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Case Report

Dual diagnosis: unravelling the complexity of mitochondrial respiratory chain disorder and familial hypercholesterolemia in early childhood

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ABSTRACT

Complex I deficiency is the most frequently encountered single mitochondrial enzyme deficiency in patients with a mitochondrial disorder. Most of patients present with symptoms similar to leukodystrophy. Pathogenic mutations identified in the majority of the 44 genes encoding the structural subunits of complex I. No cure for complex I deficiency and the treatment options restricted to symptomatic treatment. Here we report a case of mitochondrial complex I deficiency in an 11-month-old infant presented with failure to thrive, regression of milestones, and metabolic acidosis with a high anion gap and high lactate. MRI brain showed extensive white matter involvement. Before starting treatment with IEM cocktails, genetic testing was sent. Whole exome sequencing revealed homozygous variants in NDUFAF5 (Exon 6) associated with mitochondrial complex-I deficiency and heterozygous mutation in LDLR (+) familial hypercholesterolemia (FH) type 1. After starting treatment metabolic abnormalities got corrected. This rare co-occurrence highlights the importance of considering mitochondrial disorders in infants with unexplained metabolic acidosis and regression of milestones. The case emphasizes the need for early recognition and diagnosis to initiate appropriate management and genetic counselling. This unique combination of disorders expands our understanding of the genetic and phenotypic spectrum of mitochondrial diseases.

Keywords: Mitochondrial disorders, Metabolic acidosis, FH, Whole exome sequencing

INTRODUCTION

Complex I is present in cell structure called mitochondria, which transform the energy from food into a form that cells can use. There are five mitochondrial complexes that are involved in a multi-step process termed oxidative phosphorylation, via which cells acquire much of their energy.[1] Mitochondrial complex I is the first and largest enzyme of the mitochondrial respiratory chain.

Nicotinamide adenine dinucleotide (NADH): ubiquinone oxidoreductase, also known as complex I, is essential for pumping protons to maintain the electrochemical gradient across the inner mitochondrial membrane and for transferring electrons from reduced NADH to coenzyme Q10. Furthermore, complex I is also a major site for reactive oxygen species (ROS) generation.[2]

The most prevalent mitochondrial disease that manifests in the first year of birth is isolated deficiency of complex I.[3] This disease progresses quickly and always has tragic end.

This is a heterogeneous disorder that manifest clinically in a variety of ways, including infantile onset leigh syndrome, mitochondrial encephalomyopathic syndromes, and in newborn presenting with lactic acidosis. Mutations occurs in nuclear or mitochondrial DNA, lead to inherited complex I deficiency.[4]

Nine assembly factors, 17 of the 38 nuclear-encoded subunits, and all seven mtDNA-encoded complex I subunits have been found to have genetic abnormalities.[5] While most nuclear-encoded complex I defects are inherited as autosomal recessive characteristics, a small number of X-linked disorders have been documented.

Pathogenic mitochondrial DNA mutations can be spontaneous or maternally inherited.

Spectrophotometric studies of the enzyme in a muscle biopsy or other patient-derived material (liver or heart biopsy, cultured skin fibroblasts) are the standard means for the diagnosis of complex I deficiency.[6] Nowadays the increased availability of diagnostic molecular genetic tests on broad gene panels, exomes, and even entire genomes has resulted in the identification of numerous unique genetic abnormalities causing complex I deficiency.

This clinically presents as multisystem involvement, such as cardiovascular, neurological, muscular, and visual changes, or as individual organ manifestations.[7] Symptoms include nausea, vomiting, and fast breathing. Musculoskeletal involvement might appear as muscle discomfort, weakness, hypotonia, dystonia, ataxia, or involuntary movements. Neurological features may include seizures, developmental delays, and milestone regression. Visual difficulties, eye muscle paralysis, and pigmentary retinopathy can all be detected during an ophthalmological examination. Cardiomyopathy and cardiorespiratory failure may cause death.[8]

In summary, mitochondrial complex I deficiency remains a significant challenge in clinical diagnosis and management due to its diverse phenotypic presentations and genetic heterogeneity. While advancements in genetic testing have improved diagnostic accuracy, many cases remain undiagnosed or misdiagnosed. The following case report highlights a unique clinical presentation of this condition, emphasizing the need for increased awareness and early diagnostic approaches. Through this case, we aim to contribute to the growing understanding of mitochondrial disorders and highlight potential avenues for improved patient outcomes.

