

Advances in Acute Severe Hepatitis in Children of Unknown Etiology

Xuefeng Zhou¹, Hongzhou Lu^{1,*}

1. National Clinical Research Center for Infectious Diseases, Shenzhen Third People's Hospital,
Southern University of Science and Technology, Shenzhen, 518112, China

*Correspondence author.

Dr. Hongzhou Lu, luhongzhou@fudan.edu.cn.

Abstract

Since the International Health Regulations (IHR) National Focal Point (NFP) for the United Kingdom alerted the WHO of 10 cases of acute severe hepatitis in children of unknown etiology on 5 April 2022, relevant cases have been reported around the world. These patients had acute hepatitis (hepatitis viruses A-E was negative) and separated aminotransferase (AST) or alanine aminase (ALT) over 500 U/L. Furthermore, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and/or adenovirus type F41 were detected in some cases. It is hypothesized that this unknown hepatitis is induced by the viral reservoir of novel coronavirus superantigen that repeatedly stimulates the intestine to form multisystem inflammatory syndrome in children (MIS-C), which causes immune abnormalities under the assistance of human adenovirus (HAdV). Although this hypothesis has not been confirmed by any in vivo experimental or clinical studies, it indicated a possible intervention strategies.

On 5 April 2022, the International Health Regulations (IHR) National Focal Point (NFP) for the United Kingdom alerted the WHO of 10 cases of acute severe hepatitis in children of unknown etiology. These cases were spread across central Scotland, between one and five years of age, presented with clinical symptoms and signs of severe acute hepatitis, including jaundice and aminotransferase (AST) or alanine aminase (ALT) greater than 2,000 IU/L, viral hepatitis types A, B, C, D and E were negative. Some of the cases reported gastrointestinal symptoms such as diarrhoea and vomiting. Meanwhile, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and/or adenovirus have been detected in several cases. Whether these viruses are related to hepatitis of unknown etiology cause is uncertain, and no other epidemiological risk factors have been identified^[1]. Since then, related cases have been reported around the world.

On April 8, the UK Health and Safety Agency (UKHSA) published a Guidance. It requires that once a child is found with symptoms such as: urine(dark) and/or faecal (pale) discoloration, jaundice, [pruritis](#), arthralgia, myalgia, pyrexia, nausea, vomiting or abdominal pain, lethargy and or loss of appetite, further liver function tests are required. If a patient's serum transaminase (AST or ALT) is over 500 IU/L associated with symptoms of hepatitis, his serum and EDTA samples, nose and throat swabs, faecal and urine samples should be stored as soon as possible^[2].

On 15 April 2022, this acute hepatitis of unknown etiology was defined by WHO. The confirmed case: since 1 January 2022, a person presenting with an acute hepatitis (non-hepatitis viruses A, B, C, D, E) with AST or ALT over 500 U/L, who is 10 years old and under. The possible cases: laboratory test results were identical with confirmed cases, but aged between 11 to 16 years.

On April 19, twelve cases were detected in Israel, seven cases were reported by the Schneider Children's Medical Center and five by Shaare zedek Medical Center. These cases are from different locations and did not show the characteristics of cluster infection. Clinical symptoms and laboratory results are consistent with definitions published by WHO. Notably, all the cases were infected with [SARS-CoV-2](#) about three and a half months before hepatitis. Although there is no clear evidence that this unknown hepatitis is associated with [SARS-CoV-2](#)^[3].

As of 21 April, about 169 cases of acute hepatitis of unknown etiology have been reported from 12 countries. Notably, the vast majority of SARS-CoV-2 positive cases, 19 of the 20, also tested positive for adenovirus, and 18 cases were identified as F type 41^[4]. On the same day, the [United States](#) Centers for Disease Control and Prevention (CDC) issued a national health warning through the Health Alert Network (HAN), requiring doctors to notice and report all suspected cases of hepatitis of unknown origin to local health authorities. It is estimated that the first patient was found [in Alabama](#) in October 2021. Up to February of 2022, a total of nine patients have been identified, including three patients with acute liver failure, who have also tested positive for adenovirus. It seems to imply some correlations between adenovirus and acute severe hepatitis in children of unknown etiology. However, the clinical test result showed that no viral inclusions were observed on liver biopsy, and no virus evidence was detected by immunohistochemistry or electron microscopy^[5].

On April 23, the WHO published a modified version about the definition of acute hepatitis in children of unknown etiology: the original confirmed definition was cancelled, and altering the age of probable cases from 11-16 to under 16 years. It also stated that although adenovirus was considered as an underlying pathogenic factor, it did not adequately explain the current severe

clinical symptoms. Additionally, the vast majority of cases identified were not vaccinated against COVID-19, so the hypothesis of side effects of COVID-19 vaccine was invalid^[4].

