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IP International Journal of Medical Paediatrics and Oncology

Journal homepage: https://www.ijmpo.com/

Case Report

A case of recurrent liver failure during febrile episode

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ARTICLE INFO

Article history:
Received 06-01-2022
Accepted 21-01-2022
Available online 29-03-2022

Keywords:
Acute Liver Failure
Infantile Liver Failure Syndrome 2
Fever
NBAS Gene

ABSTRACT

Infantile liver failure syndrome 2 is a rare autosomal recessive genetic condition which manifests as recurrent acute liver failure episodes triggered by febrile illness. Clinical exome test which showed a homozygous sequence variant in the NBAS gene. The liver enzymes totally deranged during a febrile episopde and may make a complete recovery with conservative treatment like antipyretic therapy and other supportive measures.

1. Introduction

Acute liver failure in children has been defined as the evidence of liver dysfunction within eight weeks of symptom onset or hepatic encephalopathy with uncorrected coagulopathy with an INR >1.5 or INR of >2 without evidence of hepatic encephalopathy with no evidence of chronic liver disease either at present or in the past.[1,2] Multitudes of aetiologies have been identified as the causes for paediatric acute liver failure like infections (viral hepatitis A, B, C, D, E, cytomegalovirus, bacterial septicaemia, etc), drugs and toxins, metabolic causes (galactosemia, hereditary fructose intolerance, neonatal hemochromatosis, mitochondrial diseases and Wilson's disease), peroxisomal disorders, autoimmune causes and HLH.[3] However about 38-49 % of all paediatric ALF still remain undetermined probably owing to the lack of thorough investigations.[4]

All children with pediatric ALF should have a thorough assessment of degree of hepatocellular dysfunction and a systemic approach for evaluation of causes of ALF as the prognosis and outcomes are significantly dependent on the underlying causes. Recurrent pediatric acute liver failure with complete recovery in between the episodes are rare phenomenon in children and may be caused by fulminant viral hepatitis, autoimmune hepatitis, disorders of fatty acid oxidation and carnitine cycle, Wolcott-Rallison syndrome and genetic mutations in NBAS/LARS/RINT1 gene.[5] We herein report a toddler with recurrent episodes of acute liver failure with homozygous mutation in the NBAS gene.

2. Case Report

Fifteen months old male child born out of non-consanguineous marriage presented with low grade fever, vomiting and lethargy of one day duration. No h/o jaundice/altered sensorium/bleeding manifestations. No h/o diarrhoea/abdominal distension/abdominal pain. No h/o dysuria/hematuria/decreased urine output. No h/o sore-throat/cough/runny nose.

1. *Past history:* At 11 months of age, as part of work-up of fever of 3 days duration, he was found to have very high value of transaminases (both above 8000IU) and coagulopathy, due to which a diagnosis of acute liver failure was made. All hepatic failure work-up was negative. He was managed conservatively, with

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https://doi.org/10.18231/j.ijmpo.2022.010

supportive therapy, with which, he improved over a period of 5-6 days.
2. No history of blood transfusions/bleeding manifestations. No h/o intake of indigenous medication.
3. *Antenatal/natal/postnatal history:* uneventful. No h/o neonatal jaundice/transfusions/umbilical vein cannulation.
4. *Developmental history:* Normal.
5. *Family history:* No h/o liver disease/surgery.
6. *General examination:* Afebrile, no dysmorphic facies.
7. *Pulse rate:* 120/min good volume regular, RR 24, BP-80/60, E4V5M6 No jaundice/pallor/stigmata of chronic liver disease.
8. *Anthropometry:* Normal for age.

2.1. System examination

1. *Abdomen:* Soft; liver palpable 2 cm below the RCM, Liver span -7cm soft, minimal tenderness; spleen not palpable.
2. *Nervous system:* Alert, no focal deficits; DTR-normally elicitable; Plantar-flexor.
3. *Other systems:* Normal.
4. *Investigations:* Blood and urine routine, renal function test and electrolytes were normal. Tests for sepsis screen also negative.

VBG — Metabolic acidosis with high lactate and high ammonia.

LFT and PT aPTT values are shown in Table 1.

At admission child had stable vital signs with no features of hepatic encephalopathy. But his investigations showed strikingly elevated transaminases and INR of 9, hence a diagnosis of acute liver failure was made. Child was managed conservatively with IV vitamin K supplementation, fresh frozen plasma, dextrose infusion, IV N-acetyl cysteine infusion, carnitine supplementation, oral lactulose, IV antibiotics, antipyretics and meticulous fluid and electrolyte management.

However, over the next 12 hours, he had progressive lethargy and intermittent irritability with worsening of hepatic encephalopathy to stage 2. On 2nd day of admission child developed visible jaundice, mild hepatomegaly with an otherwise normal systemic examination. The deep tendon reflexes and the plantar reflex remained normal. Child had recurrent episodes of hypoglycaemia requiring dextrose infusion at a higher GIR. There was no further worsening of the sensorium but the liver function tests showed progressive deterioration for the first 3 days. By day 4 of PICU stay, child started to have clinical and biochemical improvement. Child made complete recovery in both clinical and biochemical parameters with the diligent supportive measures. Suspecting rare cause of acute liver failure presenting at a very young age with negative hepatic failure work up, a clinical exome sequencing was sent and it showed a novel homozygous mutation in the NBAS gene pointing towards infantile liver failure syndrome 2. The family was counselled about the disease condition, its genetic implications, the possibility of recurrence of acute liver failure with each inter current illness and the need for early medical evaluation during each febrile episode. After 3 months he was admitted once again for similar complaints, but this time his clinical features and lab parameters were better, improved within 3 days and discharged.