CASE REPORT

The 11 months child presented with failure to thrive and regression of milestones. She was term born by normal vaginal delivery with birth weight of 2.760 kg, 2nd born child of non-consanguineous married couple with no antenatal or perinatal events. Exclusively breast fed up to 6 months and complement feeds started thereafter. On examination child was drowsy, had pallor, tachycardia and tachypnoea with acidotic pattern of breathing, peripheral pulse was weakly felt, CRT was prolonged. ABG was showing severe metabolic acidosis with high anion gap. Lactate was high. Possibility of inborn errors of metabolism considered. Ammonia, electrolyte, random blood sugar, liver function test, renal function test were normal. Cholesterol and triglycerides were highly elevated. Blood C/S showed no growth.

Dehydration and shock corrected, started on metabolic drugs. TMS and urinary GCMS came negative for identifiable cause of metabolic disorder, Alternate possibility of mitochondrial disorders was considered, MRI Brain was showing features suggestive of mitochondrial disorder (T2 hyperintense, T1 hypo intense areas with diffusion restriction seen involving the pons, midbrain, and bilateral frontal, parietal and temporal subcortical white matter (Figure 1-6).

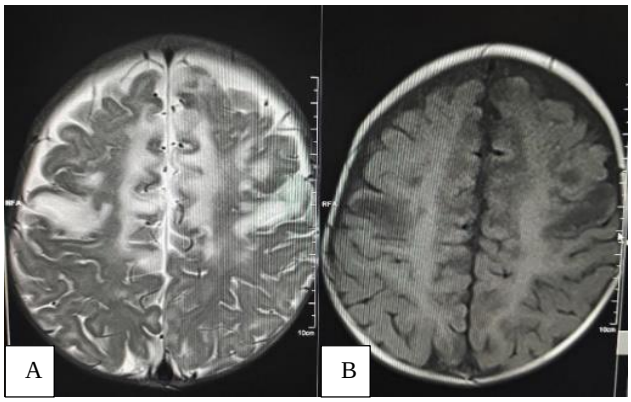

Figure 1 (A and B): Axial view-T1 and T2 images shows T1 hypo intensities, T2 hyperintensities noted in bilateral frontal, parital, subcortical white matter.

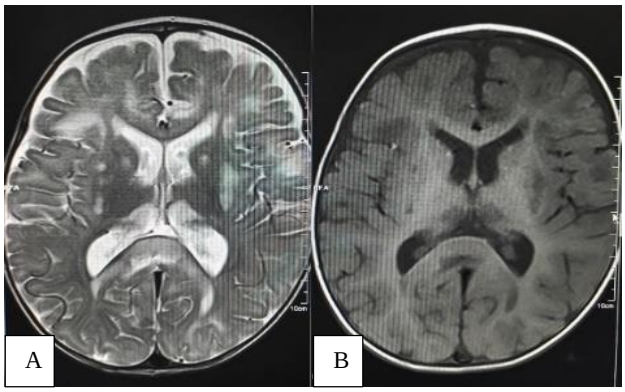

Figure 2 (A and B): Axial view-T1 and T2 images shows T2 hyperintensities and T1 hypo intensities in bilateral basal ganglia (caudate nucleus and putamen), right posterior limb of internal capsule, bilateral thalami, genu and splenium of corpus callosum.

