Acute Hepatitis Due to Co-infection with Hepatitis A and Epstein-Barr Virus

K. Jagadish Kumar[1*], Sangeetha Balaji[2], Manjunath VG[1], Satyesh Chowdary[2]

[1]Professor of Pediatrics JSS Medical College, JSS Academy of Higher Education and Research, Mysore, India
[2]Resident in Pediatrics, JSS Medical College, JSS Academy of Higher Education and Research, Mysore, India

Case Report

ABSTRACT

Hepatitis A viral infection is a common illness across the globe, particularly among the pediatric population. In 30% of infected children below 6 years, it presents as symptomatic hepatitis. *Epstein-Barr virus (EBV)* infections are common in early childhood and cause infectious mononucleosis in young adolescents. Primary EBV infection presentation as isolated hepatitis without infectious mononucleosis (IM) syndrome is very rare. In tropical countries, co-infections are common. We report acute hepatitis due to dual infection of hepatitis A and EBV in an 8-year-old child.

Keywords: Acute hepatitis, Hepatitis A, *Epstein-Barr virus*, Co-infection

Please cite this paper as:
Kumar KJ, Balaji S, VG M, Chowdary S. Acute Hepatitis Due to Co-infection with Hepatitis A and Epstein-Barr Virus. *Govaresh* 2022;26: 262-265.

Corresponding author:
K. Jagadish Kumar, MD
Professor of pediatrics, JSS Medical College,
JSS Academy of Higher Education and Research,
Mysore, India
Tel : + 91 9844281859
Fax : + 91 08212335556
Email: jagdishmandya@gmail.com
Received :06 Apr. 2021
Edited : 22 Sep. 2021
Accepted: 23 Sep. 2021

INTRODUCTION

Hepatitis A virus (HAV), *hepatitis B virus (HBV)*, and *hepatitis C virus (HCV)* are the etiological agents/ organisms accounting for > 95% of acute viral hepatitis in the United States (1). Few patients with acute viral hepatitis may be infected with other hepatotropic viruses in whom serological markers for/of the above viruses are absent (1). *Epstein-Barr virus (EBV)* infections are common in early childhood. The most common clinical presentation of EBV infection is infectious mononucleosis (IM), which includes the triad of fever, generalized lymphadenopathy, and pharyngitis (2). During the course of IM, acute symptomatic hepatitis is rare, and acute hepatitis without IM syndrome is extremely rare (3). In tropical countries, co-infections are common. We are reporting acute hepatitis due to dual infection of hepatitis A and EBV in an 8-year-old child.

CASE REPORT

An 8-year-old girl presented with complaints of fever of 7 days and jaundice for 2 days. She also had vomiting and abdominal pain. Her urine was dark yellow, and her stools were pale. On examination, her vitals were: temperature 99.4^0 F, respiratory rate 30/minute, pulse rate 96/minute, and blood pressure 100/60 mm Hg. She had severe pallor and jaundice. There was no lymphadenopathy or pedal edema. She had 3 cm tender hepatomegaly and also 3 cm splenomegaly. The rest of the systemic examination was unremarkable. Slit-lamp examination of eyes did not show any KF (Kayser-Fleischer) ring. One pint of packed RBCs was transfused to correct her severe anemia. Peripheral blood smear showed microcytic hypochromic RBCs, elliptocytes, polychromatophils, anisopoikilocytosis, nRBCs 3/100 WBCs, leukocytosis with toxic granules in neutrophils. Serology for Anti-HCV (CLIA), HbsAg (CLIA), Anti HEV IgM (ELISA), Anti HIV (CLIA), Dengue NS1 and IgM (ELISA), Leptospira IgM (ELISA),

Paul Bunnel test, Widal (Tube agglutination test), Weil Felix (Slide agglutination test) and peripheral blood for malarial parasite: All were negative. Direct and indirect Coomb's test: negative. Covid-19 RT PCR was negative. Ultrasonography of the abdomen and pelvis was done, which showed hepatosplenomegaly with gall bladder wall edema and very minimal ascites. Chest radiography was normal. Iron profile was done, which showed iron deficiency. Thyroid profile was normal. Urinalysis showed urine bilirubin and urobilinogen. Blood culture and urine culture were sterile.

Investigations are enlisted in Table 1. At admission, in view of suspicion of leptospirosis, she was started on Injection cefotaxime, which was given for 5 days. The patient had fever spikes during the first five days of the hospital stay, which resolved by the 7th day of admission. At discharge on the 10th day, she had mild jaundice, normal colored urine, hepatomegaly of 2 cm, and spleen was no longer palpable. In our patient, alkaline phosphatase was slightly elevated at 6 weeks after discharge. She was followed up for 3 months without any problems.

