World Journal of Pediatrics (2022) 18:525–528
https://doi.org/10.1007/s12519-022-00577-7

EDITORIAL

Response to the outbreak of severe acute hepatitis of unknown origin in children

Jie Chen[1] · Qiang Shu[1] · Zheng-Yan Zhao[1]

Received: 26 May 2022 / Accepted: 30 May 2022 / Published online: 23 June 2022

During October 2021 and February 2022, nine pediatric patients with acute hepatitis of unknown origin were identified in Children's of Alabama [1]. These patients were tested negative for hepatitis viruses; and several other etiologies of hepatitis in children including autoimmune hepatitis were ruled out [1]. In a short period of time, the number of cases has surged in many countries; importantly, the rate has exceeded past annual incidence in various regions [2–4]. On 23 April 2022**,** World Health Organization (WHO) has issued a warning on severe hepatitis of unknown origin in children [5]. As of May 18, 575 suspected cases have been identified in Europe, United States of American (USA), Israel, India, Japan, and other countries; 35 children required liver transplantation and 11 died [6].

No cases have been reported from the Mainland of China. However, considering the uncertain etiology and high percentage of severe pediatric cases [4], we should take measures against the possible outbreak of acute hepatitis of unknown origin in China. China has a high number of pediatric population, therefore, it is pressing to establish an integrated early warning system for severe acute hepatitis of unknown origin in children.

Epidemiology of reported cases

As of May 18, 2022, 575 cases of severe acute hepatitis of unknown origin in children have been reported from 25 countries worldwide [7]: 180 cases in the USA (5 deaths), 176 in the UK, 125 cases in the European Union in the economic zone, 44 in Brazil, 21 in Indonesia (5 deaths), 21 in Mexico, 12 in Japan, 8 in Argentina, 7 in Canada, 2 in Costa Rica, 1 in Romania, 12 in Israel, 1 in Panama, 1 in Palestine, 1 in Serbia, 1 in Singapore, 1 in South Korea and 1 in Malaysia. Cases currently reported in various countries are based on the revised WHO definition of acute severe hepatitis of unknown origin in children on 23 April 2022. Most cases were identified in Europe and the USA. Epidemiological characteristics are as follows [4]: (1) patients were aged from 1 month to 16 years (most aged 1–5 years); and they were otherwise healthy; (2) the cases were sporadic, from different countries or different regions of the same country; and most patients lacked epidemiological correlation, and no travel history was related to the place where the epidemic occurred, and (3) cases appeared at a concentrated timepoint; for example, all the 13 patients initially reported in the UK were identified in March. The association between severe acute hepatitis and COVID-19 vaccination could be preliminarily ruled out.

Underlying causes

The etiology of the current onset severe acute hepatitis cases is still under investigation. Hepatitis may have multiple causes, including infection, autoimmunity, drugs and genetic metabolic factors. Considering the epidemiological and clinical features of this unexplained severe hepatitis, as well as clustered cases in the United Kingdom and USA, researchers believe that viral infection is most likely [1, 2, 8, 9]; however, until now no sufficient evidences are available for human-to-human transmission. No common hepatitis viruses (hepatitis A, B, C, D and E) have been detected in existing cases. So what is the cause of these children's sudden hepatitis? Based on the current global case investigation and comprehensive information from the European Centers for Disease Control and Prevention (ECDC), the UK National Health Security Agency, and the USA Centers for

✉ Qiang Shu
shuqiang@zju.edu.cn

✉ Zheng-Yan Zhao
zhaozy@zju.edu.cn

[1] National Clinical Research Center for Child Health, National Children's Regional Medical Center, Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310052, China

Disease Control and Prevention (CDC), potential causes are speculated including adenovirus (HAdV) infection (normal adenovirus or new variant adenovirus), SARS-CoV-2 virus post-infection syndrome or SARS-CoV-2 new variant strain infection, drug, toxin or environmental exposures, unknown pathogens alone or coinfection [1, 8–13].

Adenovirus infection

HAdV was detected in 72% (91/126) of the UK cases, with 18 identified as subgenus F HAdV-41 [14]. US detects HAdV in more than 50% of cases [15]. Similar reports have been reported in other countries; however, the role of HAdV infection in the current outbreak of hepatitis in children is unknown. Recently, all countries have required screening for HAdV infection in patients with acute hepatitis of unknown cause, exploring the best methods for specimen collection and detection, investigating the trend of HAdV infection in recent years (including before the SARS-CoV-2 epidemic), and predicting the risk of HAdV infection in the future. However, literatures revealed that hepatitis caused by HAdV infection in the liver is relatively rare [16, 17]. In immunocompetent patients, HAdV infection is usually self-limiting; only a few cases reported that HAdV causes acute hepatitis in immunocompetent adults and infants. HAdV-41 often causes gastrointestinal infection and diarrhea in infants and young children [18, 19], and no cases of severe acute hepatitis caused by HAdV infection have been reported. Although liver cell damage or necrosis and immunoreactivity to HAdV in the liver sinusoids were found in 8 cases of liver histologically, no adenovirus was detected in the liver tissue or liver cells [2, 10, 14]. Moreover, adenovirus load titers in the blood samples of some cases were low. Therefore, whether adenovirus is a potential infectious pathogen remains to be verified.

