Human Parechovirus as a Cause of Isolated Pediatric Acute Liver Failure

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Abstract

Among infants, almost half of acute liver failure cases are classified as indeterminate, whereas only a small number of cases show a documented viral infection. We present the first reported case of isolated acute hepatic failure in an infant in the setting of a human parechovirus (HPeV) infection. HPeV also may have been contributory to the posttransplant complication of 2 intussusceptions. This is a 10-month-old girl who presented with only symptoms of fuzziness and was noted to have progressive decline in synthetic liver function as well as worsening coagulopathy requiring a liver transplant. The acute liver failure was in the setting of a positive serum RNA HPeV, subtype 3 (HPeV-3), after extensive diagnostic testing with genetic, autoimmune, and infectious causes otherwise negative. After liver transplantation, the postoperative course was complicated by both an ileal-ileal intussusception as well as a jejunal intussusception. Viral testing in pediatric acute liver failure is often performed, but the workup is frequently incomplete. This case report would support more extensive viral testing in this population of patients. In the setting of HPeV, clinicians could be alerted to the possibility of delayed gastrointestinal pathology in the posttransplant phase. Wider use of routine HPeV testing may more clearly define the variable clinical presentations and outcomes.

CASE REPORT

Acute liver failure in children may be categorized as metabolic, infectious, immunologic, toxic, drug related, or indeterminate in nature. Among infants, up to 45% of cases are classified as indeterminate, and only 4% are secondary to a documented viral infection. In the United States and Western Europe, herpes simplex virus and enterovirus were found to be the cause of pediatric acute liver failure in 16% of infants. Hepatitis A, B, and C are often suspected but seldom identified as the etiology for pediatric acute liver failure. Human parechoviruses (HPeVs) were previously classified as enteroviruses known as echovirus 22 and echovirus 23, which were first isolated in 1956. Recently, HPeVs have been reclassified to the newly assigned genus Parechovirus within the Picornaviridae as HPeV types 1 and 2. HPeV types 3 to 8 also have recently been identified. These HPeV viruses have been associated with gastrointestinal and respiratory tract infections, as well as cases of encephalitis and flaccid paralysis.

To our knowledge, HPeV has not previously been reported as a cause of isolated acute liver failure, although viral testing is often incomplete. Herein, we present the first reported case of isolated acute hepatic failure in an infant in the setting of an HPeV infection. Interestingly, HPeV also may have been contributory to the posttransplant complication of an ileal-ileal and a jejunal intussusception.

TABLE 1 Laboratory Value Trends

<table>
<thead>
<tr>
<th>Day of Illness</th>
<th>Day of Illness 11, Admission</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15 Transplant</th>
<th>16</th>
<th>17</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (IU/L)</td>
<td>657</td>
<td>624</td>
<td>375</td>
<td>252</td>
<td>193</td>
<td>134</td>
<td>2170</td>
<td>757</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>1168</td>
<td>1162</td>
<td>768</td>
<td>570</td>
<td>508</td>
<td>435</td>
<td>1973</td>
<td>1062</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>7.4</td>
<td>14.8</td>
<td>12.3</td>
<td>14.8</td>
<td>15.6</td>
<td>16.2</td>
<td>4.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Direct bilirubin, mg/dL</td>
<td>5.4</td>
<td>6.6</td>
<td>4.9</td>
<td>4.5</td>
<td>4.7</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ammonia, μmol/L</td>
<td>&lt;10</td>
<td>34</td>
<td>68</td>
<td>60</td>
<td>69</td>
<td>64</td>
<td>45</td>
<td>38</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>2.9</td>
<td>2.5</td>
<td>1.8</td>
<td>2.2</td>
<td>2.1</td>
<td>2.1</td>
<td>2.2</td>
<td>2.6</td>
</tr>
<tr>
<td>PT (s)/INR</td>
<td>38.7/3.6</td>
<td>57.9/6.6</td>
<td>59/6.8</td>
<td>66/7.9</td>
<td>87/11.3</td>
<td>118.4/15.0</td>
<td>22.7/1.9</td>
<td>21.1/1.8</td>
</tr>
</tbody>
</table>

