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Editorial: Acute Hepatitis of Unknown Origin in Children. Is Autoimmunity at Play?

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Abstract A recent global outbreak of cases of acute hepatitis of unknown origin in children has raised health alerts. Increasing numbers of cases are being reported in most countries, mainly in the United Kingdom (UK). Although the cause remains unknown, several viruses have been isolated from affected children, including adenovirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Epstein-Barr virus (EBV), and rhinovirus. Notably, the cause is not from common hepatitis viruses, as serology for hepatitis viruses A, B, C, D, and E has been negative. Current causal hypotheses include possible infection with a new adenovirus variant that affects immunocompetent children, a new pediatric manifestation of COVID-19, or coinfection with enteric adenovirus type F41. This Editorial aims to present current hypotheses regarding the etiology of acute hepatitis of unknown origin in children, including the role of autoimmune hepatitis secondary to viral infection.

Keywords: Acute Hepatitis • Adenovirus • COVID-19 • Autoimmune Hepatitis • Editorial

A recent global outbreak of cases of acute hepatitis of unknown origin in children has raised health alerts. Increasing numbers of cases are being reported in most countries. Since this condition was identified, studies in many centers have begun investigating the cause or causes. By 20th May 2022, more

than 450 cases of acute hepatitis of unknown origin in children were reported worldwide, although there is a lack of data from some countries, mainly in Africa. However, in the United Kingdom (UK), more than 181 cases of acute hepatitis of unknown origin in children were reported [1-4] (see **Figure 1**).

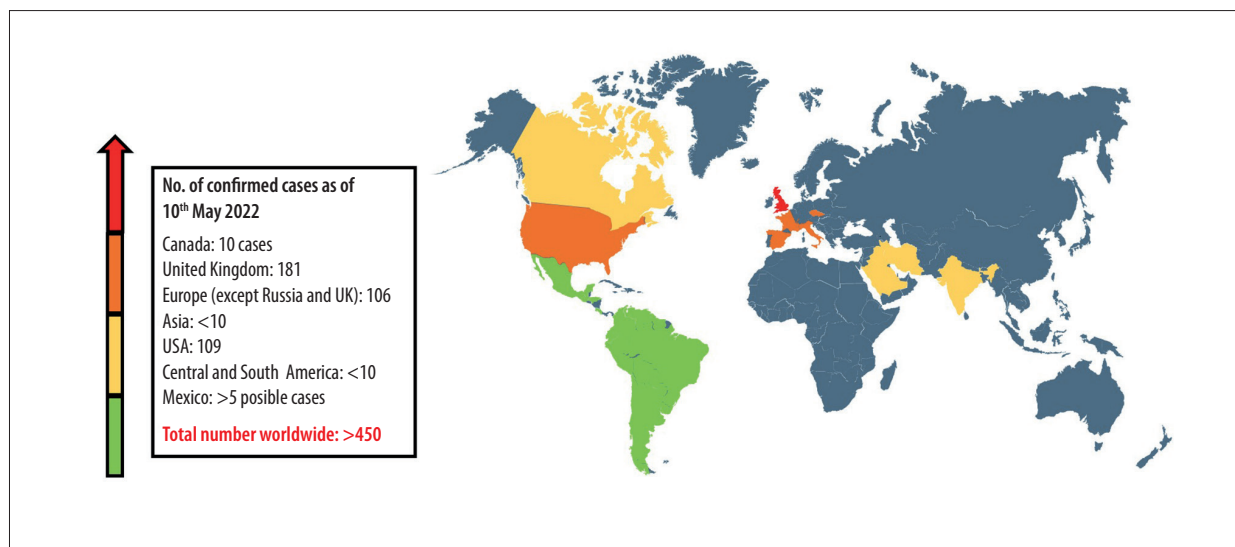


Figure 1. Global data on the number of reported cases of acute hepatitis of unknown origin in children, up to 10th May 2022. From Canada, up to 20th May 2022, and from Mexico up to 17th May 2022. The incidence of acute hepatitis of unknown origin in children is highest in Europe, with most cases identified in the United Kingdom (UK), however, there's increasing numbers in virtually all continents, including America.

Table 1. The main clinical characteristics, patient presentation, biochemical and viral serology findings in children presenting with acute hepatitis of unknown origin.

| Acute hepatitis in children of unknown cause | | | |
|---|---|---|--|
| Clinical characteristics | Biochemical properties | Histopathological findings | Viral serologies |
| Jaundice (71.2%) | <ul style="list-style-type: none"> • ALT=603-4,696 U/L • AST=447-4,000 U/L • Total bilirubin=0.23-13.5 mg/dl | Mild hepatocellular injury | Negative for Hepatitis A, B, C, D, and E |
| Vomiting (62.7%) | Established criterion: serum transaminase >500 IU/L (AST or ALT) | Massive hepatic necrosis | Adenovirus F 41 (positive) – around 70% |
| Acholia (50.0%) | | Various degrees of hepatitis with no viral inclusions | COVID-19 (positive) – around 18% |
| AT PRESENTATION: GI SYMPTOMS | | | Other positive serologies: |
| Diarrhea (44.9%) | | | |
| Nausea (30.5%) | | | |
| AT PRESENTATION: RESPIRATORY SYMPTOMS (18.6%) | | | |
| Others: fatigue, choloria, anorexia, abdominal pain | | | |

AST – alanine aminotransferase; ALT – aspartate aminotransferase.

This type of acute hepatitis affects children under 16 years of age and has a significantly higher incidence in children aged less than 5 years of age. Although statistical and epidemiological data are still lacking from several countries, mortality for cases reported in Europe and the USA is estimated to be <3% (with 11 total deaths) [5]. As of 20th May 2022, 31 children with this form of acute hepatitis have required liver transplants. Clinical presentation varies among children, with more frequent gastrointestinal symptoms than upper respiratory tract symptoms on presentation. Children with gastrointestinal symptoms most commonly present with jaundice, and nausea, vomiting, and diarrhea are less common. Constitutional symptoms include fatigue and fever in some children [5].