SARS-CoV-2 infection

Available reports indicate that 11 UK cases were positive for SARS-CoV-2 on admission (11%), 3 were positive for SARS-CoV-2 eight weeks before admission, and 1 Japanese case was found to have SARS-CoV-2 tested positive (14%) on admission [4, 14]. Of the 12 cases identified in Israel, 11 had been infected with SARS-CoV-2 in the past year (91.7%), and most of those infected were not vaccinated against SARS-CoV-2 [4]. In previous reports, SARS-CoV-2 infection can induce hepatitis, which can manifest as an elevation of alanine transaminase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and direct bilirubin, which may be caused by direct attack or the bloodstream spread of the virus and retrograde infection to the biliary tract [20]. This unexplained hepatitis may be one of the long-term symptoms of COVID-19.

Recently, Brodin et al. hypothesized that occurrence of acute hepatitis of unknown cause is related to the superposition of the new coronavirus superantigen and adenovirus 41 [10]. SARS-CoV-2, such as recently infected strains of Omicron, may change tissue tropism, becoming enterotropic, and persist in the gastrointestinal tissue of children for longer periods of time, thus allowing persistent infection [21]. Previous studies have shown that children infected with SARS-CoV-2 form a viral reservoir (i.e., SARS-CoV-2 is continuously released from host cells). Persistence of SARS-CoV-2 in the gastrointestinal tract can lead to the continuous release of virus from intestinal epithelial cells, leading to immune activation, which may be mediated by the superantigen motif in the SARS-CoV-2 spike protein [10]. Adenovirus 41 drives a type I immune response and amplifies SEB-mediated hyperimmune pathology [10]. These conclusions are speculative, without scientific conclusions, which need to be confirmed further.

Other speculations about etiology include the possible presence of a novel yet unidentified hepatotropic virus, a novel pathogen that can be infected alone or with other pathogens, infection with a novel variant of human adenovirus, infection with a novel variant of the novel coronavirus strains, factors such as drugs, toxins or environmental exposure and immune liver damage caused by one or more of the above factors.

Clinical features and diagnostic strategies

Clinical manifestations of severe acute hepatitis of unknown origin reported in different countries are similar, mainly acute hepatitis with markedly elevated transaminases (AST or ALT > 500 IU/L), accompanied by jaundice, lethargy, fatigue, nausea, and gastrointestinal symptoms such as abdominal pain, diarrhea, vomiting, etc. A report of nine children by the US CDC showed that some children had symptoms such as vomiting, diarrhea, and upper respiratory tract infection appearing before admission, and signs such as jaundice and hepatomegaly occurring after admission [1]. According to the statistics of 163 children reported by the British Health Service, the common clinical presentations were jaundice (71.2%), vomiting (62.7%), lethargy (50.0%), light-colored stools (50.0%), diarrhea (44.9%), abdominal pain (41.5%), fever (30.5%), nausea (30.5%), and less commonly respiratory symptoms (18.6%) [6]. Unexplained severe acute hepatitis is highly detrimental to the liver of children. As of May 10, 11 of the 450 children reported died, and 35 (7.8%) received liver transplantation [6].

On April 23, 2022, the diagnostic criteria for severe acute hepatitis of unknown cause in children issued by the WHO are as follows [5]: 1) confirmed cases are not available at present; 2) suspected cases present with hepatitis (non-A, B, C, D and E hepatitis viruses) with serum transaminase (ALT or AST) > 500 U/L and are 16 years or younger, since October 1, 2021, and 3) epi-linked cases are persons with acute hepatitis (non-A, B, C, D and E hepatitis viruses) of any age who have been in close contact with suspected cases since October 1, 2021. If hepatitis A, B, C, D, and E testing results are pending but other criteria are met, these results can be reported and classified as "pending classification". Cases with other explanations for their clinical manifestations are ruled out.

