Are we missing Mt DNA depletion syndrome in infants with fulminant hepatic failure?

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Introduction : Mitochondrial DNA (mt DNA) depletion syndromes (MDS) are genetically and clinically heterogenous group of autosomal recessive disorders that are characterized by a severe reduction in mtDNA content leading to impaired energy production in affected tissues and organs. MDS are due to defects in mtDNA maintenance caused by mutations in nuclear genes that function in either mitochondrial nucleotide synthesis (Tk2, SUCLA2, SUCLG1, RRM2B, DGUOK, and TYMP) or mtDNA replication (POLG and C10orf2). MDS are classified as myopathic, encephalomyopathic, hepatocerebral or neurogastrointestinal.(1)

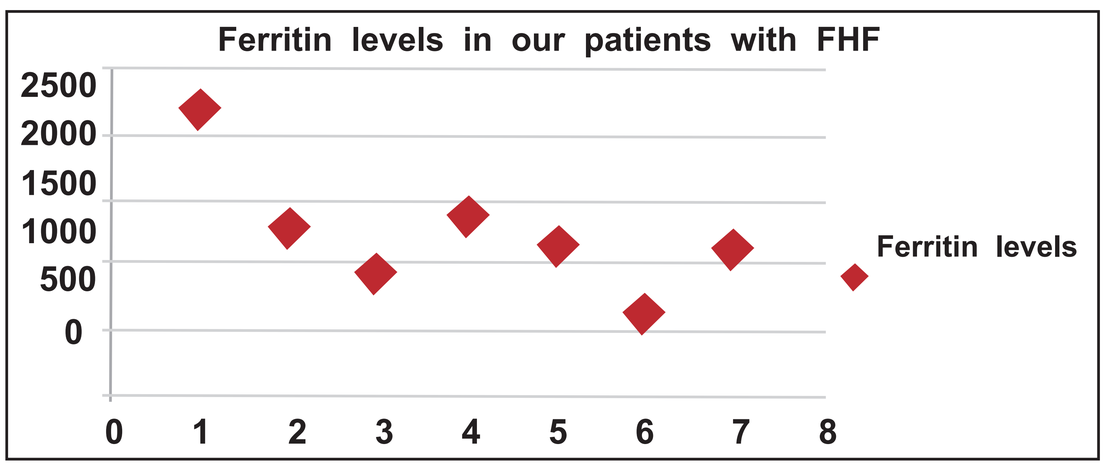
Types of MDS	Genes involved(3)	Symptoms
Myopathic	Tk2 (OMIM*188250)	hypotonia and muscle weakness
Encephalomyopathic	SUCLA2 (OMIM*603921) SUCLG1(OMIM*611224) RRM2B(OMIM*604712)	presents during infancy with hypotonia and pronounced neurological features
Hepatocerebral encephalopathy	DGUOK(OMIM*601465) POLG(OMIM*174763) C10orf2 and MPV17	Early-onset liver dysfunction and neurological involvement.
Neurogastrointestinal	TYMP	presents before age of 20 years

Objective : To screen for MtDNA depletion syndrome in patients with fulminant hepatic failure (FHF).

Materials and method : We analyzed 103 patients with liver disorders. Out of these 8 patients presented with FHF. Common IEM resulting in FHF like galactosemia, tyrosinemia, CDG, HLH, neonatal Hemochromatosis were ruled out by biochemical investigations. Total galactose and Gal - 1 - PUT enzyme were analyzed by colorimetric methods. GC-MS/SIM of urine was performed for the detection of succinyl acetone. Soluble CD25 and Sr. Ferritin were quantitated using ELISA methods. CDG screening was performed using Transferrin isoelectric focusing.

Only one patient agreed for liver biopsy and molecular studies. Histological studies and electron microscopy was performed on liver biopsy specimen. NGS was performed from DNA extracted from blood.

Result : Out of 103 patients presenting with liver disease, 8 presented with FHF, abnormal LFT, jaundice and high ferritin. In these patients galactosemia, tyrosinemia, HLH, CDG, neonatal heomochromatosis were ruled out. Mean ferritin levels were 1232.2±499.1 ng/ml. All 8 patients succumbed to death.



