Severe Acute Hepatitis of Unknown Etiology in Children: Is It Caused by Pathogens or Non-infectious Factors?

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Abstract
Recently, an outbreak of severe acute hepatitis of unknown etiology in children has been reported in more than 27 countries worldwide. However, information on its prevalence in different countries and regions is still lacking. The evidence is suggestive of a potential viral infection, but this has not been fully confirmed. Cases of this disease have been reported in children, mainly in those younger than 5 years old. The reason for the age range of the disease requires further investigation.

Keywords: Children; Hepatitis; Pathogen

Outbreak of severe acute hepatitis in children
On March 31, 2022, Public Health Scotland was alerted to five cases of severe acute hepatitis of unknown etiology (viral hepatitis types A, B, C, D, and E were excluded) in children aged 3 to 5 years. By April 5, 2022, the number of cases in children aged under 10 years in Scotland had increased to 10, which was reported to the World Health Organization (WHO) as an alert. This prevalence is higher than that reported in previous years. A retrospective investigation identified that the first case was reported as early as January 1, 2022. By April 20, 2022, 111 similar cases were reported in the United Kingdom (UK).[1–4]

As of May 10, 2022, the WHO has reported approximately 450 cases of acute hepatitis of unknown etiology in children aged 1 month to 16 years. These cases are from more than 27 countries, with the majority being from the UK (163 cases from January 1, 2022, to May 3, 2022, including cases in England, Scotland, Wales, and Northern Ireland), at least 105 cases in other European countries [Italy (35), Spain (22), Sweden (9), Portugal (8), Denmark (6), Netherlands (6), Ireland (<5), Norway (4), Belgium (3), Austria (2), Cyprus (2), France (2), Germany (1), Romania (1), Poland (1), and Serbia (1)], at least 37 cases in Asian regions [Indonesia (15), Israel (12), Japan (7), Palestine (1), Singapore (1), and South Korea (1)].[3,4]

Clinical features and outcomes
The current case definitions defined by the WHO and the European Center for Disease Prevention and Control are as follows. The definition for a confirmed case is not yet available. A probable case refers to a person who is 16 years old or younger presenting with acute hepatitis (non-hepatitis viruses A, B, C, D, and E) and with an aspartate transaminase (AST) or alanine transaminase (ALT) level of >500 U/L from October 1, 2021. An epi-linked case refers to a person of any age presenting with acute hepatitis (non-hepatitis viruses A, B, C, D, and E) who has been in close contact with a probable case from October 1, 2021. The excluding factors include specifically identified infectious diseases, drug-induced liver injury, inherited metabolic liver disorders, and autoimmune liver diseases.[3]

The clinical syndrome of the affected children is severe acute hepatitis characterized by markedly elevated levels of liver enzymes (AST or ALT level >500 U/L). Frequently observed symptoms include jaundice, lethargy, and gastrointestinal symptoms (vomiting, pale stools, abdominal pain, and diarrhea). Fever was observed less frequently than the other symptoms [Table 1]. Most of the affected children were hospitalized. A preliminary investigation of cases from England reported that, at 28 days after the initial presentation, 53.1% (43/81) of the cases were discharged or fully recovered, 8.6% (7/81) progressed to acute liver failure and underwent liver transplantation, and none had died [Table 2].[3] By May 11, 2022, at least 11 of the children had died worldwide, including five children in Indonesia, five children in the United States, and one suspected death in Palestine.[3]
Among the currently reported cases, epidemiological links have not been reported for the cases in England and America, except for two pairs of cases in Scotland.[3,4,6] The reported cases were sporadic between different countries and regions, and they were even sporadic within countries. The epidemiological features of the reported cases were investigated using a questionnaire by the UK Health Security Agency (UKHSA). The results demonstrated that most of the affected children did not receive the coronavirus disease 2019 (COVID-19) vaccination and that 70% of them owned or had contact with a pet dog. To date, no other notable features, including common exposures (medicines or toxins), environmental exposures, travel history, or immunosuppressive conditions, have been identified in the reported cases.[3]

**Potential etiology**

Severe acute hepatitis of unknown etiology in children may be caused by an infection with pathogens or non-infectious factors, such as physical, chemical, and host factors. Among the infectious agents, viruses are more closely related to hepatitis than are bacteria and fungi because all known hepatotropic pathogens are viruses (hepatitis A, B, C, D, and E viruses). Thus, we have summarized the viruses detected in the reported cases and discussed their potential as the cause of this disease [Table 3].

