and the range of motion of the hips and knees was limited. The child’s functional status was classified as Gross Motor Function Classification System (GMFCS) level V. The fundus was normal. Extraocular movements were full, pupils were equally reactive, and no facial asymmetry was noted. Basic blood tests including complete blood count, liver function test, renal function test, thyroid profile, calcium, plasma ammonia, and lactate were normal. Tests for inborn errors of metabolism in the form of blood tandem mass spectrometry (TMS) and urine gas chromatography-mass spectrometry (GCMS) were normal. MRI done at nine months of age showed hypomyelination of deep and subcortical white matter, including U fibers appearing hyperintense in T2WI and isointense in T1WI. The corpus callosum was thin (Figures 4-5). Bilateral internal capsules showed normal myelination for age with normal signals in both T1WI and T2WI. Cortical sulci, including Sylvian fissures, was diffusely prominent with dilated extra-axial spaces suggesting
cerebral atrophy (Figure 6). One more finding that was noted was an extra-axial arachnoid cyst in the right anterior temporal region, which had a signal identical to cerebrospinal fluid (CSF) in all imaging sequences. Brainstem, cerebellum, and deep gray matter nuclei were normal.
FIGURE 6: Increased extra-axial spaces suggesting cerebral atrophy

As MRI was done at nine months of age, a repeat MRI was planned at the time of current consultation to look for interval change but parents were keen to go for the next step, which was the genetic test. A genetic test, in the form of clinical exome sequencing, was done, which showed a compound heterozygous mutation in the PYCR2 (pyrroline-5-carboxylate reductase 2) gene, a heterozygous missense variation in exon 4 (p.Arg119His), and another heterozygous start-loss variation in exon 1 (p.Met1). Hence, on combining the clinical phenotype with the genetic test result, a final diagnosis of PYCR2 gene-related hypomyelination and microcephaly syndrome (also known as hypomyelinating leukodystrophy 10) was established (Figure 7). Parents were explained about the diagnosis, course, and progression of the disorder, as well as the poor outcome. The patient was given pharmacotherapy for spasticity, and physiotherapy and occupational therapy were recommended. In view of the progressive neurological condition, severe wasting, and feeding difficulties, a percutaneous endoscopic gastrostomy (PEG) tube feeding was recommended but parents were not keen on it. As genetic counseling was not available in our center, parents were advised to seek genetic counseling from another center.
FIGURE 7: Genetic test (clinical exome sequencing) report showing a compound heterozygous mutation in the PYCR2 gene
of genetics, growing awareness, and the gradual availability of genetic tests in smaller cities of developing countries is helping in the better evaluation of complex neurological disorders and establishing a complete diagnosis. A precise diagnosis helps in outlining the course, treatment (if available), and prognosis of the disease to parents and plays a vital role in planning future pregnancies.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. issued approval not applicable.

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