Childhood Myocerebrohepatopathy Spectrum Disorder due to Polymerase Gamma Pathogenic Variant

Sir

The most common cause of inherited mitochondrial disorder is polymerase gamma (POLG) mutations which lead to secondary mitochondrial damage in the form of quantitative depletion, multiple deletions, and increased load of point mutations.[1] Here, we report an Indian boy with childhood myocerebrohepatopathy (MCHS) due to pathogenic variant in *POLG* gene.

An eight-year-old boy born to consanguineous marriage is brought with developmental delay, recurrent falls, seizures, behavioral abnormality, and unresponsiveness with fever in the last 20 days. Noted history of recurrent falls in the form of tripping and falling several times a day. Following cough, cold, and fever, he became unresponsive in the past 20 days. Developmentally, he was walking without support, spoke two-word phrases with dysarthria, and could feed himself. On examination, head circumference of 47 cm (less than 3 Z score), open mouth, protruding tongue, hypertelorism, low set ears, and epicanthal folds were noted. Tone was decreased in all limbs with contractures of bilateral tendo-Achillis. After 1 week of admission, his proximal muscle power 3/5 (MRC grade), positive Gowers' sign, waddling gait [Video 1], weak hand grip, extensor planter bilaterally, cerebellar signs, dysarthria, and hepatomegaly with span of 11 cm were also observed.

On investigations, complete hemogram, renal function, and serum electrolytes were normal. Increased SGOT-188, SGPT-340, and serum creatine phosphokinase (CPK)-6775 U/L were noted. Four hours fasting arterial lactate-36 mg/dL was elevated (normal: 4.5–19.8 mg/dL). Arterial blood gas and tandem mass spectrometry were normal. Ultrasound abdomen showed liver size of 11 cm. Nerve conduction studies and magnetic resonance imaging of brain were normal. Muscle biopsy on light microscopy was normal. Enzyme activity of the respiratory chain complex I in the muscle was less than 20% of normal value. Electroencephalogram showed centrotemporal spikes. Targeted next-generation sequencing revealed a variant of uncertain significance in homozygous state at c. 2509T > C/p.Tyr837His in exon 16 of *POLG* gene and the same variant was confirmed by Sanger sequencing. Segregation analysis showed heterozygous status in both parents for same mutation. The child was treated with coenzyme Q, carnitine, biotin, and riboflavin and child has a significant improvement in development, which may be due to medications or spontaneous health recovery.

POLG are associated with a wide range of overlapping phenotypes that vary depending on the age from devastating infantile disorders such as Alpers' syndrome and myo-cerebro-hepatopathy spectrum (MCHS) to juvenile and adult onset myoclonic epilepsy, myopathy, and sensory ataxia and ataxia neuropathy spectrum and to late-onset myopathies with progressive external ophthalmoplegia.[2] Here, we describe an 8-year-old boy with global developmental delay, ataxia, seizures, behavioral problems, microcephaly, and proximal muscle weakness. Investigations showed raised CPK, SGOPT, SGPT, deficiency of respiratory complex-1 on muscle biopsy, and a homozygous missense substitution in *POLG* gene.

The clinical expression of myocerebrohepatopathy is distinct from that of Alpers–Huttenlocher syndrome.[3] MCHS is much less common and occurs at 6 months of age, i.e., much earlier than Alpers' syndrome. Infants with MCHS usually present with liver failure and lactic acidosis and then may develop encephalopathy with or without seizures. The clues to distinguish Alpers from MCHS are the presence of medically intractable seizures, associated devastating encephalopathy, and if patients survive long enough, a distinct histopathology of liver in the former disease.[4,5]

One potential emerging mechanism for phenotypic variation is ecogenetic single nucleotide variant which is usually silent but in some patients, it is activated by environmental and other interactions to cause disease.[3] The current case represents a mild form of MCHS. The identified homozygous missense substitution p.Tyr837His alters a conserved residue in the protein. In silico missense prediction tools (LRT, Mutation Taster, PolyPhen-2, FATHMM) suggest that the variant is probably damaging to the protein function. With clinical correlation, the variant can be labelled as disease causing. A diagnosis is important to avoid hepatotoxic drugs like valproate for seizures. In any child presenting with developmental delay, seizures, proximal muscle weakness, elevated liver, and muscle enzymes, a diagnosis of childhood myocerebrohepatopathy should be considered.

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Conflicts of interest

There are no conflicts of interest.

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