3. Discussion

Infantile liver failure syndrome 2 is a rare autosomal recessive genetic condition which manifests as recurrent acute liver failure episodes or occasionally with elevations in liver biochemical values triggered by febrile illness wherein the liver functions make a complete recovery with conservative treatment like antipyretic therapy and induction of anabolism with parenteral glucose and lipids.[6] These liver dysfunction often develop during infancy or early childhood and become less frequent with age. Crises are heralded by vomiting and lethargy, and start rather uniformly with massively elevated transaminases, followed by coagulopathy requiring FFP substitution with mild to moderate jaundice. Some cases presents with significant hypoglycemia, hyperammonemia, and hepatic encephalopathy secondary to ALF.[7] Our child had the typical presentations of ILFS2 with recurrent ALF following 2 febrile illness at 11 months and 15 months with similar presenting symptoms of fever, vomiting, lethargy and later progressing onto jaundice, coagulopathy and hepatic encephalopathy with strikingly high transaminases but very well responded to supportive measures.

ILFS2 was identified as cause for recurrent liver failure by Haack et al. in 2015 where they found homozygous or compound heterozygous mutation in the neuroblastoma amplified sequence gene(NBAS) in German children who presented with recurrent episodes of ALF triggered by fever.[5] The NBAS gene is located on chromosome 2p24.3 and has 52 exons encoding proteins containing 2,371 amino acids.[8] NBAS mutations were first identified in SOPH syndrome (short stature, skeletal dysplasia, optic nerve atrophy and Pelger-Huët anomaly) where the mutation was in the C terminal of NBAS gene and they commonly do not exhibit a predominant liver phenotype. But recent studies on cases carrying homozygous or compound heterozygous NBAS gene mutations in the N terminal revealed the phenotypic presentation of isolated recurrent ALF.[9,10] Our child had undergone clinical exome test which showed a homozygous sequence variant in the NBAS gene,chr2:15,51,4796delGAG(c.3637_3639 del GAG p. Glu1213 del) (exon 31). Our patient presented a predominant liver phenotype, which was consistent with reported NBAS mutation and did not have any extra hepatic

Table 1:

Date	17/10	18/10	19/10	20/10	22/10	24/10
S. Bilirubin (mg/dL)	0.8/0.5	1.7/1.3	2.5/1.5	3.7/2.3	7.5/5.5	4.5/3.5
S. Protein/Albumin (g/dL)	6.4/3.8	6.5/4.3	5.4/3.7	4.8/3.2	4.3/2.8	4.5/3
SGOT/SGPT (IU/L)	7729/9975	7929/6951	8514/8601	5730/3421	349/3305	137/2465
ALP (IU/L)	371	571	656	546	511	444
PT(sec)	>120	>120	76.6	39.5	25.4	21.3
aPTT	60	55	46	50.5	44	38
INR	9	8.3	8.55	3.8	2.24	1.8

phenotype attributing to SOPH syndrome.

The molecular pathogenesis of NBAS mutation leading onto acute liver disease and its fever dependency is not fully understood. The NBAS protein is a component of SNARE complex and syntaxin 18 complex, which is involved in Golgi-to-ER transport.[11] The NBAS protein interacts with p31 and here the NBAS protein depletion leads to reduced p31 expression and causes redistribution of Golgi recycling proteins accompanied by a defect in protein glycosylation. P31 protein defects can induce hepatocyte apoptosis by increasing the relative expression of stress response genes in the ER. Syntaxin 18 complex is thermally susceptible which causes quantitative and functional disturbances in the NBAS protein levels.[8] So a catabolic state with high energy demand during febrile infections may be the starting points of the derailment, probably due to thermal susceptibility of the syntax in 18 complex.[9]

There is no known cure treatment for patients with NBAS deficiency, but we can optimize supportive treatment and emphasize on the importance of follow-up investigations. Proactive infection prevention strategies are required to avoid ALF episodes during the interval period. Early antipyretic therapy is very effective in preventing the later occurrence of ALF.[8] The early parental application of glucose and lipids will disable the catabolic phase and ameliorate the disease severity at a faster rate and promote patient recovery.[7] Patients with hepatic encephalopathy can receive L-carnitine supplementation.[12] ALF can be lethal in patients without treatment and may end up in liver transplantation. Thus, early diagnosis is critical for the treatment and management of paediatric ALF.

4. Conclusions

Acute liver failure in children may be due to various etiologies. When a child presented with recurrent liver failure, one has to keep the possibility of Infantile liver failure syndrome-2. It may be lethal in a child without treatment. Early diagnosis and prompt supportive management are critical.

5. Source of Funding

None.

6. Conflict of Interest

The author declares that there is no conflict of interest.

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Cite this article: Ananda Kesavan T.M., Sundaresan R, Nagarjoon B. A case of recurrent liver failure during febrile episode. *IP Int J Med Paediatr Oncol* 2022;8(1):42-45.