Succinate dehydrogenase deficiency with Leigh like presentation: Case report

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• Introduction

The oxidative phosphorylation system consists of five complexes. Functioning in synergy to produce ATP through the oxidation of NADH and FADH2 is associated with the reduction of oxygen. Two electron carriers (Coenzyme Q 10 (CoQ10, Ubiquinone) and cytochrome c) facilitates the transfer of electrons complexes. Complex I receives electrons via NADH and transfers it to complex III through CoQ10 while complex II receives electrons via FADH2 and transfers it to complex III, also through CoQ10 (I). Electrons are then carried by cytochrome c to complex IV, where they react with oxygen. This transport of electrons across the mitochondrial respiratory chain creates a transmembrane proton gradient. The inner mitochondrial membrane used by the V complex is a ATPase to convert ADP to ATP. Defect in any of the mentioned complexes or electron carriers leads to disruption of ATP production, resulting in a mitochondrial disease that usually involves abnormality in the central nervous system, muscle, heart, eye, kidney and hematological systems (2). Complex II (succinate:ubiquinone oxidoreductase or succinate dehydrogenase) is a multimeric protein (has four subunits, two of which are catalytic and the other two are referred to as anchoring units )located in the inner mitochondrial membrane and It functions by transferring electrons to ubiquinone in the mitochondrial electron transport chain (ETC) and oxidizing succinate to fumarate in the citric acid cycle. These functions are carried out by (3) Presentations of mitochondrial disease associated with an isolated complex II deficiency are rare and account for an estimated 2% of respiratory chain deficiencies. (4) Complex II deficiency (OMIM #252011) has been reported to cause Leigh syndrome in children, infantile and nonspecific leukoencephalopathies and isolated neonatal cardiomyopathy. Symptoms in adulthood include mitochondrial myopathy, exercise intolerance, neurodegeneration in combination with optic atrophy and ataxia (5). Herein we report a 7 years old child who was diagnosed as succinate dehydrogenase deficiency. The affected child presented at 1 years of age with encephalopathy and developmental regression following viral illnesses. MRI changes supported a clinical diagnosis of Leigh syndrome and biallelic c.1328 C>Q and c.872 A>C SDHA variants were identified.

• Case Report

Our male patient who had unrelated parents, was born from 30 year-old mother, by normal spontaneous vaginal delivery at 40 weeks gestational age. Birth weight was 3990g (75 percentile), height 50 cm (50 percentile), head circumference 35 cm (50 percentile). At 1 year of age child presented with encephalopathy and developmental regression following viral illnesses. Laboratory findings revealed was normal. On comprehensive metabolic tests; Plasma amino acids (PAA) and Urine organic acids (UOA) showed no abnormalities. Eye examination revealed no follow-up and fixation, the fundus of the eye was normal. Echocardiography revealed normal. Diffusion Cranial MRI; Hyperintense signal increases were observed in the subcortical deep white matter in the bilateral frontal lobe and in the cortico subcortical area in the bilateral precentral gyrus, in the periventricular deep white matter in the bilateral putamen, in the head of the quadrate nucleus, and in the bilateral thalamus on T2W and FLAIR images. The described lesions show some limitation in diffusion-weighted images. The outlook may be significant in terms of Leigh's syndrome. Molecular genetic analysis showed SDHA gene (NM_001468.4:c.1328G>Q;p.Cys443Tyr) and c.872A>C(p.Glu291Ala) compound heterozygous. Mitochondrial coetyl treatment including L-carnitine, riboflavin, thiamine,biotin and ubiquinone were started. Mild clinical improvement was observed after treatment. But at the age of 7 years old examination he was unable to walk and speak.
• Discussion

Complex II is the smallest complex in the OXPHOS system and consists of only four structural subunits encoded by genes that share the same name: SDHA (5p15.33; OMIM *600857), SDHB (1p36.13, OMIM *185470), SDHC (1q23), and SDHD (11q23.1). OMIM *602690 There are four assembly factors (SDHAF1-4) to obtain the special quaternary structure of Complex II. necessary to coordinate biosynthesis (6). The majority of clinically affected individuals reported in the literature harbor genetic variants in the SDHA gene and present with a Leigh syndrome phenotype clinically defined as subacute necrotizing encephalopathy. (7). In another study, to these childhood presentations is the report of two sisters with an adult-onset phenotype characterized by progressive optic atrophy, ataxia and myopathy (8). Some cases present following viral illness; this feature is not specific to mitochondrial complex II deficiency and occurs in many other mitochondrial disease presentations.

The underlying pathomechanism is the ATP-consuming immuneresponse, often with associated fever, which can tip the delicate balance in an asymptomatic individual to perturbed ATP homeostasis. Cardiomyopathy has been described patients with complex II deficiency (9). Cardiac evaluation was not reported in all patients, but when possible were found to have heart disease and the majority to have cardiomyopathy (hypertrophic or dilated) identified in infancy has been associated with significant mortality and morbidity (5). Our patient’s echocardiography was revealed normal Pharmacological treatment in mitochondrial disease, supplement with antioxidants and vitamins that can counteract overproduction of reactive oxygen species (10). In CII deficiency, only riboflavin, a precursor for FAD has been shown to have any effect, but this seen in only three patients in shailey and friends findings (11).

• References