

Severe acute hepatitis of unknown origin in children: Clinical issues of concern

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INTRODUCTION

In central Scotland at the end of March 2022, there were reports of several cases of severe acute hepatitis of unknown origin in children (< 10 years old).^[1,2] Previously (October 2021), a children's hospital in Alabama (USA) reported a cluster of cases of severe hepatitis of unknown origin.^[3] Since then, case numbers of this disease in children have been confirmed or suspected in multiple countries worldwide.^[4] The World Health Organization (WHO) stated that until July 8, 2022, 35 countries in five WHO Regions have been reported 1010 probable cases of acute hepatitis, including 22 deaths in children aged 16 years or younger. Forty-six (5%) of the children needed liver transplantation (LT).^[4] Almost half (48%) of probable cases were from Europe. The Americas had the second highest number of probable cases, and then the Western Pacific, South-East Asia, and the Eastern Mediterranean.^[4-6]

China has reported no cases. Given the proportion of children in China's large population and the high proportion of severe cases among children,^[4] it is necessary to establish effective measures to prevent, diagnose, and treat severe acute hepatitis of unknown origin in children in China. Currently, the etiology and pathogenetic mechanisms of the disease are still under investigation.

This article briefly summarizes the current available information regarding the outbreak of severe acute hepatitis of unknown origin in children. We discuss the possible causes and review the diagnosis and treatment methods for this disease.

EPIDEMIOLOGY

Up to 8 July 2022, 35 countries have reported a total of 1010 probable cases of severe acute hepatitis of unknown origin in children.^[4] Seventeen countries have reported more than five probable cases (Figure 1). The true number of cases might be higher because of limitations of the enhanced surveillance systems in operation. The increasing availability of information and verified data will undoubtedly increase the case count. Up to July 28, 2022, no cases were reported in Mainland China.

CLINICAL SYMPTOMS

The European Center for Disease Prevention and Control (ECDC) and WHO define severe acute hepatitis of unknown origin in children as a person 16 years old or younger since 1 October 2021, presenting with acute hepatitis that has tested negative for hepatitis virus A, B, C, D, and E, and has a liver enzyme aspartate transaminase activity greater than 500 IU/L. It does not include hepatitis caused by autoimmune disorders, inherited metabolic disorders, or

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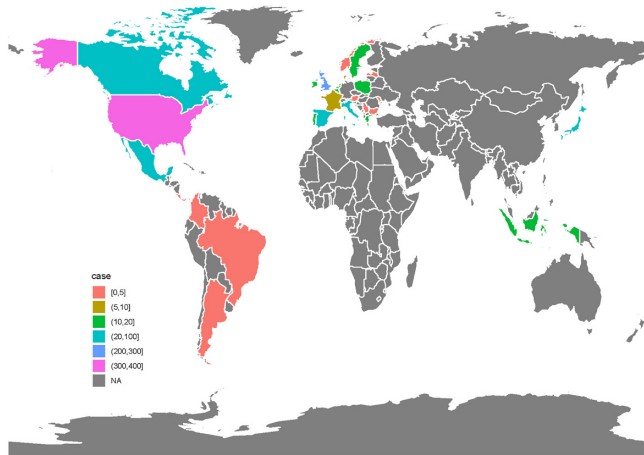


Figure 1: Worldwide distribution of reported probable cases of severe acute hepatitis of unknown origin in Children worldwide up to July 8, 2022. Seventeen countries have reported more than five probable cases. The countries are Belgium, Denmark, France, Greece, Ireland, Italy, Netherlands, Poland, Portugal, Spain, Sweden, United Kingdom, Canada, Mexico, United States of America, Japan and Indonesia.

drug toxicity.^[4,5] The most commonly reported symptoms including jaundice, lethargy, abdominal pain, fatigue, fever, and gastrointestinal manifestations, *e.g.*, nausea, vomiting and diarrhea (Figure 2). Comparatively, fever is less frequently reported.^[7,8]

THE CAUSE OF SEVERE ACUTE HEPATITIS OF UNKNOWN ORIGIN IN CHILDREN

To date, we do not know the etiologies of the present outbreak of severe acute hepatitis, which are under investigation. However, several possible etiological factors have been investigated in some countries. Studies are ongoing to find the relationship between severe acute hepatitis and certain potential factors, such as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), adenovirus, co-infection, and other risk factors.

CORONAVIRUS DISEASE 2019 (COVID-19)

In late 2019, SARS-CoV-2 emerged and caused a worldwide epidemic termed COVID-19. It is not yet clear whether all cases of severe acute hepatitis of unknown origin in children are associated with the SARS-CoV-2; however, the relationship between these two diseases should not be ignored. The WHO and ECDC stated that SARS-CoV-2 nucleic acids were detected in 39 (11.2%) of 348 reported cases using real-time polymerase chain reaction (qPCR).^[9] Serology showed that 52 (61.9%) of 84 cases were SARS-CoV-2 positive. Based on preliminary analysis,

Clinical Symptoms of the acute severe hepatitis of unknown origin in Children



Figure 2: Clinical Symptoms of severe acute hepatitis of unknown origin in Children.

the USA Centers for Disease Control and Prevention (CDC) reported the detection of SARS-CoV-2 infection in approximately 10% of patients under investigation (PUIs) using an antigen or PCR test.^[10] Up to 19 July, 2022, the UK has reported 270 confirmed cases of hepatitis in children aged 10 or under, of which 4.4% were SARS-CoV-2 positive in the first 2 weeks.^[11] However, whether there is a strong correlation with SARS-CoV-2 remains unknown and is under investigation. A positive COVID-19 test at any time before the appearance of hepatitis symptoms was not statistically significant, because 11.9% of hepatitis cases were positive for COVID-19 compared with 15.6% in the random sample. Moreover, blood sample analysis showed no significant difference in the presence of SARS-CoV2 antibodies between hepatitis cases and age-matched patient controls.^[11] Similar tests by other organizations (WHO, CDC and ECDC) suggested that the cases of severe acute hepatitis cases are not likely to be associated with previous COVID-19 infection.