WHO recommends that blood, serum, urine, fecal and respiratory samples, and liver biopsy samples, if applicable, should be tested [4]. Further strengthening of viral testing (genome sequencing and classification) is recommended, along with a thorough investigation of other infectious and noninfectious causes. The European CDC recommends various testing modalities for different samples and expands the scope of pathogen screening, for blood, feces, urine, throat swabs and anal swabs and other samples, conduct A, B, C, D and Hepatitis E virus, adenovirus, Epstein–Barr virus, cytomegalovirus, chickenpox, HIV, SARS-CoV-2, herpes virus, enterovirus (including norovirus, enterovirus, rotavirus, astrovirus, and sapovirus) and common bacteria (including Campylobacter, Salmonella, Shigella, and *Escherichia coli*) and other routine clinical pathogen screening [4].

Considerations on prevention and control strategies

The etiology of severe acute hepatitis is still unclear, so health organizations in various countries have no specific treatment methods. In view of some critically ill patients who need liver transplantation or even die, health departments of many countries have called for more attention on this disease. The National Health Commission of China (NHCC) attaches great importance to this issue, and has organized experts to pay close attention on the global trend. On May 7, NHCC published a guidance entitled "Answer to Questions about Acute Hepatitis in Children of Unknown Cause" on its official website.

There are no confirmed cases of severe acute hepatitis of unknown etiology at present. The definition of severe acute hepatitis of unknown origin in children is mainly used for disease monitoring. For suspected cases, epidemiological characteristics investigation and tracking are required, and isolation measures may be taken if necessary. Clinicians should be alert to unexplained, increasing cases of acute severe hepatitis, and to children with signs or symptoms associated with hepatitis including dark urine and/or pale stools, jaundice, pruritus, arthralgia/myalgia, fever, nausea, vomiting or abdominal pain, drowsiness or loss of appetite. Liver function tests should be performed in time. If patients had serum ALT or AST > 500 IU/L, we should pay close attention on the disease progression and the occurrence of life-threatening events. Intense clinical management and pathogenic investigation should be started as soon as possible. Treatment should be carried out to relieve symptoms by supportive treatment, rational feeding, and maintain the cellular metabolism and homeostasis. Comprehensive management through multidisciplinary cooperation is recommended. It is necessary to assess indications for blood purification and liver transplantation at any time. Treatment strategies include bed rest, nutrition support, symptomatic treatment, prevention and treatment of hepatic encephalopathy, artificial liver treatment, liver transplantation, prevention and treatment of secondary biliary infection or spontaneous peritonitis.

Overall prevention and control is challenging for individualized treatment. How to timely identify critically ill children and establish optimal diagnosis and treatment for children is crucial. To assess the potential risk of acute severe hepatitis in children of unknown etiology, risk assessment, clinical, epidemiological and virological surveillance are pressing. We should establish a long-term monitoring system and an early warning system based on clinical symptom monitoring in hospitals or institutions with pediatric health service.

There is no need to panic, however, we should establish a practical emergence response plan. In view of the severity of this disease, it is necessary to evaluate the current status of safety and accessibility of pediatric liver transplantation in China. Clinical, epidemiological and virological surveillance data need to be collected timely to assess the potential risk of acute severe hepatitis in children of unknown origin. It is important to educate families and the public that children with symptoms such as jaundice and diarrhea should seek medical attention in time and abide by the quarantine requirements for infectious diseases. Suspected cases should be reported, investigated, monitored, isolated or transferred to tertiary hospitals as soon as possible. Clinicians should be educated and trained to be capable of identifying the disease at their earliest onset. Multidisciplinary cooperation among pediatrics, emergency, infectious disease, gastroenterology, intensive care, transplantation, as well as laboratory should be highlighted. Diagnosis and treatment guidance should be issued. International information exchange and cooperation will be benefit to global public health security.

In conclusion, data on etiology of this disease are still lacking. Articles on the etiology, pathogenesis, clinical

presentations, diagnosis and treatment strategies would be welcomed by *World Journal of Pediatrics*.

Author contributions CJ and SQ and ZZY collected and analyzed the data and wrote the manuscript. All authors approved the final version of the manuscript.

Funding This study was supported by Research on New Technology of Diagnosis and Treatment of Common Diseases in Children—Establishment and Application of Intelligent System for Rapid Diagnosis of Children's Acute Diarrhea (Zhejiang Provincial Key R and D Program 2019C03037).

Declarations

Conflict of interest No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. Jie Chen is a member of the Editorial Board for *World Journal of Pediatrics*. Qiang Shu and Zheng-Yan Zhao are chief editors of the journal. The paper was handled by the other Editors and has undergone a rigorous peer-review process. Authors Jie Chen, Qiang Shu and Zheng-Yan Zhao were not involved in the journal's review or decisions making of this manuscript.

Ethical approval Not needed for the review article.

