LETTER TO THE EDITOR

Acute hepatitis of unknown etiology: a proposed diagnostic approach

Hepatitis aguda de etiología desconocida: una propuesta de abordaje diagnóstico

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Recently, acute and severe hepatitis cases in children have increased, triggering close epidemiological surveillance worldwide1. Between April 5 and May 26, 2022, 650 probable cases have been reported to the World Health Organization (WHO) from 33 countries, with the United Kingdom and the United States reporting most cases, followed by Japan, Spain, and Italy2.

The WHO defines a probable case as any person presenting with acute hepatitis (not hepatitis A-E) with serum transaminase levels > 500 IU/L (aspartate aminotransferase or alanine aminotransferase) and age ≤ 16 years (Table 1), mainly with gastrointestinal symptoms, such as vomiting, acholia, and jaundice, and respiratory symptoms in a lower percentage (Table 2)2.

Etiology of acute hepatitis

Cases have tested negative for A-E viruses. A UK study involving 126 children documented the presence of adenovirus in 72% (n = 91). It was also identified in 44% of stool and 29% of respiratory specimens. Twenty-four children (18%) had active SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection. Epstein-Barr, enterovirus, cytomegalovirus, respiratory syncytial virus, and human herpesviruses 6 and 7 were identified less frequently4-6.

According to the European Centre for Disease Prevention and Control (ECDC), several hypotheses have emerged based on present-day evidence. The most compelling relates to a cofactor affecting children that cause mild adenovirus infections to become more severe or trigger immune-mediated liver damage. This cofactor may be related to susceptibility due to a lack of prior exposure to adenovirus during the pandemic, a previous SARS-CoV-2 infection, or a toxin, drug, or environmental exposure7.
Proposed diagnostic approach

Upon identification of a probable case of hepatitis, the conventional care process should be conducted, allowing for differential diagnosis since acute hepatitis is not a new disease. Throughout history, cases of unknown or idiopathic causes have been documented after searching for the most common causes. For this reason, it is necessary to adopt a systematic evaluation, tiered by the level of care and age group, to manage cases with symptoms consistent with acute hepatitis (Figure 1).

This evaluation is intended to determine the etiology of the liver injury and not ignore other known causes of hepatitis, such as autoimmune, toxic, and other infectious diseases caused by hepatotropic and non-hepatotropic viruses, including hemophagocytic lymphohistiocytosis,

<table>
<thead>
<tr>
<th>Signs or symptoms</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Jaundice</td>
<td>71%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>63%</td>
</tr>
<tr>
<td>Acholia</td>
<td>50%</td>
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<tr>
<td>Diarrhea</td>
<td>45%</td>
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<tr>
<td>Fever</td>
<td>31%</td>
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<tr>
<td>Respiratory symptoms</td>
<td>19%</td>
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</tbody>
</table>

Table 2. Clinical presentation in children with acute hepatitis of unknown etiology

*Consider hepatitis A, B, C, and E, Epstein-Barr virus, cytomegalovirus, leptospirosis, human parvovirus B19, adenovirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and herpesvirus.

Figure 1. Diagnostic approach to suspected acute hepatitis.
ALF: acute liver failure; BMP: basic metabolic panel; CBC: complete blood count; INR: international normalized ratio; LFTs: liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, albumin, total bilirubin, direct bilirubin, and coagulation tests); PICU: Pediatric Intensive Care Unit.
*Consider hepatitis A, B, C, and E, Epstein-Barr virus, cytomegalovirus, leptospirosis, human parvovirus B19, adenovirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and herpesvirus.
in which patients present with hepatic inflammation and may develop acute liver failure.

**Ethical disclosures**

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on patient data publication.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

**Conflicts of interest**

The authors declare no conflicts of interest.

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**References**