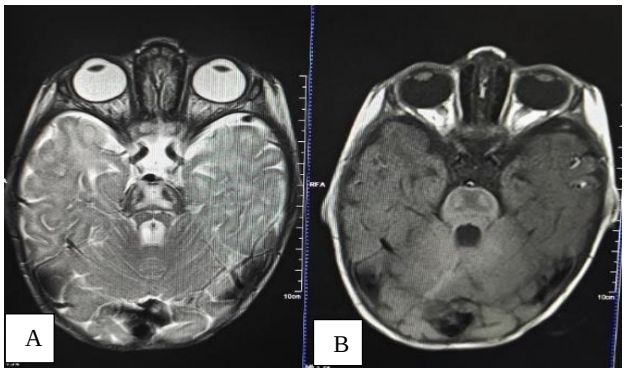

Figure 3 (A and B): Axial view- T1 and T2 images: T1 hypo intensities and T2 hyperintensities noted in brain stem structures.

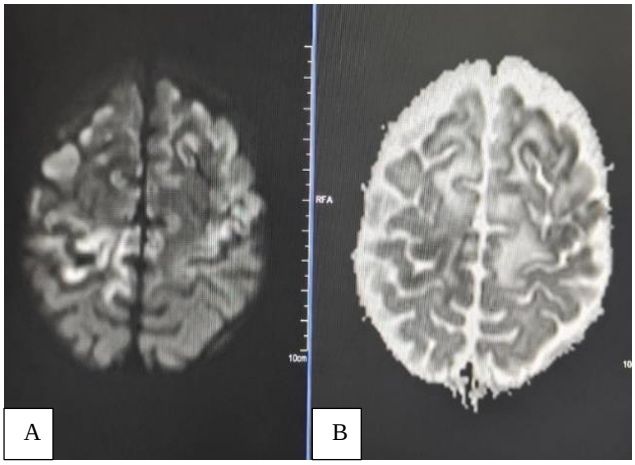

Figure 4 (A and B): Diffusion weighted images shows bilateral frontal, parital, subcortical white matter involvement.

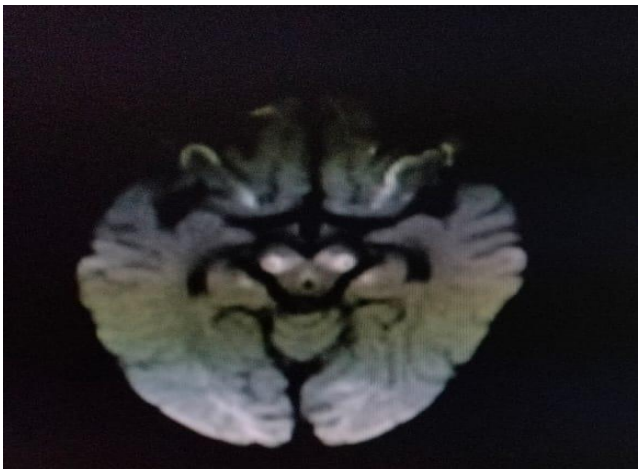

Figure 5: Diffusion weighted images shows brain stem involvement.

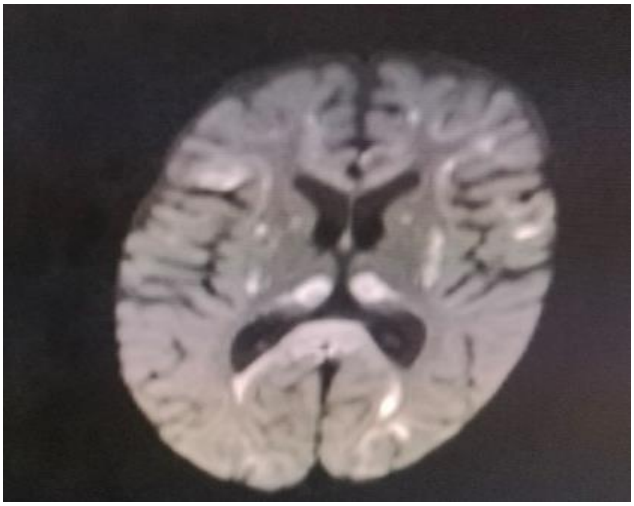

Figure 6: Diffusion weighted images bilateral basal ganglia (caudate nucleus and putamen), right posterior limb of internal capsule, bilateral thalami, genu and splenium of corpus callosum involvement.

