Case Report

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Hepatitis-E-induced cholestasis in a child: a case report

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Introduction and importance: Hepatitis E virus (HEV) is a major cause of epidemic water-borne hepatitis in tropical and subtropical countries in areas with poor sanitary conditions. The infection by HEV in children is frequent but typically asymptomatic or manifested only as a very mild disease without jaundice, and usually, it often goes undiagnosed. In this case report, the authors describe a case of hepatitis-E-induced cholestasis in a child.

Case presentation: An 8-year-old male child presented to a Pediatrics emergency with fever and features of acute cholestasis. On abdominal examination, there was non-tender hepatomegaly. The rest of the systemic examinations were normal. Ultrasonography findings were suggestive of acute hepatitis. The liver biopsy report showed hepatic cholestasis and hepatitis. The serological test for hepatitis E IgM was positive. The child was managed symptomatically.

Conclusion: Although cholestasis is uncommon in children with HEV infection, it should be considered for non-improving clinical status in children with hepatitis. Also, patients with jaundice and Hepatitis E should be followed up by treating physicians until resolution occurs. To the authors' knowledge, this is the first case report from Nepal describing cholestasis in a child due to HEV infection.

Keywords: Case report, cholestasis, Hepatitis E, jaundice

Introduction and importance

Hepatitis E virus (HEV) is a non-enveloped single-strand positive-sense RNA virus[1]. HEV is the sole member of the genus *Hepevirus* in the family Hepeviridae[2].

HEV remains poorly understood, with little comprehension of its mechanisms of replication and pathogenesis. The origin of hepatitis E also remains unknown[3]

There are eight genotypes of HEV: HEV1, and HEV2 are restricted to humans, HEV3 is found in humans, swine, rabbits, deer, and mongooses, HEV4 circulates among humans and swine, HEV5 and HEV6 are found in wild boars, and finally HEV7 and HEV8 were identified in dromedary and Bactrian camels[1].

HEV is a major cause of epidemic water-borne hepatitis in tropical and subtropical countries in areas with poor sanitary conditions. The infection is endemic to southeast and central Asia, the Middle East, and northern and western Africa. HEV has its peak incidence in early adulthood[2].

HEV genotypes 1 and 2 are water-borne transmitted and usually cause self-limiting episodes of hepatitis among individuals without comorbidities.

Although HEV infection primarily targets the liver cells, several studies have shown that HEV can multiply in other extra-hepatic tissues such as the kidneys, digestive tract, spleen, placenta, and neuronal cells. Therefore, besides the common liver injury described, HEV may induce extrahepatic manifestations in children as well as in adults[4].

The infection by HEV in children is frequent but typically asymptomatic or manifested only as a very mild disease without jaundice, and usually, it often goes undiagnosed. Clinical symptoms include fever, pain, myalgia, anorexia, jaundice, pruritus, clear stools, and dark urine[5].

Pregnant women and patients with pre-existing chronic liver diseases are at particular risk of fulminant hepatic failure upon HEV infection[6].

HIGHLIGHTS

- The infection by hepatitis E virus in children is frequent.
- Typically, the infection is asymptomatic and may be manifested only as a very mild disease without jaundice, and usually, it often goes undiagnosed.
- Children infected with hepatitis E presenting with cholestasis is uncommon.
- The literature review on hepatitis-E-induced cholestasis in children is insufficient and rare. To our knowledge, this is the first reported case of hepatitis-E-induced cholestasis in a child to be reported from Nepal.

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The diagnosis of acute HEV infection is based on the detection of HEV RNA by polymerase chain reaction (PCR) and/or anti-HEV IgM. Anti-HEV IgG emerges normally in the later course of resolving hepatitis E[7].

The infection by HEV in children follows a mild clinical course without jaundice which often goes undiagnosed. Here we report a case of acute HEV infection in a male child with acute cholestasis.

This case report has been reported in line with SCARE Criteria 2020[8].