CASE REPORT

A 10-month-old, previously healthy, full-term girl, transferred to our care from an outside hospital with acute liver failure. Initially, she presented to her primary care provider 11 days before admission with irritability, and was diagnosed with acute otitis media and prescribed amoxicillin (480 mg [40 mg/kg]) every 12 hours. She remained afebrile and experienced transient improvement in symptoms while receiving amoxicillin and acetaminophen (85 mg [7 mg/kg]) every 4 to 6 hours. However, on the fourth day of treatment, which was 7 days before admission to our center, she developed recurrent irritability and the amoxicillin was discontinued. She was admitted at an outside hospital on the eighth day of illness and a full septic workup, including chest radiograph; head computed tomography scan; and blood, urine, and cerebrospinal fluid (CSF) cultures. All results were unremarkable, with exception of a complete blood count with differential, which showed a leukocytosis of 26 000 with 41% atypical lymphocytes. Physical examination revealed oral ulcers and she was transferred to a regional tertiary care hospital due to concerns for disseminated viral illness with aseptic meningitis (CSF: white blood cells, 7; red blood cells, 100; glucose, 48; protein, 50; 20% neutrophils; 65% lymphocytes; 10% monocytes; 5% eosinophils). At that facility, an acetaminophen level was negligible, a complete metabolic panel revealed elevated transaminases (aspartate transaminase [AST] 657 IU/L, alanine transaminase [ALT] 1168 IU/L), hyperbilirubinemia (total bilirubin 7.4 mg/dL, direct bilirubin 5.4 mg/dL), and reduced synthetic liver function (albumin 2.9 g/dL, prothrombin time [PT] 39.7 seconds, international normalized ratio [INR] 3.6, ammonia <10), with all tested viral studies negative, including Epstein-Barr virus immunoglobulin M, cytomegalovirus immunoglobulin M, H1V-1,2 antibodies, influenza polymerase chain reaction (PCR) and a hepatitis panel. An abdominal ultrasound showed gallbladder sludge, but was otherwise unremarkable. She was started on vitamin K, ursodiol, and famotidine and serial laboratory follow-up demonstrated worsening transaminitis and coagulopathy.

On day 11 of illness, she was transferred to our institution, a pediatric quaternary care center, for liver transplantation evaluation. On arrival, she had decreasing transaminases (AST 520 IU/L [23–65], ALT 1178 IU/L [6–45]), increasing hyperbilirubinemia (total bilirubin 13.3 mg/dL [0–1.1], direct bilirubin 7 mg/dL), and worsening coagulopathy and synthetic liver function (PT 53.9 seconds [12.4–14.6], partial thromboplastin time 74.7 seconds [23.8–35], INR 5, fibrinogen 63 mg/dL, albumin 3 g/dL [2.9–5.5]); see Table 1 for diagnostic trends. Acetaminophen level was undetectable. Physical examination demonstrated appropriate hemodynamics and she was neurologically intact, with 3 palatal oral ulcers noted. The family denied any new environmental exposures or travel, and the patient attended an in-home day care. She was up-to-date on vaccinations and family history was unremarkable. An infectious, autoimmune, and metabolic workup were obtained, including α-1 antitrypsin phenotype, anti-actin antibodies, α-fetoprotein, antinuclear antibody panel, factors V and VII activity, herpes viral panel, cytomegalovirus PCR, Epstein-Barr virus PCR, adenovirus PCR, parvovirus PCR, and enterovirus PCR. The only positive result yielding serum Parechovirus RNA, which is included in our routine viral testing. The specimen was concluded to be Parechovirus, subtype 3 (HPeV3) (cycle threshold quantitative value was not available).