Post admission child had abnormal clonic movements and posturing; anti-seizure medications added. The electroencephalogram reported as no epileptiform activity. Auditory evoked potentials and fundus examination were normal. Echocardiogram revealed biventricular hypertrophy. Whole exome sequencing and mitochondrial genome sequencing sent; child discharged on Ryles tube feeding.

Whole exome sequencing of the child's DNA revealed variants of uncertain significance related to mutation in exon 6, c.482T>C homozygous in NDUFAF5 related to mitochondrial complex-I deficiency nuclear type 16 and exon 14 heterozygous mutation in LDLR (+) gene c.2072c>T FH type 1. This was a rare case of mitochondrial complex-1 deficiency and FH occurring together in a child.

DISCUSSION

Case report highlights the rare co-occurrence of mitochondrial complex I deficiency and FH in an 11-month-old infant, emphasizing the importance of considering mitochondrial disorders in infants with unexplained metabolic acidosis and regression of milestones. Key Findings were homozygous variants in NDUFAF5 (Exon 6) associated with mitochondrial complex-I deficiency and co-occurrence with LDLR (+) FH. Extensive white matter involvement on MRI Brain. Significant improvement in metabolic abnormalities following treatment with IEM cocktails.

The co-occurrence of mitochondrial complex I deficiency and FH presented in this case report is exceptionally rare, highlighting the complexities of genetic interactions and the importance of comprehensive diagnostic evaluations. Mitochondrial complex I deficiency is a well-established cause of neurodegenerative disorders, whereas Familial hypercholestrolemia is primarily associated with cardiovascular disease[9]. The simultaneous presence of these conditions in our patient underscores the potential for overlapping pathophysiological mechanisms, warranting further investigation. The co-existence of mitochondrial DNA mutations and LDLR variants may have contributed to the severity of the patient's phenotype. Altered cholesterol metabolism and impaired mitochondrial function may have exacerbated each other, leading to immediate presentation. In our case clinical presentation was similar to mitochondrial disorders but hypercholesterolemia was misleading. These both can be considered as separate entity occurring together.

This case highlights the importance of considering rare genetic combinations in patients with atypical presentations. This case underscores the need for tailored diagnostic and therapeutic approaches. Families with rare genetic combinations benefit from precise risk assessment and guidance. Investigating the molecular mechanisms underlying this co-occurrence may reveal novel therapeutic targets. Even though there is no curative

therapy for the condition, supportive care is essential for the survival. Coenzyme Q, carnitine, biotin, riboflavin and other supplements can be used, but there is no clear data about their effectiveness.[10] Long term follow up is required to understand the disease progression and complications.

The genetic report for our case revealed a variant of uncertain significance (VUS). But the clinical presentation and laboratory parameters were correlating in our case. This classification is likely due to the limited number of reported cases with this specific mutation, making it challenging to establish a clear association with the patient's phenotype.

We believe that publishing this case report is crucial for several reasons like co-occurrence of the simultaneous presence of mitochondrial complex I deficiency and FH is exceptionally rare, warranting documentation. There are limited literature and only a few cases with similar mutations have been reported, highlighting the need for expanded knowledge. As more cases are identified and studied, the significance of this mutation may be reclassified from VUS to pathogenic, informing diagnosis and treatment strategies. Our report will contribute to the growing body of knowledge on rare genetic variants, enhancing the accuracy of genetic testing and interpretation.

Future directions are to investigate the prevalence of this co-occurrence in larger cohorts and elucidate molecular mechanisms. Targeted therapeutic strategies to be developed for managing such cases.

CONCLUSION

This case report expands our understanding of the genetic and phenotypic spectrum of mitochondrial diseases, highlighting the importance of comprehensive diagnostic evaluations and early recognition. The co-occurrence of mitochondrial complex I deficiency and FH underscores the complexities of genetic interactions and the need for personalized medicine approaches.

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