Acute hepatitis of unknown origin in children is associated with altered laboratory biochemical findings that support liver disease, including raised transaminases, which may reach values exceeding 4000 U/L [3] (see **Table 1**). Recent studies have focussed on investigating a variant of the DNA virus, adenovirus F type 41 [1-6]. However, there is still the possibility that infection with some commonly circulating viruses may be causing hepatitis in immunocompetent children. The new adenovirus F type 4 variant may have different pathogenesis in some children. There may be an altered viral immune response due to a lack of childhood exposure during the COVID-19 pandemic restrictions. Also, altered immune responses to adenovirus may have developed from past infections or co-infection with SARS-CoV-2.

Although adenovirus has been isolated from many children with acute hepatitis of unknown origin, it is essential to note that this association does not prove causation. Adenovirus is a ubiquitous virus in children, and in children with hepatitis, it may be an incidental finding [6]. There should be caution in attributing a new disease in children during the COVID-19 pandemic to infection with the SARS-CoV-2 virus, either directly or as a co-infection. However, at this time, it is unavoidable to consider that SARS-CoV-2 may have a direct role in the cause of cases of acute hepatitis of unknown origin in children.

Acute hepatitis of unknown origin in children is assumed to affect immunocompetent children. However, because there still have been no studies to investigate whether autoantibodies are present, the use of the term, immunocompetent may be of concern. Given the high detection rate of adenovirus in affected children and what is known about the pathophysiology of hepatitis, there are three main possibilities regarding the cause of acute hepatitis of unknown origin in children: infection with an adenovirus variant; autoimmune hepatitis; and an autoimmune childhood form of COVID-19.

Firstly, adenovirus is a DNA virus responsible for many upper and lower respiratory tract infections, especially in the pediatric population with humoral immune deficiencies. Uncommon but possible presentations can include hemorrhagic cystitis, hemorrhagic colitis, meningoenzephalitis, and acute hepatitis [6].

Serotypes 40-41 have a greater affinity for the gastrointestinal tract within the adenovirus species F [6,7]. Recently identified cases of acute hepatitis of unknown origin in children have been associated with the isolation of adenovirus F type 41 in the blood, feces, and respiratory exudates [6,7]. Other isolated pathogens have included SARS-CoV-2 (in 18% of cases), rhinovirus, enterovirus and metapneumovirus [7,8].

Multiple case reports have described adenovirus-related hepatitis with high mortality rates of up to 75% in patients undergoing allogeneic hematopoietic stem cell transplantation [7,8]. Adenovirus-related hepatitis mainly presents in immunosuppressed patients with deficient adaptive cellular immune responses, including T cell-mediated immunity. This finding links the immunodeficient state in COVID-19 patients and the gastrointestinal presentation of adenovirus infection. Therefore, co-infection could be a possible cause, as adenovirus infection in up to 70% of patients and SARS-CoV-2 infection in up to 20% of patients has been reported [1,6,8].

The second hypothesis for the cause of acute hepatitis of unknown origin in children is that it is an autoimmune disease. Autoimmune hepatitis (AIH) is a progressive liver disease with three diagnostic features: hypergammaglobulinemia; identification of specific autoantibodies; and histopathology that shows an 'interface hepatitis' [9,10]. AIH is subclassified into two major groups: AIH-1 and AIH-2 [9,10]. AIH-1 is associated with antinuclear antibodies (ANA), anti-smooth muscle antibodies (SMA), and anti-neutrophil cytoplasmic antibodies (ANCA), mainly with a perinuclear distribution (p-ANCA) [9]. AIH-2 presents with autoantibodies against anti-liver/kidney microsomal antibody type 1 (anti-LKM1) [6]. There are several examples of drug-induced AIH and post-infectious AIH, especially after hepatitis A infection (HAV). HAV may rarely act as a trigger for autoimmune hepatitis, owing to immune mimicry [11]. It is possible that other pathogens, including SARS-CoV-2, could induce AIH by initiating self-perpetuating immune-mediated liver inflammation. Therefore, acute viral hepatitis and post-infectious AIH, by either SARS-CoV-2 or adenovirus,

are two possible hypotheses for the current global acute hepatitis outbreak in children.

The third hypothesis for the cause of acute hepatitis of unknown origin in children is that this is an autoimmune pediatric manifestation of COVID-19. COVID-19 has been reported to present with acute non-icteric jaundice even before the onset of respiratory symptoms are reported [12]. Reports of COVID-19 mRNA vaccines have shown an association with the onset of AIH, possibly by altering self-tolerance. Immunological studies have shown positive ANA, anti-mitochondrial, and smooth muscle antibodies in reported cases [13,14]. These autoantibodies are characteristic of AIH-1. Even though these clinical studies have shown that most affected children were not yet vaccinated, this mechanism may also be extrapolated to SARS-CoV-2 as a cause of acute hepatitis. However, seemingly immunocompetent pediatric patients are yet to be tested for specific autoantibodies against hepatic antigens. Even though testing for all autoantibody types may be impractical, the previous cases of post-infectious AIH make the possibility of this disease following the same course as adult AIH feasible. Analyzing pediatric patient serum for autoantibodies associated with AIH may bring a clearer understanding of the cause of acute hepatitis of unknown origin in children.

Conclusions

Recent recognition of acute hepatitis of unknown origin in children has resulted in a search for the cause. Adenovirus infection may play an important role in the etiology. However, future studies should include the investigation of autoantibodies and autoimmune responses in affected children.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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