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Case Report

Progressive familial intrahepatic cholestasis-2 and concomitant cytomegalovirus infection in an infant: a case report

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ABSTRACT

Conjugated hyperbilirubinemia (CH) in infancy can have anatomic, infectious, auto-immune and metabolic causes. We reported a case of CH presented at 2 months and 20 days, with clinical jaundice and evidence of acute on chronic liver failure. Significant history of elder sibling death at the age of 5 months due to hepatic failure and intracranial bleed was present. Investigations revealed a normal gamma glutamyl transpeptidase (GGT) levels. Toxoplasmosis, rubella, cytomegalovirus and herpes simplex (TORCH) panel showed cytomegalovirus (CMV) immunoglobulin M (IgM), immunoglobulin G (IgG) and deoxyribonucleic acid polymerase chain reaction (DNA PCR) positive with mother's serum CMV IgG, so she was started on oral valganciclovir in addition to other treatment for cholestasis. A clinical exome panel was also sent which showed homozygous two base-pair deletion in exon 27 of the ABCB11 gene [c.3659 3660del (p.Ser1220Ter)] suggestive of benign recurrent intrahepatic cholestasis (BRIC)/progressive familial intrahepatic cholestasis-2 (PFIC-2). The child responded initially to treatment showing reduced serum conjugated bilirubin level and near normalization of INR. However, she was re-admitted with deranged coagulation profile and rising conjugated bilirubin levels after 30 days of discharge and expired due to fulminant hepatic failure with encephalopathy at 6 months of age while she was being prepared for live donor (father) liver transplantation. We presented this case because we found evidence of CMV infection in a child with PFIC-2. The relative contribution of either aetiology needs to be ascertained in view of early recurrence of CH despite standard management protocol including oral valgancyclovir for CMV infection.

Keywords: PFIC-2, Cytomegalovirus, Neonatal cholestasis, Conjugated hyperbilirubinemia

INTRODUCTION

Bile salt export pump deficiency (BSEP) is an autosomal recessive disorder due to novel mutations in ABCB11 gene. It is responsible for two phenotypes with varied clinical course namely, progressive familial intrahepatic cholestasis-2 (PFIC-2) and benign recurrent intrahepatic cholestasis-2 (BRIC-2). PFIC-2 presents as a rapidly progressive disease with liver failure that requires early liver transplantation (LT) while BRIC-2 is characterized by intermittent attacks of cholestasis and there is no progression to liver cirrhosis and hence life expectancy is good.[1]

Cytomegalovirus (CMV) is the most common congenital viral infection affecting 0.6 to 0.7% of live births. Clinical features include microcephaly, growth retardation, sensorineural hearing loss and multi organ disease. CMV hepatitis is a cause of cholestatic jaundice and subsequent liver failure in infants.[2] Here we presented an infant with CH with PFIC-2 and CMV infection.

CASE REPORT

A female baby, born of non-consanguineous marriage came to our hospital with complaints of yellowish discoloration of urine and skin for 2 days and vomiting for

2 days at the age of two and half months. She was delivered by lower segment caesarean section and weighed 2.6 kg. Her newborn screening and tandem mass spectrometry were normal at birth. She had a family history of sibling death at 5 months of age due to hepatic failure and intracranial bleed, where final etiological diagnosis was not established.

On examination, she was alert but was deeply icteric. She weighed 4.2 kg (less than 3rd centile), had a length of 57 cm (between 3rd to 50th centile) and head circumference of 37 cm (between 3rd to 50th centile). She had an enlarged firm liver with a span of 5.5 cm without splenomegaly.

Laboratory findings at admission included total bilirubin of 26.4 mg/dl (normal 0.2-1.2 mg/dl) with a direct component of 19.2 mg/dl, raised liver enzymes of serum glutamic-oxaloacetic transaminase (SGOT)-1765 U/l (normal 22-63 U/l), serum glutamic pyruvic transaminase (SGPT)-916 U/l (normal 12-45 U/l) and alkaline phosphatase 1084 U/l (normal 50-469 U/l) with normal gamma-glutamyl transferase (GGT) (39 U/l). Her total proteins and albumin were 4.6 mg/dl (normal 6-8.7 gm/dl) and 3.6 mg/dl (normal 3.5-5.5 gm/dl) respectively with raised prothrombin time/international normalized ratio (PT/INR) of 28.9 seconds/2.63 (normal PT 11-16 s/INR 1-1.46). Abdominal ultrasound showed mild hepatomegaly with parenchymal inflammation with normal biliary architecture. She was started on intravenous antibiotics, water soluble forms of vitamins A, D, E, K and appropriate nutritional support.

