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Original Article

Clinical and magnetic resonance imaging findings in patients with Leigh syndrome and *SURF1* mutations

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Abstract

Background: Mutation in the *SURF1* is one of the most common nuclear mutations associated with Leigh syndrome and cytochrome *c* oxidase deficiency. This study aims to describe the phenotypic and imaging features in four patients with Leigh syndrome and novel *SURF1* mutation. *Methods:* The study included four patients with Leigh syndrome and *SURF1* mutations identified from a cohort of 25 children with Leigh syndrome seen over a period of six years (2006–2012). All the patients underwent a detailed neurological assessment, muscle biopsy, and sequencing of the complete mitochondrial genome and *SURF1*. *Results:* Three patients had classical presentation of Leigh syndrome. The fourth patient had a later age of onset with ataxia as the presenting manifestation and a stable course. Hypertrichosis, facial dysmorphism and hypopigmentation were the additional phenotypic features noted. On magnetic resonance imaging all patients had brainstem and cerebellar involvement and two had basal ganglia involvement in addition. The bilateral symmetrical hypertrophic olivary degeneration in these patients was striking. The *SURF1* analysis identified previously unreported mutations in all the patients. On follow-up three patients expired and one had a stable course. *Conclusions:* Patients with Leigh syndrome and *SURF1* mutation often have skin and hair abnormalities. Bilateral symmetrical hypertrophic olivary degeneration was a consistent finding on magnetic resonance imaging in these patients.

Keywords: Leigh syndrome; COX deficiency; *SURF1* mutation; Dentate nucleus; Inferior olivary nucleus

1. Introduction

Leigh syndrome associated with cytochrome *c* oxidase (COX) deficiency is one of the most common disorders of the mitochondrial respiratory chain in infancy and childhood [1]. Complex 4 (COX), the terminal component of the mitochondrial respiratory chain is a hetero oligomeric complex made of 13 subunits .The three larger subunits are coded by mitochondrial genome while smaller 10 subunits by nuclear genome [2,3].

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There are several other nuclear genes that are required for the assembly of complex 4. These ancillary genes are known as the COX assembly genes [4] and the most important one is the *SURF1*. Mutation in the *SURF1* is one of the most common nuclear mutations consistently associated with Leigh syndrome and COX deficiency [1,5].

The first confirmed case of COX negative Leigh syndrome with *SURF1* mutation was described by Zhu et al in 1998 [6]. By using the microcell mediated chromosome transfer the gene defect was mapped to chromosome 9q34 and analysis of the candidate gene lead to the discovery of *SURF1*. The truncated gene was thought to have some role in biogenesis of mitochondria. But the first patient with *SURF1* mutation probably was described in 1977 [7]. This report described a child with Leigh syndrome who presented at the age of two years with hypotonia and ataxia and expired at the age of six years following progressive neurological deterioration. Measurement of the respiratory chain enzyme complexes demonstrated reduced cytochrome *c* oxidase activity in cultured fibroblasts and muscle. The *SURF1* mutation analysis was performed on genomic DNA three decades later and demonstrated homozygous transition (370G > A) in the *SURF1* cDNA [8]. There have been numerous reports on *SURF1* mutation and Leigh syndrome [9–11]. It is necessary to characterise the clinical and imaging features in this rare disorder to derive genotype–phenotype correlations for targeted genetic testing. The current study describes four patients with *SURF1* mutation from a tertiary health care centre from South India and highlights the phenotypic and imaging features.

2. Patients and methods

2.1. Phenotypic features

Over a period of six years (2006–2012) 25 patients with Leigh syndrome were seen atthe National Institute of Mental Health and Neurosciences Bangalore India, a tertiary care university hospital. All the patients were seen and followed up by two physicians (PSB, ABT). All these patients underwent complete mitochondrial genome sequencing and sequencing of the *SURF1*. Four patients had mutations in *SURF1*. The phenotypic features of these patients were extracted from the clinical records.Clinical and imaging findings in one of the patient is already been reported [12]. All patients underwent routine haematological and biochemical testing and a metabolic panel consisting of urine screening for abnormal metabolites, tandem mass spectrometry for amino acids and acyl carnitine profile, and limited lysosomal enzyme profile (Serum Aryl sulfatase A and B, and Serum hexosaminaidase – Total A and B) and serum ammonia which yielded normal or negative results. The study was approved by the ethics committee of National Institute of Mental Health and Neurosciences, Bangalore, India.

2.2. Magnetic resonance imaging

Magnetic resonance imaging was done after obtaining informed consent on Siemens-Magnetom vision 1.5 Tesla MRI scanner (Erlangen, Germany) using standard procedures and protocols. Spin echo T1-weighted (repetition time [TR] = 650 ms, echo time [TE] = 14 ms) images in axial and sagittal plane were taken,with acquisition time of 2.5 mt, matrix of 256 × 256 and a 230 mm field of view. T2-weighted images (TR = 4000 ms, TE = 120 ms) were acquired in axial and coronal planes. Fluid attenuated and inversion recovery (FLAIR) sequences were obtained in axial plane (TR = 9000 ms, TE = 119 ms, inversion time = 2457 ms). The slice thickness was 5 mm. MRI sequences included T1W (with and without contrast), T2W and FLAIR in all and MRI spine in one.

2.3. Histopathology

Open muscle biopsy (biceps/quadriceps) was processed with Hematoxylin and eosin (H&E), Modified Gomori's trichrome (MGT), Succinic dehydrogenase (SDH), Nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR) and Adenosine triphosphotase (ATPase pH 9.5 and 4.6).in 4 and cytochrome *c* oxidase (COX), Succinic dehydrogenase- cytochrome *c* oxidase SDH–COX in 3.

2.4. Biochemical analysis

Enzyme analysis of all the four complexes 1–4 and citrate synthase was done in three patients on the muscle homogenates as per the protocol given by Kirby et al. [13].

2.5. Molecular analysis

Total (nuclear and mitochondrial) DNA was extracted from peripheral blood leukocytes using commercially available DNA isolation kits (Gentra Systems Inc., Minneapolis, MN) according to manufacturer's protocol.

Mitochondrial genetic analysis: The entire mtDNA from blood was amplified using 24 sets of overlapping primers spanning the genome. Cycle Sequencing of PCR products were carried out with both forward and reverse primers using the Big Dye Terminator ready reaction kit (Perkin Elmer). The sequences obtained were edited and aligned with the Cambridge Reference Sequence (CRS) and the consensus was made using the Auto Assembler software (Applied Biosystems). All the variations along with their position were noted