Mitochondrial DNA Depletion Syndrome Causing Liver Failure

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Background: Mitochondrial DNA depletion syndromes are disorders of Mitochondrial DNA maintenance causing varied manifestations, including fulminant liver failure. **Case characteristics**: Two infants, presenting with severe fatal hepatopathy. **Observation**: Raised serum lactate, positive family history (in first case), and absence of other causes of acute liver failure. **Outcome**: Case 1 with homozygous mutation, c.3286C>T (p.Arg1096Cys) in *POLG* gene and case 2 with compound heterozygous mutations, novel c.408T>G (p.Tyr136X) and previously reported c.293C>T (p.Pro98Leu), in *MPV17* gene. **Message**: Mitochondrial DNA depletion syndrome is a rare cause of severe acute liver failure in children.

Keywords: *Acute liver failure, Genetic diagnosis, Hepatocerebral mitochondriopathy, Metabolic disorders.*

Mitochondrial disorders are inherited disorders of energy metabolism, caused by mutations either in mitochondrial genome (mtDNA) or in nuclear genes encoding proteins used either in the respiratory chain enzyme complexes or regulating the mtDNA functioning [1]. In childhood, most of the disorders occur due to mutations in the nuclear genes, inherited in autosomal recessive or *X*-linked recessive jmanner. Over the last decade, a growing number of syndromes associated with mitochondrial dysfunction resulting from tissue-specific depletion of mtDNA have been reported in infants [2]. MtDNA depletion syndromes are transmitted as an autosomal recessive trait, and cause respiratory chain dysfunction with prominent neurological, muscular, and hepatic involvement [3,4]. Acute hepatic failure is usually a sporadic phenomenon; mitochondrial disorders are usually not considered in diagnosis due to lack of awareness and resources to prove it. Although there are no specific pointers to mitochondrial etiology, but it should be suspected whenever there is a family history of similar occurrence or parental consanguinity. Unexplained elevated plasma lactates also provide useful clues. We report mitochondrial disorders causing acute hepatic failure in two infants.

CASE REPORTS

Case 1: An 8-month-old boy from Afganistan presented with progressive hepatic failure and encephalopathy for 4-6 weeks. The boy was the third child, born to consanguineous couple with a previous child death at 18 months of age with similar illness. The present child's illness started at four months of age with mild hepatomegaly and derangement of liver enzymes noted during episode of gastroenteritis. At presentation to us, main clinical features were altered sensorium, seizures (requiring ventilation and critical-care management), hypotonia and mild hepatomegaly. Relevant results on investigations are included in ***Table* I**. Child deteriorated rapidly because of liver failure and died within two weeks of admission.

In view of classical features – mainly hepatic failure and central nervous system (CNS) involvement (encephalopathy, seizures), high plasma lactate levels – and family history, a clinical diagnosis of mitochondrial disorder of the mtDNA depletion (Alpers – Huttenlocher syndrome or Pyruvate carboxylase deficiency) was made. Liver and skin biopsies were sent for mitochondrial electron transport chain (ETC) enzymology, pyruvate carboxylase enzyme assay and mtDNA depletion studies. The enzymology in liver revealed significant reduction in activity in complexes I and III (1%) and borderline low activity in complex IV (15%), whereas it was normal in all complexes studied (I, III and IV) in cultured skin fibroblasts. Simultaneous measurement of control enzyme (citrate synthase) in both liver and cultured fibroblasts was normal, indicating good quality of sample. Pyruvate carboxylase enzyme activity was normal.

Next generation sequencing (NGS) was performed for four genes implicated in mtDNA depletion syndromes (*POLG, MPV17, DGUOK and TWINKLE*). The NGS followed by Sanger sequencing in the patient revealed a previously reported homozygous mutation, *c.3286C>T (p.Arg1096Cys)* in POLG gene, thus confirming diagnosis of *POLG*-related hepato-cerebral form of mtDNA depletion syndrome overlapping with Alpers-Huttenlocher syndrome.

Case 2: This 6½-month-old boy born to a non-

consanguineous couple presented with persistent jaundice and abdominal distension since four months of age. Hepatomegaly (without ascites) was noted by pediatrician along with jaundice, cholestasis and coagulopathy at five months of age. There was poor weight gain since three months of age. There was no history of rashes, itching, and clay colored stools, loose stools or vomiting. History of irritability, seizures or altered consciousness was also about. There was no bleeding or any hepatotoxic drug intake.

On examination, the baby had icterus. Without any pallor, edema or scratch marks. His weight was 6 kg and height was 60 cm (both <3rd centile). Abdomen was soft and distended liver was palpable (7.5 cm below right costal margin, firm with smooth surface. Spleen was not palpable and there was no ascites. Rest of the systemic examination was normal.