For the evaluation of infectious causes of hepatitis, TORCH titres of mother and baby were sent which showed positive IgG CMV for mother and positive IgG and IgM for baby. CMV infection was confirmed with serum DNA PCR) and she was started on oral valgancyclovir at a dose of 16 mg per kg per dose. Her hearing and vision were assessed and were normal. She had no other stigmata of congenital/perinatal CMV.

She was additionally evaluated for metabolic and inherited causes which showed a raised alpha-feto protein (38419 IU/ml), normal glucose-6-phosphate dehydrogenase (G_6PD) levels, normal levels of galactose-uridyl transferase, normal levels of urinary amino acids and no alpha-1-anti-trypsin deficiency. A clinical exome panel was also sent as she had a significant family history of jaundice.

She responded to the supportive measures as evidenced by normalising of INR, fall in serum bilirubin and gain in weight (Table 1). She also required packed cell and fresh frozen plasma transfusions for her falling haemoglobin and deranged INR. Meanwhile, after a month's stay in our ward, the clinical exome panel reported a homozygous base pair deletion in exon 27 of ABCB11 gene which was suggestive of PFIC-2/BRIC-2. The parents were informed about the nature of the disease and the need for LT in the future. She was discharged home with medications as she had good response to medical therapy and was gaining weight. Her parents were advised regular follow-up.

Table 1: Liver function and weight trends in ward.

Day of admission	1	6	12	21	38
Serum bilirubin/direct	26.4/19.2	24.7/18.4	17.6/12.1	17.6/12.1	12.7/9.6
SGOT/SGPT (U/l)	1765/916	366/300	286/82	273/54	302/47
GGT (U/l)			82	54	37
Total protein/albumin (mg/dl)	4.6/3.6	4.6/3.4	4.9/3.1	4.9/3.2	5.2/3.4
PT (seconds)/INR	28.9/2.63	35.7/3.27	26.7/2.42	23/2.07	18.7/1.67
Hemoglobin (g/dl)	9.0	8	11.5	11	11.2
Total leucocyte count (per cumm)	13,030	19820	15330	15300	12780
Platelets (per cumm)	74000	161000	191300	153300	167000
Weight (grams)	3700	4040	4100	4440	4650

Child was re-admitted at 5 months of age for rising bilirubin and INR along with evaluation by LT team. However, she expired at 6 months of age due to development of hepatic encephalopathy and coagulopathy before live donor LT could be performed.

DISCUSSION

PFIC-2 is a progressive liver disease with autosomal recessive inheritance resulting from accumulation of bile acids due to defect in BSEP. PFIC accounted for 3-13% of neonatal cholestasis among which PFIC-2 was the most prevalent subtype. The incidence of PFIC was estimated at 1/50,000 to 1/1, 00,000. Children usually presented in early infancy with jaundice with/without pruritus and failure to thrive.[1,3] This child presented to us at 2 months 20 days of life with CH with a significant family history of elder sibling death. There was improvement in clinical and laboratory parameters with medical management along with anti-CMV therapy, however she relapsed within one month progressing rapidly to hepatic encephalopathy with

deranged coagulation profile with fatal outcome before live donor LT could be done.

Neonatal cholestasis can be due to anatomical, infectious, auto-immune and metabolic conditions. Since PFIC is a rare cause, children with neonatal cholestasis should be evaluated for other causes including TORCH infections. CMV infection in infancy can be congenital or perinatal and might lead to growth retardation, sensori-neural hearing loss, hepatitis and microcephaly.[4] Diagnosis was done by a DNA PCR test in the urine, saliva or serum with or without positive CMV IgM. However, in resource limited settings, where DNA PCR was not available a positive IgM in a symptomatic infant may be considered as infection.[5] Injectable gancyclovir and oral valgancyclovir were used for treatment of symptomatic infection however, a case-based approach was needed while deciding the need for treatment and route of administration.[2,4] Our case was positive for CMV IgG, IgM and DNA-PCR, along with signs of hepatic failure, hence a decision was taken to start her on oral valgancyclovir for 6 months.

