Leigh Syndrome and SURF1 Gene Presenting with Febrile Seizure

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A 3-month-old male infant with previously normal development was brought with complaints of one episode of the fever-triggered seizure (left focal) lasting for 10 min. He had upper respiratory tract infection (fever, cold, and cough) for 2 days. The period before this illness and birth of the child was uneventful. On examination, apart from fever and mild central hypotonia, no other abnormalities were detected. Investigations revealed normal hemogram, blood sugar, serum calcium, and normal serum electrolytes. His arterial blood lactate levels were elevated (7.4 mmol/L). Magnetic resonance imaging (MRI) of the brain showed symmetrical T2 and FLAIR hyperintense signal changes in the putamen, thalamus, and midbrain, with diffusion restriction and inverted lactate doublet peak at 1.3 ppm in magnetic resonance spectroscopy [Figure 1]. Cerebrospinal fluid lactate was also high (9.7 mmol/L), but other parameters were normal. Electroencephalogram showed multifocal epileptiform abnormalities. Next-generation sequencing detected compound heterozygous likely pathogenic intronic variants (intron 8 [c.833 + 1G > A] and intron 4 [c.324-11T > G]) in the SURF1 gene suggestive of Leigh syndrome due to COX IV deficiency. The in silico prediction by various bioinformatic tools indicated that both the variants were damaging. He was started on Levetiracetam and mitochondrial cofactor vitamins and the parents were counseled about the disease course and recurrence in future pregnancies.

Leigh syndrome is one of the mitochondrial cytopathies involving the central nervous system, characterized by a variable combination of developmental delay, often regression of development milestones following minor febrile illness, central hypotonia, swallowing difficulty, brain stem dysfunction leading to respiratory abnormalities including central respiratory failure and impaired thermoregulation, epileptic seizures, and extrapyramidal features (dyskinesia, akinesia, dystonia) in later childhood.[1] While the MRI brain shows relatively symmetrical signal abnormalities involving brain stem and/or basal ganglia, diencephalon, and sometimes

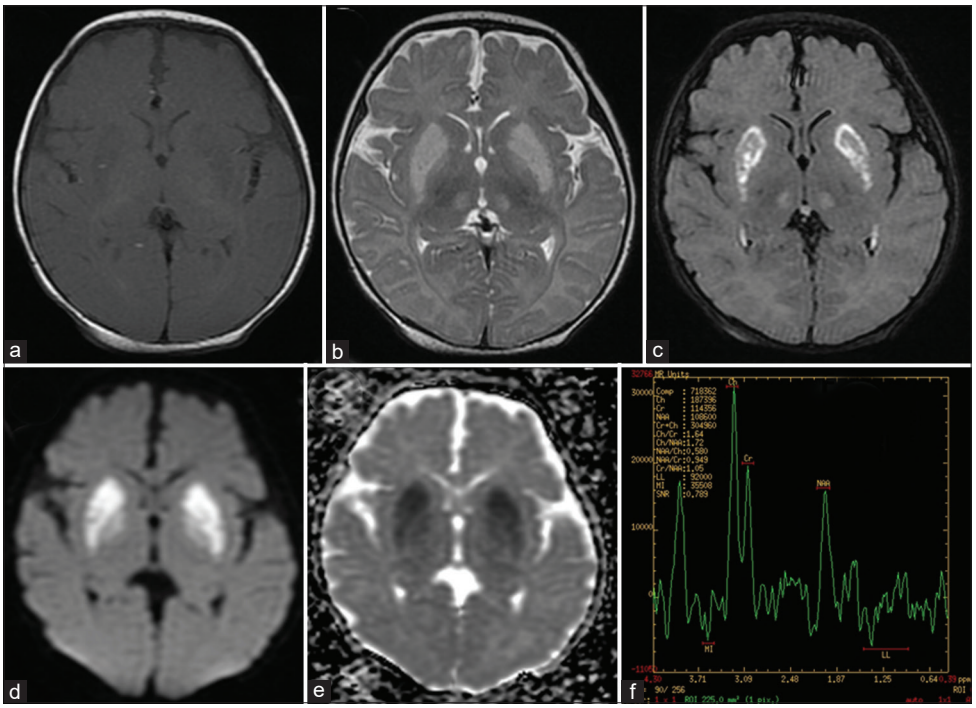

Figure 1: . Magnetic resonance imaging of the brain of a child with Leigh's syndrome. T1-weighted axial image (a) shows bilateral symmetrical hypointense signal changes in the putamen, and thalamus. These changes are hyperintense on T2-weighted (b), FLAIR (c), and diffusion-weighted sequences (d). The corresponding ADC map (e) shows hypointense signal changes. Magnetic resonance spectroscopy shows inverted lactate doublet peak at 1.3 ppm (f)

in the cerebellum and spinal cord, MRS shows inverted lactate doublet peak at 1.3 ppm specific for mitochondrial disorders like our case. In addition, CSF lactate levels and lactate/pyruvate ratio is usually higher than normal in these patients.[1] Other manifestations include ophthalmological abnormalities like nystagmus, optic atrophy, ophthalmoplegia, ptosis, and cardiac abnormalities like hypertrophic/dilated cardiomyopathy and arrhythmia/conduction defect. Underlying genetic mutations usually affect proteins involved in mitochondrial respiratory chain complex or pyruvate dehydrogenase complex and may be found in mitochondrial or nuclear DNA. *SURF1* gene mutation is the most frequent cause of cytochrome C oxidase (COX) deficient Leigh syndrome. The patients with *SURF1* variants often have hypertrichosis and peripheral neuropathy, predominantly demyelinating variety, apart from other features of Leigh syndrome.[2] Epileptic seizures have been reported in children with Leigh syndrome, most commonly focal seizures, and the onset usually occurs in infancy. West syndrome and Epilepsia partialis continua have also been reported in Leigh syndrome.[3,4] As clinical symptoms of mitochondrial disorders usually manifest for the first time or worsen following a febrile illness, it may mimic as febrile seizures in young children. Although the American Academy of Pediatrics classically does not recommend any blood investigations, MRI brain, or EEG for simple febrile seizures, in the cases of recurrent complex febrile seizures, often it is prudent to further evaluate these cases.[5] Although every case of fever triggered seizures in young children does not warrant extensive laboratory investigations and following a convulsive seizure, blood lactate may remain elevated for few hours, the cases with an atypical presentation, multiple recurrences despite on antiepileptic drugs or abnormal neurological examination should undergo a search for any underlying etiology. In such cases, if the initial blood lactate level was found to be highly elevated than it should be repeated the next day to rule out the mitochondrial disorder. Currently available arterial blood gas analyzers are of considerable help in this regard because with as little as 0.5 mL blood, it can give values of multiple parameters like serum electrolytes (Na, Ca, Mg) and blood sugar, apart from routine parameters. It also provides blood lactate values and helps in suspecting mitochondrial disorders. Moreover, genetic sequencing in atypical cases with multiple fever-triggered seizures is also essential to detect sodium channelopathies, including Dravet syndrome and GEFS+, which often mimic febrile seizures.[6]

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Conflicts of interest

There are no conflicts of interest.

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