Profile of hepatitis A infection with atypical manifestations in children

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Abstract
We assessed the clinical course and biochemical profile of symptomatic children with viral hepatitis A who had atypical manifestations. Of 229 children with hepatitis A, atypical manifestations were found in 32 (14\%) subjects. Prolonged cholestasis (n = 14), acute liver failure (9), relapse (9), ascites (8), and hematological problems (8) were the common presentations. Liver histology was suggestive of chronic liver disease in six children with protracted jaundice. Patients with atypical presentations were older (7.7 \[1.6\] years vs. 6.5 \[2.6\] years; p=0.012) and had higher total serum bilirubin (13.7 \[8.1\] mg/dL vs. 7.2 \[4.0\] mg/dL; p=<0.001) than those with typical presentation. Approximately 15\% of children with acute hepatitis A infection have atypical presentation which is associated with increased morbidity.

Keywords
Acute liver failure · hepatitis A virus · prolonged cholestasis

Introduction
Hepatitis A virus (HAV) infection is an enterically transmitted disease, endemic in many developing countries, including India. Because of the improvement in living standards, the pattern is changing from asymptomatic/mild childhood infection to an increased incidence of symptomatic/severe disease.\(^1\) Over the last few years, we came across quite a number of atypical presentations of hepatitis A in children, which prompted us to study the course of the disease.

Methods
After taking informed consent from the guardian, all children (age 1–12 years) attending Kolkata Municipal Corporation-run Primary Health Clinics between the period of September 2004 and August 2008 with features suggestive of acute hepatitis were sent to Liver Clinic of our department for screening. Acute hepatitis was defined as acute illness with discrete onset of symptoms (e.g., nausea, anorexia, fever, malaise, or abdominal pain) with rise of total serum bilirubin (≥2 mg/dL) or elevation of serum alanine aminotransferase (ALT; ≥ twice the upper limit of normal) at any point in the course of the disease in the absence of underlying chronic liver disease.\(^2\) Patients with positive HAV IgM titer and negative serological markers (HBsAg, anti-HBc IgM, anti-HCV, anti-HDV IgM, anti-HEV IgM) for other hepatotropic viruses were enrolled. Anti-HAV antibody titer was performed by fully automated bidirectionally interfaced chemiluminescent immunoassay (CLIA) method using HAVAb-IgM Reagent kit [6C30] (Architect, Abbott Diagnostics, Wiesbaden, Germany). Values ≥1.2 were considered as positive.

Typical presentation was defined as presence of all of the following: symptoms/signs and disease course as expected of acute viral hepatitis, with disappearance of jaundice (serum bilirubin <2 mg/dL) within 12 weeks of the onset of symptoms, along with no atypical feature or complication. Relapse was described as decrease in serum ALT levels by ≥50\% value, followed by an increase in value by ≥50\% of the minimum value or similar fluctuations of serum bilirubin.\(^3\) In these cases, the parameters of the second episode were taken. Prolonged cholestasis (protracted form) was defined by elevated serum bilirubin levels >2 mg/dL at 3 months after the onset of illness.\(^4\) Signs of encephalopathy (ranging from confusion and mood changes to coma) with absolute prothrombin time >16 seconds was termed as acute liver failure (ALF).\(^5\)
All the patients in our study were counseled about the normal course of the disease and asked to report twice weekly or earlier, if atypical features appeared. Testing of sera for biochemical markers was done at frequent intervals; the values at the point of maximum clinical deterioration were used for analysis. The study was approved by Institutional Ethics committee and informed consent was obtained from a parent/guardian. For statistical analysis, 95% confidence intervals were considered.

Results

Two hundred and eighty-nine consecutive patients with acute viral hepatitis A were evaluated; 18 children were excluded from the study as they were positive for other viral markers (HEV 10, HBV 6, HCV 2) in addition to HAV. We also excluded 42 subjects as they did not follow up regularly. Thus, our study was confined to 229 children.

Atypical presentations were present in 32 (14%) to these cases. Prolonged cholestasis was the most common atypical presentation, and was seen in 14 children of whom four had ALF. Liver biopsy in six of them revealed extensive periportal fibrosis with inflammatory cell infiltrate. In two cases, fibrosis extended up to the center of the lobule. Pseudolobule was seen in one child. Repeat biopsy, done 3 months after resolution of hepatitis in three of these children, was normal.

Nine patients had relapse. The mean time to relapse was 3.4 weeks with a range of 2–6.7 weeks. Five patients had a protracted course with cholestasis, two had intractable pruritus, requiring use of two chloretic agents. Two children developed ascites and one showed signs of liver failure. Among the biochemical markers, serum bilirubin (initial: mean [SD] 6.1 [5.7] mg/dL, range 2.5–18.1 mg/dL vs. at relapse 15.6 [6.6] mg/dL, 3.8–25.5 mg/dL; p=0.005) and serum alkaline phosphatase (initial: 733.5 [391.2] IU/L, 343–2129 IU/L vs. at relapse 2083.3 [1292.7] IU/L, 611–4368 IU/L; p=0.003) were significantly higher, and serum albumin values (initial: 3.7 [0.3] g/dL, 3.4–4.1 gm/dL vs. at relapse 3.2 [0.3] g/dL, 2.8–3.8 g/dL; p=0.009) were lower during relapse as compared to those in the initial episode.

One child who developed ALF died. He developed stage 4 encephalopathy within 12 days of the onset of icterus and succumbed after 3 days of encephalopathy. Of the rest eight cases of ALF, six were in stage 1, and one each in stage 2 and 4 encephalopathy. The icterus-to-encephalopathy interval varied between 3 and 41 days (mean 12.8 days).