Management of PFIC-2 required close collaboration between paediatricians, hepatologists and surgical teams. The initial medical management included appropriate nutrition and supplementation with water soluble vitamins, medium chain triglycerides and minerals. Medical management includes ursodeoxycholic acid (UDCA) at 15 mg/kg/day, cholestyramine, rifampicin, naltrexone and ondansetron. Agarwal et al had conducted a study on 19 children with PFIC-2 of which 12 improved on medical therapy.[3] Some children with PFIC might benefit from steroids as demonstrated by Engelmann et al where they used steroids in 2 children for different indication (systemic lupus erythematous and colitis) but it resulted in a decrease in the serum bilirubin.[6] In our case, we started the child on UDCA, cholestyramine and rifampicin which resulted in initial control but could not stop the progression of hepatic failure.

Children who failed to respond to medical management usually needed surgical intervention. Biliary diversion procedures can be done in children with preserved liver function and intractable pruritus. However, most of the children have end stage liver disease and require LT. In the study conducted by Agarwal et al 3 of 19 children required LT.[3] In another study by Liu et al all 5 children of PFIC required LT.[7] In our case, the child had been registered as a liver recipient and was undergoing pre transplant work-up along with her father as the prospective live donor. Father was found unfit by the transplant team after extensive investigations. The child succumbed while her mother was being investigated as a prospective live donor.

While investigating a child with cholestasis, it is important to treat other illnesses which can worsen the disease course. Swed-Tobia et al in their series of 3 cases found concomitant CMV infection which was treated with valgancyclovir and there was worsening of symptoms on stopping the antivirals.[8] In our case after starting treatment with valgancyclovir, there was an initial stabilisation of parameters. It might be due to control of CMV infection resulting in slowing down the progression of liver failure. This is critical for the child before LT. In our literature search this will be the first such case to be reported having PFIC-2 with CMV co-infection.

CONCLUSION

Extensive evaluation of infants with cholestasis is necessary especially when there is a significant family history. Even if primary aetiology of the cholestasis is established, other associated infections especially congenital CMV infection has to be controlled to stabilise the child and improve the on-going liver damage before LT.

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REFERENCES

1. Jacquemin E. Progressive familial intrahepatic cholestasis. Clin Res Hepatol Gastroenterol. 2012;36(1): 26-35.
2. Hasosah MY, Kutbi SY, Al-Amri AW, Alsahafi AF, Sukkar GA, Alghamdi KJ, et al. Perinatal cytomegalovirus hepatitis in Saudi infants: A case series. Saudi J Gastroenterol. 2012;18:208-13.
3. Agarwal S, Lal BB, Rawat D, Rastogi A, Bharathy KG, Alam S. Progressive Familial Intrahepatic Cholestasis (PFIC) in Indian Children: Clinical Spectrum and Outcome. J Clin Exp Hepatol. 2016;6(3):203-8.
4. Bilavsky E, Schwarz M, Bar-Sever Z, Pardo J, Amir J. Hepatic involvement in congenital cytomegalovirus infection - infrequent yet significant. J Viral Hepat. 2015;22(9):763-8.
5. Abolurin OO, Senbanjo IO, Adekoya AO, Ajibola ED. Congenital cytomegalovirus infection as an important cause of infantile cholestatic jaundice: a case report. Pan Afr Med J. 2020;36:106-8.
6. Engelmann G, Wenning D, Herebian D, Sander O, Dröge C, Kluge S, Kubitz R. Two Case Reports of Successful Treatment of Cholestasis with Steroids in Patients With PFIC-2. Pediatrics. 2015;135(5):1326-32.
7. Liu Y, Sun LY, Zhu ZJ, Wei L, Qu W, Zeng ZG. Liver Transplantation for Progressive Familial Intrahepatic Cholestasis. Ann Transplant. 2018;23:666-73.

8. Swed-Tobia R, Kassis I, Weiss K, Tal G, Shaoul R, Falik-Zaccai TC, Mandel H, Meir M. Concomitant congenital CMV infection and inherited liver diseases. Eur J Med Genet. 2021;64(8):104249.

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