After a comprehensive evaluation, the patient was registered on the liver transplant waiting list under the United Network for Organ Sharing Status A1 category. The patient underwent urgent live donor liver transplantation on day 15 of her illness. Pathologic examination of the native liver revealed massive, global hepatocellular necrosis, collapse of the reticulin framework, and reactive...
bile ductular epithelium. There were some viral cytopathic changes in the few remaining hepatocytes, but these were nonspecific. Her operative course was complicated by an ileal-ileal intussusception on postoperative day 1, which was manually reduced. Subsequent second-look laparotomy and staged abdominal closure confirmed viability of the entire small and large intestine. The abdomen was closed with a polytetrafluoroethylene fascia interposition graft to avoid compression of the liver. On postoperative day 10, she underwent full abdominal closure. The patient recuperated well and tolerated a diet. At 3 weeks after transplantation, she developed another episode of intussusception at the jejunum that presented with currant jelly stool. A computed tomography scan confirmed the diagnosis and the patient underwent an emergency laparotomy, segmental small bowel resection, and primary bowel anastomosis. The patient recuperated well and was discharged to home.

**DISCUSSION**

Failure to definitively determine the etiology of pediatric acute liver failure commonly results in an indeterminate classification. However, in many instances this may reflect a failure to accurately diagnose viral hepatitis with appropriate screening assays. Schwarz et al. published an elegant multicentered study analyzing viral testing in pediatric acute liver failure and identified 20.2% of this patient population to have a positive viral test, with 11.6% of those from herpes simplex virus. HPeV is a common viral pathogen, which is infrequently tested during routine screening assays. Patients with HPeV infections have a wide variability of clinical presentations, including gastrointestinal symptoms, respiratory symptoms, sepsis, meningitis, encephalitis, myositis, and myocarditis. A Dutch study in 2006 used real-time PCR and detected HPeV in 4.2% of the 761 CSF samples from children age <5 years with most of the children presenting with concern for sepsis, meningitis, or encephalitis. A recent national surveillance study in Denmark with routine testing of all CSF, fecal, and tissue samples in 2014 identified HPeV in 3% of the specimens from 4808 children. In 2009, a Scottish study isolated 14 of 1575 CSF samples with HPeV on screening with real-time PCR and typing revealed infection with HPeV3. HPeV3 was also described in a case of neonatal hepatitis-coagulopathy syndrome, as well as a case of Scottish twins with hepatitis and coagulopathy. In both cases, the patients presented with systemic inflammatory response syndrome before hepatic dysfunction which resolved and the patients were discharged in their previous state of health. Our patient presented with acute hepatic failure and never exhibited hemodynamic instability or evidence of organ hypoperfusion. Although it is possible that there may have been another etiology for liver failure with Parechovirus being an incidental finding, this seems less likely given the extensive diagnostic evaluation, nondetectable acetaminophen level, and temporal associations of viral symptoms with liver failure. Unfortunately, in our microbiology laboratory, our tissue culture media are not optimized to grow parechoviruses, thus it is often difficult to isolate this specific virus from standard tissue culture. Tissue molecular testing may offer improved reliability in identifying viral isolates; however, we have not yet clinically validated this testing on tissue specimens, including liver, thus no PCR testing was performed on the explant. That being said, there is very limited information regarding the incidence of isolated viral tissue specimens from a necrotic liver, such as that of our patient’s liver. Thus, although confirmed tissue virology for HPeV from the explanted liver would be helpful in solidifying the causality, conditions were not ideal to do this with reliability.

The ileal-ileal and jejunal intussusceptions were suspected to be secondary to the Parechovirus, although unclear if it was related, we felt it was at least of clinical interest. Although not the most common virus, Parechovirus has been known to be associated with cases of intussusception, often in children <1 year of age. Perhaps, as viral detection panels, including for human Parechovirus, become more routine, we can learn more about the relevance and clinical presentations of the virus.

**CONCLUSIONS**

Viral testing in pediatric acute liver failure is often performed, but the workup is incomplete. This case report would support more extensive viral testing in this population of patients. Inclusion of HPeV testing as part of a more comprehensive testing may more clearly define the variable clinical presentations and outcomes. We also felt it important to add to the discussion the 2 occurrences of intussusception in this patient, so that clinicians could be alerted to the possibility of delayed gastrointestinal pathology in the posttransplant phase, in the setting of HPeV.

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**ABBREVIATIONS**

ALT: alanine transaminase  
AST: aspartate transaminase  
CSF: cerebrospinal fluid  
HPeV: human parechovirus  
HPeV3: HPeV subtype 3  
INR: international normalized ratio  
PCR: polymerase chain reaction  
PT: prothrombin time
REFERENCES


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