However, a rapid risk assessment report published by the European Centre for Disease Prevention and Control (ECDC) on April 28 noted that adenovirus and SARS-CoV-2 were the pathogens with the highest detection rate in children with unexplained acute hepatitis in Europe. Up to 50% of cases in Scotland, 75.5% in England tested positive for adenovirus. Subtype analysis of 11 cases in the UK found that these adenovirus were all type 41F, which is the same subtype found in previously several cases reported from the US. Therefore, the European CDC has made the following assumptions about the cause of this unknown hepatitis: a cofactor rendering normal mild adenovirus infections more severe, or causing them to trigger immunopathology; a novel variant adenovirus or SARS-CoV-2; a drug, toxin or environmental exposure; a novel pathogen either acting alone or as a coinfection^[6].

With icosahedral protein capsid, human adenovirus (HAdV) is a non-enveloped, double-stranded DNA virus of the family Adenoviridae, which consists of 11 different structural proteins. More than 100 different types (types 1-51 were sera type, types 52-103 were gene type) of human adenoviruses have been identified and divided into seven species termed A-G, many of them have well-characterized tropisms for specific tissues^[7]. Human adenovirus infection usually causes upper respiratory, gastrointestinal or conjunctival lesions. The vast majority of patients are self-restricting and generally heal within a few weeks, so fatal and disseminated infections are uncommon. In addition, clinical manifestations in patients with types 40 / 41 (species F) include fever, vomiting, diarrhea and occasionally lead to persistent and acute gastroenteritis in young children^[8]. It seems to suggest that the single infection of human adenovirus is not associated with

acute severe hepatitis in children of unknown etiology. Coincidentally, the WHO and the Pan-American Health Organization (PAHO) issued a new relevant technical note on May 10th. It said that although adenovirus was detected in the blood or plasma of multiple children, viral titers were low and no adenovirus was detected in the liver tissue. Presumably, adenovirus infection is more like a coincidental factor^[9].

Is this unknown hepatitis caused by SARS-CoV-2? As we know, the SARS-CoV-2 invades cells by binding to the host cell receptors angiotensin converting enzyme 2 (ACE2) through its spike glycoprotein. Although the most typical clinical manifestation of SARS-CoV-2 infection is respiratory symptoms, ACE2 does not only have the tissue specificity of lung, it is also highly expressed in multiple human organs, such as colon, biliary tract and liver^[10]. Moreover, an excessive inflammatory state caused by excessive cytokines production following SARS-CoV-2 infection, which is known as the cytokine storm syndrome. Accompanied with significant elevation of key proinflammatory cytokines such as IL-1, IL-2, IL-6, TNF- α and IFN- γ , the cytokine storm causes acute respiratory distress syndrome and multiple organ failure, and even death in severe cases^[11]. These are the theoretical basis for the emergence of liver lesions after SARS-CoV-2 infection. Several studies have pointed out that liver injury is relatively common in patients with severe COVID-19^[12]. According to statistics, the incidence of liver injury in COVID-19 deaths is about 58%-78%^[13]. Liver biopsy experiments in COVID-19 patients showed a large increase in ballooned hepatocytes and liver lobular inflammation, which are considered as evidence of viral injury^[14]. Therefore, this unknown hepatitis may be one of the long-term symptoms of COVID-19.

On May 13, The Lancet Gastroenterology & Hepatology presented a new opinion: SARS-CoV-2 superantigen may be the cause of acute hepatitis in children of unknown etiology. The literature has been reported that SARS-CoV-2 infection keeps the virus in the gastrointestinal tract to form a viral reservoir, resulting in repeated release of viral proteins in enterocytes and repeated immune activation. This activation of immune cells is thought to be a pathogenic mechanism in the multisystem inflammatory syndrome in children (MIS-C)^[15]. So MIS-C is considered as a new clinical manifestation associated with SARS-CoV-2 infection, which affects multiple organ systems. During the onset of the MIS-C, shock, gastrointestinal symptoms, hypercoagulability, disseminated intravascular thrombosis, were described in patients^[16]. It should be noted that some of the clinical features of MIS-C are similar to toxic shock syndrome (TSS) and Kawasaki disease (KD), so more attention needs to be paid to their differences during diagnosis and therapy. In general, the majority of MIS-C patients have symptoms of abdominal pain, diarrhea, or vomiting, which is comparatively uncommon in Kawasaki disease^[17]. So far, the pathogenesis of MIS-C remains unknown. An uncontrolled cytokine storm involving high inflammatory markers, or a superantigen-like motif in the "spike" protein of SARS-CoV-2, has been proposed as the cause of MIS-C^[18]. If such SARS-CoV-2 viral reservoir is present in children and subsequently coinfects with adenovirus, such superantigen-mediated effects may be more pronounced and lead to immune abnormalities, leading to the occurrence of acute severe hepatitis. Therefore immunomodulatory therapies should be considered in the treatment of this unknown hepatitis. Although this hypothesis has not been confirmed by any in vivo experimental or clinical studies, this article indicated a research direction and possible intervention strategies. Perhaps when we are treating this unknown hepatitis, we should also focus on whether other organs are

affected. At the same time, it also gives us a revelation: in the process of treating some diseases that can form viral reservoir, such as AIDS. On the one hand, attention should be paid to the clearance of the viral reservoir. On the other hand, we should also avoid some factors that may reactivate the viral reservoir like co-infection of other viruses and immune system disorders.

