Acute hepatitis of unknown etiology in children: Many clues but few clear answers

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INTRODUCTION

Six hundred and fifty probable cases of acute hepatitis of unknown etiology in children have been reported to the World Health Organization (WHO) between 5 April and 26 May 2022 [1]. The absence of any link between these cases and the currently known hepatitis agents has prompted the investigation of this emergent condition to elucidate its possible etiology, pathogenesis, and outcome. One of the alarming features of acute non-HepA-E hepatitis in children appears to be the unusually high proportion of severe cases that necessitated liver transplantation in a fraction of the affected cases [1]. In this editorial, we summarize the latest evidence on this topic and discuss the most possible pathogenetic mechanisms.

Timeline

During October 2021–February 2021, clinicians at a children's hospital in Alabama identified nine pediatric patients with severe hepatitis of unknown etiology and adenovirus viremia upon admission. Three patients developed acute liver failure, two of whom were transferred to a different medical facility and underwent liver transplantation [2]. On 31 March 2022, Public Health Scotland was notified of 5 cases of acute hepatitis of unknown origin, which were referred to the Glasgow children's hospital within a period of 3 weeks [3]. Apparently, this cluster significantly exceeded the expected number of cases of pediatric hepatitis of unknown etiology, which was estimated to be fewer than 4 per year across Scotland [4]. Subsequently, the WHO was notified of 10 cases of severe acute hepatitis of unknown etiology in previously healthy children in Scotland, on 5 April 2022 [5]. A multi-disciplinary team of experts was formed to review the epidemiological and clinical data of this initial cohort. All children required hospitalization, while one patient underwent liver transplantation [3]. Additional investigations identified 64 further cases (*i.e.,* a total of 74 cases) across the UK from 1 January up until 8 April 2022. In light of this evidence, the WHO published an alert, regarding cases of severe acute hepatitis of unknown origin in children, on 15 April 2022 [5].

Definitions and current status

Following this announcement, an increasing number of cases has been reported in several countries across the globe. The WHO and the European Centre for Disease Prevention and Control (ECDC) elaborated the currently applied working case definitions: (i) **Confirmed case**: not available at present; (ii) **Probable case**: a person presenting with an acute hepatitis (non-hepatitis viruses A, B, C, D, E) with serum transaminase >500 IU/L (AST or ALT), who is 16 years and younger, since 1 October 2021; **Epi-linked case**: a person presenting with an acute hepatitis (non-hepatitis viruses A, B, C, D and E) of any age who is a close contact of a probable case, since 1 October 2021. If the criteria are fulfilled but serology results for hepatitis A-E are awaited, these cases can be reported and shall be classified as "pending classification". Cases of hepatitis with a known underlying condition should not be reported under this protocol. Cases with other explanations for their clinical presentation are discarded [1,6,7].

According to the aforementioned criteria, 650 probable cases and 99 cases pending classification from 33 countries have been reported to the WHO as of 26

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May 2022. The majority of them have been identified in European countries (n=374; 58%) and, particularly, in the UK and Northern Ireland (n=222; 34%), while probable cases have also risen in USA (n=216; 33%) [1]. In Greece, at least 9 probable cases have been reported according to the National Public Health Organization [8]. Most of the reported cases are not epidemiologically linked and thorough investigations are ongoing to recognize common exposures, risk factors, or links between patients.

Clinical Presentation and Associated Pathogens

The mainly affected population are young children with no comorbidities. The majority of the cases reported through the European Surveillance System (TESSy) are children <5 years of age (75.4%), while the median age of the patients is 3 years according to reports from case series in the US and the UK [2,9]. The most common manifestation appears to be jaundice (68.8%), followed by vomiting episodes during the preceding weeks (57.6%). The presence of pale stools (42.7%) and lethargy (48.6%) are also frequently reported symptoms. At presentation, many children experience gastrointestinal symptomatology, such as diarrhea (43.1%), nausea (25.7%), or abdominal pain (36.1%). Interestingly, fever (28.5%) or respiratory symptoms (18.1%) are less commonly recognized [9].

Out of the 650 probable cases, at least 38 (6%) children required liver transplantation and 9 (1%) died according to the WHO [1]. Out of 156 cases registered *via* TESSy with hospitalization data available, 13.6% of the children were admitted to intensive care unit and 10.7% underwent liver transplantation [7]. Intriguingly, positive testing for human adenovirus (HAdV) infection among affected patients was reported to be as high as 68.6% in whole blood specimens, suggesting a potential role for HAdV in disease pathogenesis. Adenovirus characterization in a subgroup of 35 patients revealed that HAdV serotype F 41 was the predominant type (77%) [9]. Most of the patients had not received COVID-19 vaccination (84.7%), while SARS-CoV-2 was detected in 11.8% of the cases [7]. A range of other pathogens of uncertain significance, including adenovirus-associated virus (AAV) and human herpes virus 6 (HHV6), were identified in a low proportion of children [9].