References

1. 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;71:638–40.
2. Mücke MM, Zeuzem S. The recent outbreak of acute severe hepatitis in children of unknown origin—what is known so far. J Hepatol. 2022;77:237–42.
3. World health organization. acute hepatitis of unknown a etiology–the United Kingdom of Great Britain and Northern Ireland [EB/OL]. 2022. https://www.who.int/emergencies/disease-outbreak-news/item/acute-hepatitis-of-unknown-aetiology---the-united-kingdom-of-great-britain-and-northern-ireland. Accessed 18 May 2022.
4. World health organization. Multi-country-acute, severe hepatitis of unknown origin in children [EB/OL]. 2022. https://www.who.int/emergencies/emergency-events/item/2022-e000081. Accessed 18 May 2022.
5. Organization. WHO: disease outbreak news; multi-country–acute, severe hepatitis of unknown origin in children. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON376 (23 April 2022). Accessed 19 May 2022.
6. Agency UHS. Acute hepatitis: technical briefing. https://www.gov.uk/government/publications/acute-hepatitis-technical-briefing. Accessed 18 May 2022.
7. European centre for disease prevention and control. increase in acute hepatitis of unknown origin among children-United Kingdom [EB/OL]. https://www.ecdc.europa.eu/en/news-events/increase-acute-hepatitis-unknown-origin-among-children-united-kingdom. Accessed 18 May 2022.
8. de Kleine RH, Lexmond WS, Buescher G, Sturm E, Kelly D, Lohse AW, et al. Severe acute hepatitis and acute liver failure of unknown origin in children: a questionnaire-based study within 34 paediatric liver centres in 22 European countries and Israel. Euro Surveill. 2022. https://doi.org/10.2807/1560-7917.ES.2022.27.19.2200369.
9. 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. https://doi.org/10.1002/jmv.27856.
10. Brodin P, Arditi M. Severe acute hepatitis in children: investigate SARS-CoV-2 superantigens. Lancet Gastroenterol Hepatol. 2022;S2468–1253:00166–72.
11. Zhu Z, Zhang NY, Mao Y, Xu WW. Consideration on the emerging of severe acute hepatitis cases with of unknown etiology in children worldwide. Zhonghua Yufang Yixue Zazhi. 2022;56:1–3.
12. van Beek J, Fraaij P, Giaquinto C, Shingadia D, Horby P, Indolfi G, et al. Case numbers of acute hepatitis of unknown aetiology among children in 24 countries up to 18 April 2022 compared to the previous 5 years. Euro Surveill. 2022. https://doi.org/10.2807/1560-7917.
13. Şahin GÖ, Mondelli MU, Matičič M, Sandulescu O, Irving W, ESCMID study group for viral hepatitis (ESGVH). Acute severe hepatitis of unknown aetiology in children: a new non-A-E hepatitis virus on horizon? Clin Microbiol Infect. 2022. https://doi.org/10.1016/j.cmi.2022.05.001.
14. UK health security agency. Technical briefing: investigation into acute hepatitis of unknown aetiology in children in England. Retrieved April 25, 2022, from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1071198/acute-hepatitis-technical-briefing-1_4_.pdf. Accessed 18 May 2022.
15. Centers for disease control and prevention. children with hepatitis of unknown cause. Retrieved May 6, 2022, from https://www.cdc.gov/ncird/investigation/hepatitis-unknown-cause/overview-what-to-know.html. Accessed 18 May 2022.
16. Hiroi S, Morikawa S, Nakata K, Kase T. Surveillance of adenovirus respiratory infections in children from Osaka, Japan. Jpn J Infect Dis. 2017;70:666–8.
17. Lee J, Choi EH, Lee HJ. Clinical severity of respiratory adenoviral infection by serotypes in Korean children over 17 consecutive years (1991–2007). J Clin Virol. 2010;49:115–20.
18. Banerjee A, De P, Manna B, Chawla-Sarkar M. Molecular characterization of enteric adenovirus genotypes 40 and 41 identified in children with acute gastroenteritis in Kolkata, India during 2013–2014. J Med Virol. 2017;89:606–14.
19. Lu L, Zhong H, Su L, Cao L, Xu M, Dong N, et al. Detection and molecular characterization of human adenovirus infections among hospitalized children with acute diarrhea in Shanghai, China, 2006–2011. Can J Infect Dis Med Microbiol. 2017;2017:9304830.
20. Zhang X, Yu Y, Zhang C, Wang H, Zhao L, Wang H, et al. Mechanism of SARS-CoV-2 invasion into the liver and hepatic injury in patients with COVID-19. Mediterr J Hematol Infect Dis. 2022;14:e2022003.
21. Brodin P. SARS-CoV-2 infections in children: understanding diverse outcomes. Immunity. 2022;55:201–9.