As of 27 May, 650 cases of acute severe hepatitis in children of unknown etiology have been reported in 33 countries. More recent cases have been reported with more severe clinical symptoms and a higher proportion of acute liver failure, at least 38 (6%) children have required liver transplants, and 9 (1%) deaths have been reported. Consequently, WHO assesses the risk of this unknown hepatitis at the global level as moderate^[19].

At present, no related cases have been found in China, and health authorities and medical institutions are paying close attention to and continuously monitoring the situation of hepatitis of unknown etiology. The main preventive measures are to avoid children going to crowded public places without air circulation, cut off droplet contact and fecal-oral transmission routes, ensure adequate child sleep and nutrition, wash hands frequently, wear masks, maintain social distancing. If children appear in jaundice, digestive tract and other hepatitis diseases symptoms, they need to seek medical treatment as fast as possible.

Reference

[1] World Health Organization. "Acute Hepatitis of Unknown Aetiology-the United Kingdom of Great Britain and Northern Ireland." Switzerland. WHO. 15 April 2022.

<https://www.who.int/emergencies/disease-outbreak-news/item/acute-hepatitis-of-unknown-aetiology---the-united-kingdom-of-great-britain-and-northern-ireland>

[2] The UK Health and Safety Agency. "Increase in Acute Hepatitis Cases of Unknown Aetiology in Children." UKSA. 8 April 2022.

<https://www.gov.uk/government/publications/hepatitis-increase-in-acute-cases-of-unknown-aetiology-in-children/increase-in-acute-hepatitis-cases-of-unknown-aetiology-in-children>

[3] Israeli Ministry of Health. "The Ministry of Health Informed of 12 Cases of Children with Acute Hepatitis without Clear Background." Israeli. MoH. 2022.

<https://www.gov.il/en/departments/news/19042022-01>

[4] World Health Organization. "Multi-Country-Acute, Severe Hepatitis of Unknown Origin in Children." Switzerland. WHO. 23 April 2022.

<https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON376>

[5] Health Alert Network. "Recommendations for Adenovirus Testing and Reporting of Children with Acute Hepatitis of Unknown Etiology." American. HAN. 21 April 2022.

<https://emergency.cdc.gov/han/2022/han00462.asp>

[6] European Centre for Disease Prevention and Control. "Increase in severe acute hepatitis cases of unknown aetiology in children." Sweden. ECDC. 21 April 2022.

<https://www.ecdc.europa.eu/en/publications-data/increase-severe-acute-hepatitis-cases-unknown-aetiology-children>

[7] Lion, T., Adenovirus persistence, reactivation, and clinical management. FEBS Lett, 2019. 593(24): p. 3571-3582.

[8] Uhnou, I., et al., Importance of enteric adenoviruses 40 and 41 in acute gastroenteritis in infants and young children. J Clin Microbiol, 1984. 20(3): p. 365-72.

[9] Pan American Health Organization/World Health Organization. "Technical Note: acute, severe hepatitis of unknown origin in children." PAHO/WHO. 10 May 2022.

<https://www.paho.org/en/news/10-5-2022-technical-note-acute-severe-hepatitis-unknown-origin-children>

[10] Dong, M., et al., ACE2, TMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19. *Biomed Pharmacother*, 2020. 131: p. 110678.

[11] Zanza, C., et al., Cytokine Storm in COVID-19: Immunopathogenesis and Therapy. *Medicina (Kaunas)*, 2022. 58(2).

[12] Brisca, G., et al., SARS-CoV-2 Infection May Present as Acute Hepatitis in Children. *Pediatr Infect Dis J*, 2021. 40(5): p. e214-e215.

[13] Zhang, B., et al., Clinical characteristics of 82 cases of death from COVID-19. *PLoS One*, 2020. 15(7): p. e0235458.

[14] Gu, J., B. Han and J. Wang, COVID-19: Gastrointestinal Manifestations and Potential Fecal-Oral Transmission. *Gastroenterology*, 2020. 158(6): p. 1518-1519.

[15] Brodin, P. and M. Ardit, Severe acute hepatitis in children: investigate SARS-CoV-2 superantigens. *Lancet Gastroenterol Hepatol*, 2022.

[16] Klok, F.A., et al., Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res*, 2020. 191: p. 148-150.

[17] Ramphul, K. and S.G. Mejias, Kawasaki disease: a comprehensive review. *Arch Med Sci Atheroscler Dis*, 2018. 3: p. e41-e45.

[18] Pang, J., et al., SARS-CoV-2 Polymorphisms and Multisystem Inflammatory Syndrome in Children. *Pediatrics*, 2020. 146(6).

[19] World Health Organization. "Acute hepatitis of unknown aetiology in children-Multi-country." Switzerland. WHO. 27 May 2022.

<https://www.who.int/emergencies/disease-outbreak-news/item/DON-389>

Funding

This work was supported by the National Natural Science Foundation of China (No. 92169119), and the Shenzhen Scientific and Technological Foundation (No. JSGG20220301090005007).