Working hypotheses: Spotlight on Adenovirus

Although hAdV infection alone is rarely associated with fulminant hepatitis in immunocompetent patients, the most plausible hypothesis continues to encompass the role of adenovirus, considering its high prevalence among affected children [6,9]. hAdVs are nonenveloped, double-stranded, linear DNA viruses, and consist of 7 different species (HAdV A–G); they can be further classified into >100 types using whole-genome sequencing [10]. Inhalation of aerosolized droplets, fecal-oral spread, and direct exposure to infected tissue or blood represent the principal routes of transmission. The most common method to establish diagnosis is polymerase chain reaction (PCR) testing of respiratory secretions, plasma, stool, or urine samples [6]. Adenovirus infections can occur throughout the year. Following an incubation period that ranges from 2 to 14 days, hAdVs typically cause self-limited infections, which, depending on the cell tropism of the serotype, can affect the upper or lower respiratory tracts (mainly serotypes 1-5, 7, 14, and 21), the conjunctiva (serotypes 8, 19, and 37), or the GI tract (notably serotypes 40 and 41) [11]. Indeed, 5-10% of pediatric febrile illnesses have been attributed to hAdV-associated infections [6]. In addition, hAdVs have been reported to cause disseminated infection or acute hepatitis, leading to increased mortality, in immunocompromised patients [12,13]. Supportive care is the main therapeutic option for hAdV infections, while evidence supporting the administration of antivirals is scarce [11].

In the UK, the number of adenoviral infections among children aged 1 to 4 years from November 2021 to April 2022 has not only returned to pre-pandemic levels, but has spiked drastically and surpassed the expected number as estimated from the reported cases in the previous 5 years [9]. Interestingly, this period coincides with the emergence of cases of acute hepatitis of unknown origin in children, implicating a detrimental effect of adenovirus in this setting [6,14,15]. Indeed, hAdV 41 is associated with GI-related symptoms, such as vomiting, nausea, or abdominal pain, which are consistent with the symptomatology preceding the manifestation of acute hepatitis. However, even though adenoviruses may induce liver injury in immunosuppressed or less frequently in healthy children, hAdV 41 is not among the serotypes exhibiting features of hepatotropism [11,16]. In addition, histopathologic examination of liver biopsies in 6 cases did not yield findings indicative of adenovirus or other viral hepatitis [2].

It is hypothesized that other contributing factors, which undermine the host's defense mechanisms and alter the course of a typical hAdV infection, could induce

liver injury through a complementary manner [6,9,15]. First, lower circulation of hAdV and other pathogens, due to COVID-19 restrictions, has precluded the exposure of children to relevant stimuli [17]. As counties worldwide are starting to lift public health measures, a delayed exposure could elicit vigorous immune system responses precipitating hepatic damage in a subset of children [9]. In parallel, this delayed epidemiological peak of naturally occurring adenovirus infections could have possibly revealed a sporadic, albeit underrecognized, complication of hAdV infection [6,9]. Furthermore, a prior or concomitant infection with SARS-CoV-2, or another infectious agent might lead to increased susceptibility or impaired immune response to hAdV [6,9]. In fact, SARS-CoV-2 has been detected in a subset of children with acute hepatitis of unknown etiology [7], while hepatic involvement has been previously described in pediatric COVID-19 cases [18]. Nevertheless, it typically occurs as asymptomatic/mild hepatitis with preserved liver function, whereas severe acute hepatitis can rarely be presented as a complication of COVID-19-associated multisystem inflammatory syndrome [18]. Nishiura et al. have shown that countries reporting hepatitis cases experienced a significantly higher burden of Omicron cases, suggesting that previous exposure to SARS-CoV-2 Omicron variant may entail a risk for the development of post-infectious severe hepatitis among children [19]. However, further cofactor studies with serology tests will be required to clarify the effect of consecutive or coincidental infections with hAdV and SARS-CoV-2, or other pathogens.

Other theories suggest that the current outbreak may be due to the emergence of novel hAdV or SARS-CoV-2 variants that exhibit potent liver tropism with or without the contribution of the aforementioned cofactors [6,9,15]. However, data to corroborate this assumption are lacking, and the results of whole genome sequencing studies from numerous cases are eagerly awaited. At present, COVID-19 vaccination as a triggering event for hepatitis can be safely excluded, considering that most affected children had not received vaccination [1,6,15]. Finally, toxins, drugs, or other environmental stimuli leading to liver injury, alone or in combination with another cofactor, have not been identified, but cannot be entirely excluded yet [6].

CONCLUSIONS

The etiology of this seemingly rare but threating condition remains elusive. It is possible that liver injury occurs as a consequence of a "double-hit" process, in which adenovirus infection imparts a detrimental role. However, the association between cases and hAdV could be overestimated due to increased community transmission and enhanced laboratory testing. Outbreak risk assessment requires further epidemiological, clinical, laboratory, histopathological, and toxicological investigations of all the possible cause(s) of these cases. A methodical approach using standardized definitions, common diagnostic algorithms, and exchange of information as well as multinational collaboration need to be implemented to achieve a rapid and effective global response.

