"SURF1 Mutations in Leigh Syndrome: A Deep Dive into Two Cases"

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INTRODUCTION : Leigh Syndrome, a mitochondrial disease with a prevalence of 1-in-40000, displays genetic diversity, with 15% exhibiting complex 4 deficiency, notably due to pathogenic SURF1 variants.[1,2] This study explores two cases with a SURF1 variant, one with a novel mutation. Both patients had developmental delay upon diagnosis, but had not experienced any attacks leading to metabolic decompensation; maintaining stable neurologic and social functions. Despite mitochondrial supplementary therapy, sudden respiratory failure and metabolic decline resulted in dependency on respiratory support, encephalopathy and severe neuromotor retardation.

CASES: The first case, aged 23 months, had height and weight below the 3rd percentile with normal head circumference. The patient had bulging eyes, pectus excavatum deformity, trunkal ataxia and titubation and was brought in due to inability to walk independently. He had two word sentences, and was socially active. He had a history of two surgeries for undescended testicles leading to genetic panel testing which revealed a variant of unknown significance; a homozygous nonsense mutation in AMHR2. Family history revealed first degree consanguinity. Blood tests showed elevated lactate levels and neuroimaging was remarkable for symmetric restricted diffusion of focal areas of the brainstem. Clinical exome sequencing revealed a novel SURF1 frameshift deletion, confirming Leigh Syndrome.

The second case, at 18 months, was referred for high anion gap acidosis detected during investigations for excessive crying where hypercalciuria was observed . He exhibited similar percentile issues with height below the 3rd percentile and weight between 3-10 percentiles. He had coarse facial features and hirsutism almost giving the impression of a storage disease. He could walk with support. First degree consanguinity was present and family history included the deaths of three siblings; two brothers , aged 30 and 48 months, who died after experiencing respiratory distress and another brother found deceased in bed at 30 months without a diagnosis. Whole exome sequencing showed a homozygous pathogenic SURF1 mutation.

Treatment involved a low glycemic index diet enriched with medium-chained triglycerides, coenzyme Q10, alpha-lipoic acid, N-acetylcysteine, and vitamin E for the first case and coenzyme-Q10 supplementation for the second. Both cases remained neurologically stable initially but faced acute respiratory distress and metabolic decompensation during treatment, leading to extended intensive care, tracheostomy, and home-ventilator support. Both patients showed gross cognitive and motor regression, particularly after metabolic attacks. Seizures and abnormal electrographic findings appeared during the drastic course; levatiracetam treatment was initiated for both patients. Unfortunately, the first patient deceased after recurrent respiratory infections six months later.

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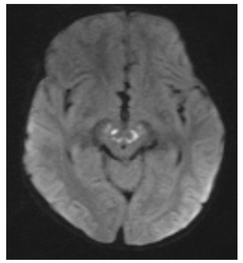
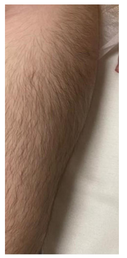
CONCLUSIONS: SURF1 gene encodes a mitochondrial protein required for the assembly and maintenance of Cytochrome c oxidase(COX); the terminal component of the mitochondrial respiratory chain. Recessive mutations of the SURF1 gene leads to complex 4 deficiency and Leigh syndrome. While there is no cure for Leigh syndome, vitamin and cofactor supplementation aims to prevent future attacks.[5]

In SURF-1-related Leigh Syndrome more than 120 mutations have been identified. In European populations c.845_846delCT and c.312_312del10insAT are the most common, whereas in Turkey, c.796G>A mutation has been reported as the most frequent. [3,4] Our first case had a previously unreported homozygous frameshift mutation, c.498_493del, and the second case had a pathogenic homozygous c.845_846del mutation. Presence of hirsutism in the second patient was intriguing for us; it's noteworthy to mention that up to 80% of cases with homozygous C.845_846del mutations were reported to be associated with hirsutism.[3]

Leigh Syndrome is mostly diagnosed during acute respiratory failure and metabolic decompensation with subsequent developmental regression. On retrospective analysis however, most cases show developmental delay as the initial finding. Unfortunately most of the time this finding goes unnoticed until an acute attack leading to severe neurological regression occurs. Currently there is no cure for Leigh syndrome but vitamin and cofactor supplementations are widely used to prevent possible future attacks. Both our cases had an established diagnosis before experiencing metabolic decompensation; they both were neurologically stable. Despite early intervention, both cases experienced disease progression and severe permanent sequelae. Early diagnosis before the vegetative state, offers hope, emphasizing the importance of specific treatment development.



Brain magnetic resonance imaging of case 1.



Hirsutism on left leg, case 2.

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