Case presentation

Our patient was an 8 years-old male child who belong to a Tharu family in the southern part of eastern Nepal. The child presented to a Paediatrics emergency with complaints of fever, vomiting, and jaundice. Fever was documented and the maximum recorded temperature at home was 101.8 °F. Vomiting was non-bilious, non-projectile, and non-foul smelling. The patient developed decreased appetite and jaundice, which was first noticed by the child's mother on 3rd day of the fever. There was a history of dark-coloured urine and altered stool colour. There was no recent travel history of the patient and his family members or history of illicit drug use, herbal remedies, or blood transfusions. There is no history of a similar episode of jaundice and prodromal symptoms in the past.

On examination at presentation, the child had a fever of 100.4 °F, was icteric and his vitals were within normal limits. On abdominal examination, there was non-tender hepatomegaly extending about 4 cm below the right costal margin in the mid-clavicular line, but the enlargement of the spleen was not detected. The cardiovascular system, respiratory system, thyroid, and neurological examinations were normal. He was hemodynamically stable with no clinical evidence of hepatic encephalopathy. Blood investigations were done which showed a deranged liver function test (LFT) and the child was admitted to the Paediatrics ward. In the ward, a LFT was requested along also tests for hepatitis A, B, and C, autoantibodies, ferritin, ceruloplasmin, and α1-antitrypsin.

LFT was deranged but other test results were negative. Then ultrasound of the liver was performed which showed decreased overall echotexture and patent liver vasculature. The gall bladder and the biliary tract were regular and there was no ascites. Due to inconclusive results, a test for hepatitis E was performed and a liver biopsy was planned. Serological test for hepatitis E IgM came out to be positive (407 mg/dl) which confirmed the diagnosis of hepatitis E infection. Tests for viral loads, such as reverse transcriptase polymerase chain reaction was not performed.

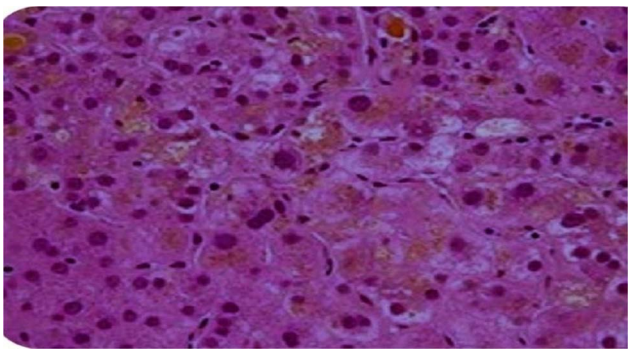

Figure 1. Liver histology of hepatitis E. Accumulation of bile pigment in hepatocyte cytoplasm and mild inflammation in the sinusoidal space (H and E ×400). H and E, hematoxylin and eosin.

Table 1

Summary of patient's liver function tests during the course of Illness

	Day of admission	Day 8	Day of discharge
Bilirubin (0.1–1.2 mg/dl)	5.6	6.4	1.7
ALT (0–50 IU/l)	300	580	102
AST (10–40 IU/l)	80	100	34
ALP (40–150 IU/l)	176	190	155
GGT (0–55 IU/l)	88	96	57
Albumin (3.5–5 g/dl)	4.1	3.8	4.6
PT (12–16 s)	14	13.5	14.2

ALT, Alanine transaminase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; GGT, Gamma Glutamyl transferase; PT, Prothrombin time

Investigations	Result
Hepatitis A -IgG	-
-IgM	-
Hepatitis E -IgG	Negative
-IgM	Positive

The patient was managed symptomatically, and regular monitoring of his vitals (pulse rate, blood pressure, respiratory rate, and temperature) and urine output was done. Despite symptomatic management, the child's condition did not improve for which a liver biopsy was performed which showed hepatic cholestasis and inflammation of sinusoidal space as shown in Figure 1. Symptomatic management was continued, and more vigorous monitoring of the child was done. With time the child's condition improved and the child was discharged to follow-up in OPD after 2 weeks or when needed (Table 1).

Clinical discussion

In 1978, hepatitis E was first identified by Dr. Mohammad S Khuroo as an outbreak of non-A, non-B hepatitis in Kashmir, India[4] however, it was first characterized in detail in 1983 during an outbreak of non-A non-B, non-C hepatitis among Soviet soldiers on a military mission in Afghanistan[9].