DISCUSSION

EBV is a gamma herpes virus that infects humans around the world with a high prevalence (3). EBV infection is mostly asymptomatic in children under 5 years and causes IM in young adolescents(3,4). Primary EBV infection presenting as isolated EBV hepatitis without IM syndrome is very rare (3). In EBV infection, sub-clinical infection of the liver is common (4). Infrequently, primary EBV infection can present as acute cholestatic hepatitis(2). While most EBV hepatitis cases are self-limited, few fatal cases have been reported(2,5). Although raised serum transaminases levels are found in 80% of patients, jaundice occurs in only 5% (2, 4, 5). In EBV infection, transaminases are typically elevated to less than five-fold normal levels. Elevations greater than 10 times are less likely and rarely above 1000 IU/L(2,5).

In a study by Kofetridis and colleagues, among 41 EBV infected cases, jaundice was observed in only 6% of cases, whereas anicteric cholestatic liver disease with elevated A*lkaline phosphatase* (ALP) and serum gamma glutamyl transferase (γ-GT) were seen in 59% of cases(2). In a similar study, Yang and co-workers observed jaundice in 5.6% of the cases and elevated ALP and γ-GT levels in 39% of patients (5). The exact cause for the cholestasis in EBV infection is unknown. It is postulated to be due to the effect of the virus on systemic and intrahepatic production of pro-inflammatory cytokines, which interfere with the activity of both the sinusoidal and canalicular transporting systems that may result in cholestasis(2). Jaundice may also be a consequence of virus-induced hemolysis(6).

In children, HAV infection is a self-limiting disease associated with non-specific symptoms, such as fever, malaise, anorexia, vomiting, nausea, abdominal pain, and diarrhea. Jaundice usually occurs one week after the onset of symptoms. In children younger than 6 years, symptomatic hepatitis occurs in approximately 30% of infected children, and jaundice usually lasts for less than two weeks(7). When older children and adolescents are infected, they are usually symptomatic for several weeks(7). It is difficult to clinically differentiate the presentation of hepatitis A from other causes of acute viral hepatitis because of coinciding symptoms with many other gastrointestinal and febrile conditions(8).

In tropical countries, co-infections are common. Weissman and colleagues reported an EBV case with a negative hepatitis A panel during the early period of illness, which was then found to be positive weeks later(9). Out of 103 children with EBV, only three had acute hepatitis, and co-infection was found in two of them (one was echovirus, and the other was hepatitis A)(10). Kang and others reported acute hepatitis secondary to IM concomitantly infected with hepatitis A in a young adult (4).

Our child presented with fever for one week and jaundice for 2 days. On examination, she had icterus and severe pallor along with hepatosplenomegaly. She continued to have a fever for one more week after admission. Her hemoglobin was 4.8 g/dL, reticulocyte count 5.2%, and Lactate Dehydrogenase (LDH) was 593 U/L, but the Coombs test was negative. Jaundice with severe pallor in a febrile child with features of hemolytic anemia prompted us to send EBV viral capsid IgM antibody and hepatotropic virus panel. In IM, acute hemolytic anemia is a rare complication (6). Hepatitis A transmission occurs via the fecal-oral route and replicates in the liver. After 10-12 days, it is excreted via the biliary system into the feces.

Table 1: Investigations

Investigations	On admission day	3rd day of admission	6th day of admission	6weeks after discharge
Hb [11.5-15.5g/dL]	4.8	7.4	7.1	11.7
PCV [35-45%]	17.2	25.9	24.5	37.3
RBC count [4-5.2million/mm^3]	3.06	3.94	3.73	4.92
MCV [77-95fL]	56.2	65.7	65	75.8
MCH [25-33pg]	15.8	18.8	19	23.8
MCHC [33-35g/dL]	28	28.6	29	31.4
TLC [4000-11000cells/mm^3]	18,640	11,490	10,290	6970
N/L/E/M/B	67/27/0.8/4.2/0.1	68/25/0.8/4.8/0.1	57/35/1.1/5.6/.3	46/45/4/3.6/0.3
Platelets [1.5-4.5lakh/mm^3]	5.72	7.08	7.8	3.5
Reticulocyte count [2-5%]	5.2	5.5		
RDW [12-14.5%]	37.6			24.9
Mentzer index	18			
ESR [<20mm in 1 hr]	50	120		
CRP [<5mg/L]	2.3	4.8		
Urea [12.6-42.6mg/dL]	20			
Creatinine [0.2-.7mg/dL]	0.3			
Random sugar [70-140 mg/dL]	97			
Na/K/Cl [mEq/L]	135/4.5/97		133/4.6/94	
Bilirubin (total/direct) [N=<1.2/<0.2mg/dL]	8.3/7.6		5.3 / 5.09	0.24/0.15
AST [N=<32IU/L]	389		114	96
ALT [N=<33IU/L]	762		176	143
Albumin [N=3.5-5.2 g/dL]	3.3		3.1	4.5
Total protein [N=6-8.3 g/dL]	6.1	6.9		7.1
LDH [N=135-214U/L]	593		370	
ALP [N=<300U/L]	366		490	313
PT [N=11-14.2secs]	13.6			13.7
APTT [N=21-36secs]	32.2			35
INR	1.05			
EBV antibody to Viral Capsid Antigen (VCA) , IgM = 27.36 U/ml [more than 12 is positive][CLIA]				
Anti Hepatitis A Virus [HAV] , IgM = 14.59 index [more than 1.20 is positive][ELISA]				