Eight children developed ascites during the course of illness. Six of them also had a protracted course. One child developed spontaneous bacterial peritonitis which responded to treatment. Two children had pleural effusion without ascites. Both pleural effusion and ascites were present in one child with ALF.

Four children had severe anemia. Two of them had positive antinuclear antibody titer. One child developed ALF within 3 days of the onset of symptoms. Glucose-6-phosphate dehydrogenase (G6PD) enzyme was deficient in one case; his serum bilirubin was 47.6 mg/dL. One child presented with purpura and had transient depression of all three hematopoietic cell lines in peripheral blood smear, which lasted for 8 days. One child responded to steroids.

Five patients had bleeding manifestations, out of which two cases had developed coagulopathy due to ALF. Of the two children with isolated decrease in platelet count (<50,000/mm³), bone marrow examination in one case revealed features of immune thrombocytopenic purpura. The child responded to intravenous immunoglobulin. In the other patient, thrombocytopenia remitted spontaneously after 11 days. Transient vasculitis lasting more than 3 days was seen in two children; none of them was receiving any drug that could cause vasculitis. Table 1 summarizes the biochemical parameters of atypical presenters.

Children who had atypical features of hepatitis A were older (mean [SD] age 7.7 [1.6] years vs. 6.5 [2.6] years; p=0.012) and had higher peak value of serum bilirubin (13.7 [8.1] mg/dL vs. 7.2 [4.0] mg/dL; p<0.001) as compared to those who did not. The baseline values of ALT (887.4 [401.3] IU/L vs. 895.3 [712.3] IU/L) and serum bilirubin (3.1 [1.8] mg/dL vs. 3.0 [1.4] mg/dL) were similar in children with atypical and typical presentations.

Discussion

Compared to the West, published literature on viral hepatitis A on a large sample of Indian pediatric population is relatively scant. However isolated case studies describing the various unusual associations with hepatitis A in children have been sporadically reported.

The clinical features during relapse in our patients were similar with those in a previous study, except that seven out of nine children with relapse in our study had a severe second episode. We have previously reported that ALF is quite common in HAV and it is the most common cause of ALF in eastern India. Reactogenic phenomena like pleural effusion have been described previously. Though there are a number of case reports of hematological disturbances with HAV, only one was confirmed to be immune thrombocytopenic purpura. Affection of neurological, nephrological, and cardiovascular system has been also documented; none of our patients had these manifestations. Henoch Schonlein purpura as an exceptional extra-hepatic manifestation of hepatitis A infection has been reported.

Thus, approximately 15% of children with acute hepatitis A have atypical presentation. Children with this presentation are older and have higher serum bilirubin values as compared to those who have typical course of the disease.
Table 1 The various parameters of the major groups of atypical presenters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Atypical presenters (n=32)</th>
<th>Prolonged cholestasis (n=14)</th>
<th>Relapse (n=9)</th>
<th>Acute liver failure (n=9)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD) 7.7 (1.6)</td>
<td>7.9 (1.5)</td>
<td>6.1 (5.6)</td>
<td>7.6 (1.8)</td>
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<td></td>
<td>95% CI 7.1–8.2</td>
<td>7–8.7</td>
<td>1.5–10.7</td>
<td>6.4–8.8</td>
</tr>
<tr>
<td>Male : Female</td>
<td>13 : 19</td>
<td>7 : 7</td>
<td>4 : 5</td>
<td>3 : 6</td>
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<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>Mean (SD) 13.7 (8.1)</td>
<td>20.4 (5.6)</td>
<td>15.6 (6.6)</td>
<td>18.8 (9.3)</td>
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<tr>
<td></td>
<td>95% CI 10.7–16.7</td>
<td>17–23.7</td>
<td>10.2–21</td>
<td>11.2–26.4</td>
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<td>Alanine aminotransferase (IU/L)</td>
<td>Mean (SD) 1593.4 (655.9)</td>
<td>1359 (703.8)</td>
<td>1773 (556.5)</td>
<td>1214.1 (624.9)</td>
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<td>95% CI 1352.4–1833.6</td>
<td>937.3–1780.6</td>
<td>1319.3–2226.7</td>
<td>704.6–1723.6</td>
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<td>Serum alkaline phosphatase (IU/L)</td>
<td>Mean (SD) 1316.6 (666.9)</td>
<td>1406.6 (783.1)</td>
<td>2083.3 (1292.7)</td>
<td>859.9 (390.0)</td>
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<td>95% CI 1072–1561.2</td>
<td>937.4–1875.7</td>
<td>1029.3–3137.2</td>
<td>541.9–1177.9</td>
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<tr>
<td>Serum albumin (g/dL)</td>
<td>Mean (SD) 3.1 (0.5)</td>
<td>3.1 (0.4)</td>
<td>3.2 (0.3)</td>
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</tr>
<tr>
<td></td>
<td>95% CI 2.9–3.2</td>
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<tr>
<td>Absolute prothrombin time (seconds)</td>
<td>Mean (SD) 21.6 (13.4)</td>
<td>16.1 (3.7)</td>
<td>14.7 (2.7)</td>
<td>29.7 (13.4)</td>
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<td></td>
<td>95% CI 16.7–26.5</td>
<td>13.9–18.3</td>
<td>12.5–16.9</td>
<td>18.8–40.6</td>
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<tr>
<td>Anti-HAV IgM antibody titer</td>
<td>Mean (SD) 5.5 (3.1)</td>
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<td>95% CI 3.9–7</td>
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</table>

Acknowledgments

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References