HEV has been described as uncoated icosahedral particles with a "spiky" surface and 27–30 nm in diameter. Latest studies indicate that the HEV exists in two forms: uncoated, naked virions, which are eliminated in the bile and faeces to mediate inter-host transmission, and membrane-coated (a lipid membrane), quasi-enveloped virions that circulate in the blood flow to mediate the spread of the virus in the host[4].

The mean incubation time of HEV is 40 days, and the highest rate of involvement is between 15 and 40 years of age. It affects more men than women, with a ratio of 2:1 in developing countries and greater than 3:1 in developed countries[3].

HEV infection has been recognized as a travel-associated infectious disease [Minkoff and colleagues]. HEV infection may challenge the immunosuppressed and those with underlying disorders especially when they travel to endemic regions[10].

HEV infection may trigger an immune cascade leading to Autoimmune hepatitis. Clinical, laboratory and histopathologic features of such patients are not specific for HEV and can mimic Autoimmune hepatitis, thereby creating a diagnostic dilemma[11].

Our diagnosis of hepatitis E was confirmed with serum ELISA IgM HEV. The diagnosis of HEV can also be based on the detection of the HEV genome in serum or faeces by polymerase chain reaction.

Our patient is different in that he is a male child 8 years old who develop cholestasis from Hepatitis E infection which resulted in the long duration of hospital admission.

Although Pregnancy has been shown to be associated with a higher incidence of progression to acute liver failure, this did not apply to our case[12].

Acute HEV infection is an important diagnosis to consider in paediatric travellers returning ill with fever and a gastrointestinal symptom complex from HEV-hyperendemic regions, especially if they are VFR travelers[11]. Our case is different in that neither child nor any of the family members have a recent travel history. Also, there is no history of blood transfusion or organ transplantation.

The infection by HEV in children is frequent but typically asymptomatic or manifested only as a very mild disease without jaundice, and usually, it often goes undiagnosed[6,13]. But in our case, the child developed jaundice and features of cholestasis.

Additionally, tests for anti-nuclear antibody, Rheumatoid factor, Smooth muscle, and Anti-Mitochondrial antibodies were found to be negative in our case. Some of the studies showed the presence of autoantibodies like anti-nuclear antibody in patients with hepatitis E infection[14,15].

Prolonged cholestasis, characterized by a protracted period of jaundice (lasting > 3 months), has been described in up to 60% of patients with acute HEV[16]. Patients may be asymptomatic or have symptoms of pruritus due to cholestasis. In general, cholestatic hepatitis resolves spontaneously within weeks to months with no sequelae[17]. Recovery is marked by viral clearance, an increase in IgG anti-HEV titres, and a decrease in IgM anti-HEV levels[18].

In our case, the patient had features of cholestasis like jaundice, dark-coloured urine, and altered stool colour but not pruritis. Similarly, cholestatic hepatitis resolved within weeks, but not in months. During the recovery period, serological investigations were not done in our case.

In a case reported by Sebode and colleagues liver histology of acute hepatitis E showed acute lobular hepatitis with signs of regeneration; cholestatic hepatitis was also present, represented by proliferating neoductuli[7]. Whereas in our case, liver histology showed an accumulation of bile pigment in hepatocyte cytoplasm and mild inflammation in the sinusoidal space.

The diagnosis of HEV should be considered in patients who present with acute or chronic hepatitis that cannot be explained by other causes[19].

Conclusion

Though jaundice/cholestasis is uncommon in children due to HEV infection, it should be considered in non-improving clinical status in children with hepatitis. Also, patients with jaundice and hepatitis E should be followed up by treating physicians until resolution occurs.

Ethical approval

None.

Consent

Written informed consent was obtained from the patient's father for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

S.P. and A. Bhusal.: literature review, follow-up the patient, writing the manuscript, and final approval of the manuscript. N.K.: Supervisor, literature review, treating physician of the patient, and final approval of the manuscript. H.B.B. and A. Banjade: literature review and final approval of the manuscript.

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There are no conflicts of interest.

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