**Adenovirus**

The current hypothesis is mainly focused on adenovirus, the virus most frequently detected in these patients (at least 74 cases). Three different studies reported different ratios of children testing positive for adenovirus, including 5/13, 40/53, and 9/9 [Table 3].[2,4,6] The age of the patients with severe acute hepatitis of unknown etiology is consistent with that previously reported for adenovirus-infected children.[7] Furthermore, the adenovirus DNA levels in those who had undergone liver transplantation were approximately 12-fold higher than the adenovirus DNA levels in those who had not.[11] A preliminary study identified the virus causing the infection as adenovirus type 41F via molecular testing, but this was performed without full genome sequencing.[5] Previous studies have not demonstrated that adenovirus 41F can induce liver inflammation. However, other adenovirus types may also induce hepatitis.[10] If adenovirus 41F recombines with other viruses and becomes a hepatotropic variant, it may induce hepatitis. However, it is necessary to confirm this hypothesis.

**COVID-19 vaccination or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection**

The majority of the affected children were younger than 5 years old and did not receive the COVID-19 vaccination. Thus, the disease cannot be attributed to the COVID-19 vaccination. It has been reported that SARS-CoV-2 nucleic acids are detected in 16%–23% of children with severe acute hepatitis of unknown etiology by real-time polymerase chain reaction at the time of presentation,[2,4] but they were not detected in most of the children with severe acute hepatitis of unknown etiology [Table 3].[2,4,6] However, SARS-CoV-2 infection cannot be fully excluded, as it is highly prevalent in the population during the omicron wave. As reported, a substantial percentage (68%) of young children (aged 1 to 4 years) have been infected with SARS-CoV-2 with the recent ending of COVID-19 restrictions, such as the relaxation of social distancing measures and SARS-CoV-2 quarantine suspension in relevant countries.[6,10] Thus, performing a seroepidemiological survey of SARS-CoV-2 infection in children with severe acute hepatitis of unknown etiology is necessary. It has been reported that liver impairment is a manifestation of post-acute COVID syndrome (long COVID) after SARS-CoV-2 infection in children younger than 10 years old.[11,12] Thus, the association between past or current SARS-CoV-2 infection and severe acute hepatitis requires further confirmation.
Other viruses
The usual transmissible agents that cause infectious hepatitis, including the hepatitis A, B, C, D, and E viruses, were not detected in the affected children. It cannot be ruled out that other unidentified hepatitis viruses are causing this non-A-E hepatitis disease. In addition to hepatitis viral infections, other viral infections, including those from the Epstein-Barr virus, cytomegalovirus, and rhinovirus, have been detected in some cases and can lead to hepatitis. A survey conducted by the UKHSA demonstrated that 70% of the affected children owned or had contact with pet dogs, suggesting the possibility of a zoonotic viral transmission, which also needs to be considered.

Indirect association with the COVID-19 pandemic
The increased susceptibility of the host to other viral infections may arise from the lack of exposure to pathogens during the COVID-19 pandemic. This is of particular concern because it has been reported that routine vaccinations for other common infectious diseases, such as measles, have significantly declined.

Non-infectious factors
In addition to viral infections, toxins, drugs, or environmental exposures can cause liver injury and hepatitis. These factors might be indirectly associated with liver inflammation in children, but they may exacerbate the acute hepatitis induced by adenoviral infection. Thus, these factors cannot be ruled out and require further clarification. Additionally, it is unclear whether autoimmune disorders, systemic diseases, and the genetic susceptibility of the host contribute to this disease.