His metabolic workup, including screening for Galactosemia, Tyrosinemia type 1, amino acids, organic acids and fatty acid oxidation defects, was normal. Plasma lactate was elevated on several occasions. Fasting ultrasound abdomen revealed enlarged liver with increased echogenicity and partially distended gall bladder with wall edema. Spleen and kidneys were normal. His liver biopsy showed mild biliary duct proliferation, intrahepatic cholestasis, pan-lobular steatosis (micro and macrovesicular) and fibrosis. Echocardiogram revealed dilated left ventricle with normal ejection fraction. ECG was normal. Other relevant investigations are provided in ***Table* I**. Neuroimaging showed non-specific changes related to liver dysfunction and hyperammonemia. In view of a progressive cholestatic liver disease and failure to thrive, having excluded many of the metabolic and infectious causes, molecular genetic studies were performed keeping in mind the high index of suspicion of a mitochondrial disorder. NGS was carried out for a panel of 514 genes causing childhood onset recessive disorders. The NGS panel results were further confirmed by Sanger sequencing in our laboratory. The results revealed compound heterozygous mutations, in *MPV17* gene – one novel, c.408T>G (p.Tyr136X), and another previously reported, c.293C>T (p.Pro98Leu), thus confirming the diagnosis of hepato-cerebral type of MDS. Parents were tested further, and detected to carry one mutation each, in heterozygous form. The child died few months later because of progressive liver failure. Liver transplant was not performed in view of mitochondrial etiology and neurological involvement (as evident on neuroimaging).

DISCUSSION

Mitochondrial disorders are infrequently diagnosed in India, mainly because of lack of advanced diagnostic facilities (respiratory chain enzymology and blue native gel electrophoresis) and molecular studies. With increasing availability and feasibility of genetic testing (gene sequencing – either single or panel testing using NGS), it is now becoming possible to confirm these diagnoses – to guide for further management of the child as well as for accurate counseling and prenatal diagnosis in future pregnancies in the families. NGS helped in making diagnosis of *MPV17*-related mtDNA depletion syndrome in case 2, similar to reports earlier [5]. Awareness of these disorders is essential as there are no specific pointers other than raised lactate along with organ-specific dysfunction. An index of suspicion should be raised whenever any child is noted to have the constellation of symptoms of hepato-cerebral or myopathic form or even with isolated liver disease, along with positive family history or consanguinity. Accurate diagnosis can guide pedia-tricians for appropriate management and prognosis of the disease. In our cases, both children were candidates for liver transplantation, but diagnosis of mitochondrial DNA depletion syndrome with multiple organ involvement led to avoidance of the transplant. The decision of avoiding transplant was based on poor outcomes (55% mortality) and progression of disease post-transplant [6]. Patients with MDS also need to be advised against valproate therapy, as it may trigger a crisis and fulminant hepatic failure in children who may not have had hepatic involvement [7,8]. Prenatal diagnosis is now feasible in future pregnancies to rule out 25% risk of recurrence in siblings.

TABLE I BIOCHEMICAL PROFILE IN THE TWO CHILDREN

Investigations	*Case 1*	*Case 2*
Lactate (mg/dL)[#]	115-163*	30.6-8.5
Pyruvate (mg/dL)[#]	1.1	1.7
Lactate: Pyruvate	>20	18
Liver function tests		
AST (IU/L)	133; 583	748
ALT (IU/L)	107; 312	260
GGT (IU/L)	121	96
Alkaline Phosphatase (IU/L)	348	879
S. albumin (g/dL)	1.9	4.3
S. bilirubin (mg/dL); T/D	NA	19.4/ 14.4
Prothrombin time (sec); INR	80.4; 7.2	13; 1.48
APTT (s)	51.2	36.9
S. AFP (IU/mL)	11.1	99600
Plasma ammonia (µmol/L)	79	21
Plasma amino acids (TMS)	Normal	Normal

**Value in mmol/L; [#]plasma values; T=total; D=Direct.*

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Immune Reconstitution Inflammatory Syndrome in CNS Tuberculosis

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Background: Immune Reconstitution Inflammatory Syndrome (IRIS), an exaggerated inflammatory response with clinical worsening due to immune recovery during treatment, is rare in the immune-competent population. **Case characteristics**: A 5-½-year old immune-competent girl with CNS tuberculosis without HIV who developed paradoxical IRIS. **Outcome**: Response to supportive care along with Anti-tuberculosis treatment. **Message**: IRIS can occur in tuberculosis, even in the immuno-competent.

Keywords: *Hypersensitivity, Immunity, Tuberculosis.*

Immune Reconstitution Inflammatory Syndrome (IRIS) is a heightened inflammatory response to a pathogen in the setting of immunologic recovery after immunosuppression. It occurs in those who have undergone a reconstitution of the immune responses against an antigen. It is mostly described in HIV-infected patients initiated on highly active antiretroviral therapy (HAART). It can also occur in patients with solid organ transplant, bone marrow transplant, cytoreductive chemotherapy, and rarely, in tuberculosis [1,2]. IRIS includes increased lymphoproliferative response to mycobacterium antigens, restoration of cutaneous response to tuberculin, and increased activation markers like CD38, TNFA-308*1 and IL6-174*G [3]. We report a girl who developed IRIS after initiating Anti Tuberculosis Treatment (ATT).

CASE REPORT

A 5½-year-old girl was admitted with low grade fever of 1 week duration, drowsiness of two days, signs of