One of our patient, B/O SR presented at 2 days of age with recurrent seizures, altered sensorium, hypotonia, hypoventilation, hepatomegaly, acute liver failure. Metabolic studies did not reveal any specific disorder. We found deranged LFTs and grossly elevated ferritin (1,135 ng/ml). Postmortem Liver Biopsy was performed.

Histopathology (H/E Staining) revealed coarse brown granular pigment in the hepatocytes and periportal areas, suggestive of iron. Perls Iron stain highlighted the pigment confirming Iron.

Electron microscopy of postmortem liver Bx showed features consistent with MtDNA depletion syndrome. Hepatocytes showed back to back arrangement with rare intervening lymphocytes and collagen fibers. The entire cytoplasm was packed with mitochondria assuming on oncocytic change. Almost all the mitochondria showed distortion of shape. Most of the mitochondria showed loss of normal arrangement of the cristae. Few iron particles were also seen in the mitochondria. An occasional myelin like whorled membranous body was noted

Molecular genetic analysis revealed homozygous defect in DGUOK gene. An unreported homozygous splice variation which affects the 4th base from the exon-intron junction (c.142+4 A>C;ENST00000264093.4) was detected.

Discussion : MDS are phenotypically heterogeneous and may affect either a specific organ or a combination of organs, including muscle, liver, brain, and kidney. Hepatocerebral MDS, an infantile - onset disorder, can present with a spectrum of combined hepatic, neurologic, and metabolic manifestations. Affected individuals typically present with manifestations of liver dysfunction, including jaundice, cholestasis, and coagulopathy the vast majority of affected individuals, liver disease progresses to liver failure typically during infancy or early childhood.

We analyzed 103 patients with liver disorder out of which 8 patients presented with fulminant hepatic failure. Of these only one underwent histological and molecular studies for mt DNA depletion syndromes. He was confirmed to have a novel homozygous mutation in the DGOUK gene, supporting the diagnosis.

Friesinger et al studied 12 children with infantile hepato - encephalopathies and mtDNA depletion syndrome and found pathogenic DGUOK mutations in 6[2]. Approximately 100 individuals have been reported with DGUOK related MDS which has two presentations – one neonatal onset multi organ illness like our patient and another little late presentation in infancy or childhood with isolated hepatic disease occasionally following viral illness[1].

Multiorgan form of MtDNA depletion syndrome may be suspected on Newborn screening by elevation of Tyrosine and Phenylalanine[1]. The neonatal onset variety has progressive illness and usually fatal. Hepatocellular carcinoma has also been reported in one patient[1].

Since this disorder has a rapid onset, most of times within 1 week of birth with rapid progression, it has a very poor prognosis. Treatment options suggested are nutritional modulation (avoidance of hypoglycemia, use of corn startch), cofactor use (oral Folinic acid supplementation in children with low CSF Folate), liver transplantation and stem cell therapy[1]. However since it is a multi organ disorder, the role of liver transplantation is controversial[3]. Liver transplantation has been performed in about a third of affected individuals with MPV17 related MDS ; the outcome has not been satisfactory, with half of transplanted children dying in the post transplant period because of multi-organ failure and/or sepsis[1].

In our case, the progress was very rapid and before we could even discuss the possibility of transplant with parents, the child expired within 5 days of birth. However we have offered them a possibility of prenatal diagnosis which in Indian situation is more acceptable as urgent liver transplantation is almost impossible and very costly.

Conclusion : MtDNA depletion syndrome should be considered in any critically ill infant with fulminant hepatic failure, high ferritin, especially when other disorders have been ruled out. Electron microscopy of LiverBx and molecular studies are essential for the diagnosis. Urgent Liver Transplant may be considered as a therapeutic option wherever possible. Prenatal diagnosis can be offered to affected families.

Conflict of interest : None

Abbreviation : CDG : Congenital Disorders of Glycosylation, FHF - fulminant hepatic failure, HLH: Hemophagocytic lympho - histiocytosis, LFT: Liver Function Tests, MDS - mitochondrial DNA depletion syndrome

References :

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