Report of an Indian Family with Sengers Syndrome

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To the Editor: A five-month-old boy presented with congenital cataract and global developmental delay. Antenatal and birth history was uneventful. Anthropometric examination showed normal height and weight with microcephaly (head circumference: 37.5 cm; −3.42 SD, WHO standards). On examination bilateral aphakia (post cataract surgery), respiratory distress, hepatomegaly and central hypotonia were noted. Arterial lactate values were elevated to 10–14 mmol/L. Echocardiography showed concentric left ventricular hypertrophy with 25% ejection fraction. Creatine phosphokinase was 217 U/L (normal = 20–200 U/L). Thyroid function test, urine gas chromatography/mass spectrometry and blood tandem mass spectrometry were unremarkable.

Trio whole exome sequencing revealed homozygosity for a novel splice site variant c.1046_1046 + 1dup in acyl glycerol kinase (AGK) in proband and parents were heterozygous for the same. This variant is predicted to disrupt the highly conserved donor splice site of intron 14. In the subsequent pregnancy, prenatal diagnosis was offered and the fetus was unaffected.

Sengers syndrome (MIM 212350) first reported in 1975, is a rare inherited mitochondrial disease with a constellation of findings including congenital cataract, lactic acidosis, cardiomyopathy and skeletal myopathy [1]. Furthermore, the variable severity results in a wide spectrum of presentations, notably from death in early infancy to mild manifestations in adults. AGK gene is implicated in the disease pathogenesis [2]. AGK is located in the mitochondrial inner membrane and is important for the biosynthesis of phospholipids.

To date, about 40 families with Sengers syndrome have been reported in the literature to the best of our knowledge [3]. The reported phenotype-genotype correlation suggests that homozygous nonsense mutations usually manifest with severe forms

whereas the presence of at least single splice-site mutation results in milder presentations [3, 4]. On the contrary, our case had severe phenotype with novel homozygous splice-site mutations. Similar observations were recently reported [5].

Our case adds to the existing mutation spectrum of the disease, expands the genotype-phenotype correlations and reiterates the importance of genetic diagnosis in the index case to prevent recurrences.

Besides, it emphasizes that Sengers syndrome should be kept as a differential diagnosis in any child presenting with white reflex, especially in association with lactic acidosis and/or hypertrophic cardiomyopathy.

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Compliance with Ethical Standards

Conflict of Interest None.

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