PCV (Packed cell volume), RBC (Red blood cells), MCV (Mean corpuscular volume), MCH (Mean corpuscular haemoglobin), MCHC (Mean corpuscular hemoglobin concentration),TLC (Total leucocyte count), RDW (red cell distribution width), CRP (C-reactive protein) , ESR(Erythrocyte sedimentation rate), AST (Aspartate aminotransferase), ALT (Alanine transaminase), ALP (Alkaline phosphatase), PT (prothrombin time), APTT (Activated Partial Thromboplastin Time), INR (International normalized ratio), LDH (Lactate dehydrogenase).

The incubation period of hepatitis A is approximately 28 days (range 15-50 days). EBV is one of the most prevalent human viruses in the world (11). Transmission of EBV occurs via intimate contact with body secretions, primarily oropharyngeal secretions, and to a lesser degree through genital secretions. The incubation period of EBV is 4-6 weeks(12). It is possible that these two viruses may have infected our child at around the same time, and both their incubation periods might have overlapped, causing jaundice simultaneously. It is also plausible that the presence of jaundice is due to hepatitis A infection and that EBV infection is coincidental.

To conclude, Even though acute hepatitis is caused by HAV, HBV, and HCV in > 95% of cases, other viruses

should be borne in mind if there are atypical findings clinically or investigations suggest otherwise. After the exclusion of common viral agents, EBV should be Considered. In Tropical Countries Like India, Co-Infections Are Common; Therefore, A High Index Of Suspicion Is A Must So That Close Follow-Up Can Be Done To Avoid Preventable Complications.

REFERENCES

1. Guidelines For Viral Hepatitis Surveillance And Case Management th feb 2021
2. Kofteridis DP, Koulentaki M, Valachis A, Christofaki M, Mazokopakis E, Papazoglou G, et al. Epstein Barr virus hepatitis. Eur J Intern Med 2011;22:73-6.
3. Moniri A, Tabarsi P, Marjani M, Doosti Z. Acute Epstein - Barr virus hepatitis without mononucleosis syndrome: a case report. Gastroenterol Hepatol Bed Bench 2017;10:147-49.
4. Kang MJ, Kim TH, Shim KN, Jung SA, Cho MS, Yoo K, et al. Infectious mononucleosis hepatitis in young adults: two case reports. Korean J Intern Med 2009;24:381-7.
5. Yang SI, Geong JH, Kim JY. Clinical characteristics of primary Epstein Barr virus hepatitis with elevation of alkaline phosphatase and γ-glutamyltransferase in children. Yonsei Med J 2014;55:107-12.
6. Shaqsi L A, Beamish J. P566 EBV related autoimmune haemolytic anaemia with a negative direct coomb's test – a case report. Arch Dis Child 2019;104(Suppl 3):A380.1-A380
7. Quirós-Tejeira R E. Overview of hepatitis A virus infection in children. Eds:Edwards M S, Rand E B. UpToDate. Accessed on 18 th feb 2021.
8. Matheny SC, Kingery JE. Hepatitis A. Am Fam Physician 2012;86:1027-34; quiz 1010-2.
9. Weissman S, Auyeung G, Atoot A, Atoot A. A Rare Presentation of Epstein-Barr Virus-induced Hepatitis With an Interesting Twist: A Case Report Involving a Clinical Pearl. Cureus 2018;10:e2808.
10. García-Peris M, Jiménez Candel MI, Mañes Jiménez Y, Pariente Martí M, González Granda D, Calvo Rigual F. Primoinfección por el virus de Epstein-Barr en niños sanos [Epstein-Barr virus primary infection in healthy children]. An Pediatr (Barc). 2019;90:376-85. Spanish.
11. Pinkbook: Hepatitis A | CDC. Hepatitis A Centers for Disease Control and Prevention Epidemiology and Prevention of Vaccine-Preventable Diseases, 13th Ed. April, 2015. Page 135. https://www.cdc.gov › vaccines › pubs › pinkbook › hepa. Accessed on 15th may 2021.
12. Shetty K. Epstein-Barr Virus (EBV) Infectious Mononucleosis (Mono) Clinical Presentation.Ed. Bronze M S. https://emedicine.medscape.com/article/222040-clinica. Topic last updated: April 21,2021.Accessed on 15th may 2021.