HUMAN ADENOVIRUS INFECTION

According to the currently published data^[7,8,12-16] and reports from the UK National Health Security Agency, the ECDC, and the CDC, pathogens such as adenovirus were detected by PCR in a number of the cases.^[4,5,11,17] Of 398 probable cases, 217 cases were detected as positive for adenovirus by PCR in the European region.^[9] UK investigations suggested that the recent cases of hepatitis might be similarly linked to adenovirus infection. According to the CDC reports, in June 2022, among 252 (83%) PUIs tested for adenovirus in at least one specimen type (stool, respiratory fluid, serum, plasma, or whole blood), 45% were positive. Laboratory assessments showed that some of the children in Alabama were positive for adenovirus type 41, which usually causes severe stomach illness in children.^[3] There have been similar reports in other countries.^[4,5,11]

Human adenovirus (HAdVs), which are members of the family Adenoviridae, are common pathogens comprising small, non-envelope DNA viruses with a doublestranded genome with more than 88 different HAdV types (known as serotypes) and a worldwide distribution.^[18-20] HAdVs cause approximately 5–10% of all febrile illnesses in young children and almost all adults have serological evidence of previous infection with one or more HAdVs.^[21,22] HAdVs cause acute respiratory disease, gastroenteritis, keratoconjunctivitis, and obesity. Generally, these diseases are self-limiting; however, in immunocompromised hosts, they can be severe and even deadly.^[23,24] Children's immune systems are less well developed; therefore, they are more susceptible to HAdV infection. Although it is reasonable to hypothesize that adenovirus infection is the etiology of severe acute hepatitis of unknown origin in children, adenovirus usually causes mild, self-limited gastrointestinal or respiratory tract infections in young children, and cannot fully explain some of the more serious clinical manifestations of the disease; therefore, the close relationship between severe acute hepatitis of unknown origin in children and adenovirus needs to be further studied.^[7,12]

COVID-19 VACCINE

Many of the confirmed cases of severe acute hepatitis of unknown origin occurred in children under 5 years old, most of whom had not received the COVID-19 vaccine. This suggested that COVID-19 vaccination should be excluded as playing a role in this emerging disease. However, according to ECDC and the WHO,^[25] some of the confirmed cases are children older than 5 years old, who might have received the vaccine. Some scientists think that the severe acute hepatitis of unknown origin in children is potentially related to the COVID-19 vaccine.^[26-29]

THE ANTIGEN-MEDIATED HYPOTHESIS

At the beginning of the COVID-19 epidemic many children were very well protected by various lockdowns, which reduced their exposure to other pathogens that they would normally encounter, which might have resulted in a weakened immune system. Some recent studies have provided insights into this matter. Brodin and Arditi^[30] proposed an antigen-mediated hypothesis, in which superantigen-mediated immune-cell activation might be the possible cause of severe acute hepatitis with unknown cause in children. The hypothesis explored the possibility that when the SARS-COV-2, Human adenoviruses, or other viruses infect children, their weakened immune system cannot eliminate the viruses, and viral persistence in the

gastrointestinal tract could result in repeated release of viral proteins across the intestinal epithelium, causing immune activation. This recurrent immune activation might be caused by a superantigen motif in the SARS-CoV-2 spike protein that is similar to the Staphylococcal enterotoxin B6, which triggers broad and non-specific activation of T-cells.^[31-33]

OTHER VIRUS INFECTIONS

The confirmed cases of severe acute hepatitis of unknown origin in children were not detected as positive for hepatitis A–E viruses;^[34] however, other pathogens, including Influenza virus, rhinovirus, and Epstein–Barr virus, were detected in some cases and can lead to hepatitis, according to reports from the WHO, the ECDC, and the CDC.^[9]

THE TREATMENT OF SEVERE ACUTE HEPATITIS OF UNKNOWN ORIGIN IN CHILDREN

Although we do not know the cause of the severe acute hepatitis of unknown origin in children, some effective control measures still need to be taken to protect children.

Given that many of the confirmed cases have shown a positive result for Human adenovirus or SARS-CoV-2, measures to reduce children's exposure to viruses are required. For example, adequate hygienic practices in places attended by children. These include not only personal hygiene, *e.g.*, hand and body hygiene, but also environmental hygiene, such as cleaning and the sterilization of surfaces. These practices might reduce the spread of viruses through direct contact with infected persons and breath spit, or indirectly by exposure to contaminated environments or objects.

The “Four-Anti and Two-Balance” strategy comprises anti-secondary infection, anti-hypoxemia, anti-shock, and antiviral measures; and the maintenance of the water, electrolyte, and acid/base balance and the microecological balance. This strategy has been applied to H7N9 avian influenza and COVID-19, and can improve the cure rate and reduce the mortality rate.^[35,36] In addition to the guideline-recommended treatment options,^[37] the strategy may also be considered to treat severe acute hepatitis of unknown origin in children.

CONCLUSION

The outbreak of the severe acute hepatitis of unknown origin in children represents a significant challenge to social health systems worldwide, particularly because its

cause is unknown. The most likely causes still require further investigation. We lack specific treatments or vaccines because of our limited knowledge regarding the pathogenesis of this disease. Therefore, further study is needed to determine the transmission route of severe acute hepatitis of unknown origin in children, to develop vaccines and to treat critical cases.

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Conflict of Interest

The authors declare that they have no competing interests.

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