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REFERENCES

1. World Health Organization. Disease outbreak news: acute hepatitis of unknown aetiology in children - Multi-country. 27 May 2022. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/DON-389. [Accessed 6 June 2022].
2. Baker JM, Buchfellner M, Britt W, Sanchez V, Potter JL, Ingram LA, et al. Acute Hepatitis and Adenovirus Infection Among Children — Alabama, October 2021–February 2022. MMWR Morb Mortal Wkly Rep 2022; 71(18):638–40.
3. Marsh K, Tayler R, Pollock L, Roy K, Lakha F, Ho A, et al. Investigation into cases of hepatitis of unknown aetiology among young children, Scotland, 1 January 2022 to 12 April 2022. Euro Surveill. 2022; 27(15):2200318.
4. Braccio S, Irwin A, Riordan A, Shingadia D, Kelly DA, Bansal S, et al. Acute infectious hepatitis in hospitalised children: a British Paediatric Surveillance Unit study. Arch Dis Child. 2017; 102(7):624-8.
5. World Health Organization. Disease outbreak news: acute hepatitis of unknown aetiology - the United Kingdom of Great Britain and Northern Ireland. 15 April 2022. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON368. [Accessed 6 June 2022].
6. Mücke MM, Zeuzem S. The recent outbreak of acute severe hepatitis in children of unknown origin - what is known so far. J Hepatol. 2022; S0168-8278(22):00271-9.
7. European Centre for Disease Prevention and Control/WHO

Regional Office for Europe. Hepatitis of Unknown Aetiology in Children, Joint Epidemiological overview. 31 May 2022. Available at: https://cdn.ecdc.europa.eu/novhepsurveillance/ [Accessed 6 June 2022].
8. National Public Health Organization. Επιδημιολογική έκθεση οξείας ηπατίτιδας αγνώστου αιτιολογίας. 8 June 2022. https://eody.gov.gr/epidimiologiki-ekthesi-oxeias-ipatitidas-agnostoy-aitiologias-3/ [Accessed 13 June 2022].
9. UK Health Security Agency Technical briefing. Investigation into acute hepatitis of unknown aetiology in children in England. Version 3. 19 May 2022. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1077027/acute-hepatitis-technical-briefing_3.pdf [Accessed 6 June 2022].
10. Seto D, Chodosh J, Brister JR, Jones MS; Members of the Adenovirus Research Community. Using the whole-genome sequence to characterize and name human adenoviruses. J Virol. 2011; 85(11):5701-2.
11. Lynch JP 3rd, Kajon AE. Adenovirus: Epidemiology, Global Spread of Novel Serotypes, and Advances in Treatment and Prevention. Semin Respir Crit Care Med. 2016; 37(4):586-602.
12. Gu J, Su QQ, Zuo TT, Chen YB. Adenovirus diseases: a systematic review and meta-analysis of 228 case reports. Infection. 2021; 49(1):1-13.
13. Ronan BA, Agrwal N, Carey EJ, De Petris G, Kusne S, Seville MT, Blair JE, Vikram HR. Fulminant hepatitis due to human adenovirus. Infection. 2014; 42(1):105-11.
14. Hakim MS. The recent outbreak of acute and severe hepatitis of unknown etiology in children: A possible role of human adenovirus infection? J Med Virol. 2022; doi:10.1002/jmv.27856.
15. Sallam M, Mahafzah A, Şahin GÖ, on behalf of ESCMID Study Group for Viral Hepatitis—. Hepatitis of Unknown Origin and Etiology (Acute Non HepA-E Hepatitis) among Children in 2021/2022: Review of the Current Findings. Healthcare. 2022; 10(6):973.
16. Munoz FM, Piedra PA, Demmler GJ. Disseminated adenovirus disease in immunocompromised and immunocompetent children. Clin Infect Dis. 1998; 27(5):1194-200.
17. Groves HE, Piché-Renaud PP, Peci A, Farrar DS, Buckrell S, Bancej C, et al. The impact of the COVID-19 pandemic on influenza, respiratory syncytial virus, and other seasonal respiratory virus circulation in Canada: A population-based study. Lancet Reg Health Am. 2021; 1:100015.
18. Perez A, Cantor A, Rudolph B, Miller J, Kogan-Liberman D, Gao Q, et al. Liver involvement in children with SARS-COV-2 infection: Two distinct clinical phenotypes caused by the same virus. Liver Int. 2021; 41(9):2068-75.
19. Nishiura H, Jung SM, Hayashi K. High population burden of Omicron variant (B.1.1.529) is associated with the emergence of severe hepatitis of unknown etiology in children. Int J Infect Dis. 2022; S1201-9712(22):00290-9.

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