Acute Severe Hepatitis of Unknown Origin in Children Across the World: A 2022 Source of Concern

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At the beginning of April 2022, the World Health Organization (WHO) identified 10 cases of acute severe hepatitis in children younger than 10 years of age, across central Scotland. None of the typical hepatitis viruses (A–E) that are known to cause acute viral hepatitis were isolated from any of those cases, and no common environmental exposures were found. Based on the latest data (up to 26 May 2022), approximately 152 cases of acute severe hepatitis were reported in the European Union and 222 cases in the UK. Moreover, more than 38 of the cases received a liver transplant and at least 14 deaths were reported (Table 1).2,3

The WHO, European Centre for Disease Prevention and Control, and UK Health Security Agency have posted reports trying to inform about the recent cases of acute hepatitis of unknown origin. Concerning the case definition by WHO, a description of a confirmed case is not available at present, while a probable case is considered a person presenting with acute hepatitis that cannot be attributed to the hepatitis viruses A–E, with serum aminotransferase levels >500 IU/L (aspartate aminotransferase or alanine aminotransferase), who is 16 years or younger, since October 2021 (Table 2).2–4

As for the clinical presentation, most of the cases presented with gastrointestinal symptoms, including vomiting, diarrhea, and abdominal pain, while a proportion of them presented jaundice and acute liver failure.5 More precisely, a technical briefing derived from England involved 144 cases with a median age of 3 years and equally distributed among both sexes (50% were female).6 The most common symptom was jaundice (68.8%), followed by vomiting (57.6%), diarrhea (43.1%), pale stools (42.7%), and abdominal pain (36.1%).6 Noteworthy, a previous review of all available liver specimens (n=14) was undertaken and demonstrated a relatively wide spectrum of disease severity, ranging from mild hepatocellular injury to massive necrosis of the hepatic parenchyma.6 A non-specific pattern of the hepatic injury was identified, whilst no causal factor was observed in histological specimens.6

Potential pathogen investigations

As we initially outlined, the common viruses responsible for acute hepatitis (hepatitis viruses A–E) have not been detected in any of the cases worldwide. Among 181 cases that have been tested for human adenovirus (HAdVs) and were reported to WHO, 110 (60.8%) were HAdVs-positive.2 Of a small sample size that has been typed so far in the UK, 77% (27 out of 35 cases) have been identified as HAdV F type 41.4 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was PCR-detected in 23 out of the 188 (12.2%) cases, while a fewer number of patients were detected with a SARS-CoV-2 and adenovirus co-infection.2 However, it should be noted that a detection of a specific adenovirus in blood was not accompanied by the detection of the same virus in other non-blood samples, raising a concern for potential mixed infection.6

HAdVs are non-enveloped double-stranded DNA viruses, common pathogens that usually cause a self-limited infection transmitted from person-to-person. Among 50 distinct adenoviruses accounting for mostly respiratory diseases, the adenovirus F type 41 commonly presents as diarrhea, vomiting and fever, whereas in some cases there is accompaniment by respiratory symptoms.7 While infections by HAdV have been associated with acute hepatitis in immunocompromised children, a link between adenovirus type F 41 infection and hepatitis in immunocompetent children had not been described so far.7

Coronavirus disease 2019 (COVID-19) and acute hepatitis

There are hypotheses concerning the potential correlation between SARS-CoV-2 infection or immunization and HAdVs infections. We shall point out that during the COVID-19 pandemic, a lower circulation of respiratory viruses, including HAdVs has been observed and consequently, the children are more susceptible to those viruses due to the delayed epidemiological exposure.9 However, Brodin et al.9 proposed that a previous SARS-CoV-2 infection could potentially reserve virus particles that over time could lead to super antigen-mediated immune cell activation. Upon a subsequent HAdV infection, that superantigen T-cell activation could lead to interferon-γ-mediated excessive apoptosis of hepatocytes...
Moreover, a possible relation between a previous SARS-CoV-2 infection by omicron (B.1.1.529) variant and a concomitant HAdV infection is also under investigation. Nonetheless, speculations related to side effects of COVID-19 immunization can be ruled out, since most of the children affected have not been vaccinated.

**Perspectives**

From our point of view, gathering additional data is of cardinal importance to further investigate those hypotheses and explain the recent cases of acute hepatitis. Beyond the initial cases reported in the UK, the subsequent increment in the diagnosis of new HAdV infections worldwide could potentially incorporate a bias since it could be the result of increased testing and high surveillance by Health Authorities worldwide. Meanwhile, there is also the possibility of a novel HAdV with its own characteristics that causes human infection with liver specification or a HAdV/another pathogen co-infection as well as either an environmentally or food-derived toxin that acts as a hepatotoxic agent.

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**Table 1. Number of identified cases, liver transplantations and deaths by the hepatitis of unknown origin per territory and country, as of 26 May, 2022**

| Country         | Cases | Liver Transplantations | Deaths |
|-----------------|-------|------------------------|--------|
| EU/UK Total     | 374   | 38                     | 14     |
| Austria         | <5    |                        |        |
| Belgium         | 14    |                        |        |
| Bulgaria        | <5    |                        |        |
| Cyprus          | <5    |                        |        |
| Denmark         | 7     |                        |        |
| France          | <5    |                        |        |
| Greece          | <5    |                        |        |
| Ireland         | 7     | <5                     | 1      |
| Italy           | 27    | <5                     |        |
| Netherlands     | 14    | <5                     |        |
| Norway          | <5    |                        |        |
| Poland          | <5    |                        |        |
| Portugal        | 11    |                        |        |
| Romania         | <5    | <5                     |        |
| Slovakia        | <5    |                        |        |
| Slovenia        | <5    |                        |        |
| Spain           | 29    | <5                     |        |
| Sweden          | 9     |                        |        |
| United Kingdom  | 222   | 11                     |        |
| Outside of EU/UK|       |                        |        |
| Argentina       | <5    | <5                     |        |
| Canada          | 10    | <5                     |        |
| Indonesia       | <5    |                        | 6      |
| Israel          | 12    | <5                     |        |
| Japan           | 31    |                        |        |
| Maldives        | <5    |                        |        |
| Mexico          | 10    |                        | 1      |
| Moldova         | <5    |                        |        |
| Palestine       | <5    |                        | 1      |
| Panama          | <5    |                        |        |
| Serbia          | <5    | <5                     |        |
| Singapore       | <5    |                        |        |
| South Korea     | <5    |                        |        |
| USA             | 216   | 15                     | 5      |
Few epidemiological-linked cases have been reported, a pandemic cannot be fully assessed. Along this line, since the investigation, the realistic likelihood of emergence as well as the pattern of transmission are still un-known. Therefore, further practices, while encouraging medical attention upon presentation of suspect symptoms. Conclusively, further work is required to identify new cases, infectious or non-infectious causes, potential risk factors, and in depth-with sequencing-virus characterization.

Conflict of interest
EC has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2021. LC has no conflict of interests related to this publication.

Author contributions
Study concept and design (LC, EC), acquisition of the data (LC), analysis and interpretation of the data (LC), drafting of the manuscript (LC), critical revision of the manuscript for important intellectual content (EC), administrative, technical, or material support (EC), and study supervision (EC). All authors have made a significant contribution to this study and have approved the final manuscript.

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