Management of severe acute hepatitis of unknown etiology
According to the clinical presentations, symptomatic and supportive treatments, with monitoring of the disease progression, are the basis for the management of the affected children. For children with disease that has progressed to liver failure, urgent liver transplantation is required to save their lives. Whether artificial liver support is helpful or not needs to be verified. In cases of severe adenoviral viremia, anti-adenovirus treatment, such as cidofovir, may be useful. If the affected children are characterized by a systematic inflammatory syndrome, glucocorticoid therapy may be initiated. However, if the affected children are immunodeficient, glucocorticoid therapy must be avoided, and intravenous immunoglobulin may be beneficial. To develop effective therapeutic regimens, the etiological agents and pathological mechanisms of acute hepatitis of unknown etiology must be clarified. As there is no consensus on the treatment of acute hepatitis of unknown etiology, performing randomized controlled trials may be necessary to confirm the efficacy of these strategies.

Unmet issues in the field
There are many unmet issues in the diagnosis and treatment, as well as the etiological understanding, of severe acute hepatitis of unknown etiology in children. The following aspects require further investigation.

First, the current definition of acute hepatitis of unknown etiology is ambiguous. In future ongoing surveillance, a clear definition of the diagnosis of acute hepatitis of unknown etiology is needed. The clinical course of the disease needs to be studied, and the genetic background needs to be characterized. In a survey of epidemiological and clinical features, comparisons between the different clinical outcomes of the affected children should be performed to identify the risk factors for liver failure and mortality.

Second, because adenovirus infection is usually a self-limiting disease and progression to hepatitis after the infection is uncommon, it is still unknown whether adenovirus (including type 41F) is the causative agent of acute hepatitis of unknown etiology. Some patients tested negative for adenovirus infection. Is the adenovirus viral load associated with the clinical course and outcomes of adenovirus-infected patients? What is the incidence of acute hepatitis in children with adenovirus type 41F infection? Can adenovirus type 41F be detected in the liver? What factors contribute to the association between adenovirus infection and diseases, such as mutations or recombination of the adenovirus genomes, or immune deficiency or genetic susceptibility in infected children?

Third, the pathogenic mechanisms of acute hepatitis of unknown etiology, including viral, immunological, and pathological factors, remain unknown. The type of immune reaction underlying the pathogenesis of this disease, directly or indirectly, remains unknown. Some evidence suggests the involvement of the interaction between SARS-CoV-2 superantigens and a subsequent adenovirus infection. However, the coinfection of SARS-CoV-2 (including historic positive) and adenovirus was observed in only 3 of 13 cases in Scotland and in only 3 of 80 cases in England. Thus, is it a manifestation of long COVID? How can this condition be effectively prevented and treated?

Fourth, is the COVID-19 pandemic lockdown associated with the outbreak of acute hepatitis of unknown etiology? Is this due to a decline in immune training due to a lack of antigen exposure? Do significant differences exist in the incidence rates among different countries with different COVID-19 combating strategies? Could hygiene measures, such as hand washing, reduce the incidence of acute hepatitis of unknown etiology? How can children safety be ensured after lifting COVID-19 containment measures? The answer is not only important for the effective control of acute hepatitis of unknown etiology but also crucial to the social and economic recovery from the COVID-19 pandemic.

In the context of the COVID-19 pandemic and the continuing evolution of SARS-CoV-2, we are facing another unknown condition. There is a global race to identify the causes of severe acute hepatitis of unknown etiology. Therefore, more effort in achieving this is required. First, international cooperation among different countries is required to identify active cases, investigate the prevalence rate, develop a consensus diagnostic definition, and characterize manifestations of acute hepatitis of unknown etiology. Second, cooperation between clinical practitioners and basic scientists is important for clarifying the pathological mechanisms and developing effective treatment strategies for acute hepatitis of unknown etiology. Third, protecting children from potential exposure to viruses by commonly used preventive measures, such as hand washing and the disinfection of surfaces, will be effective.

Finally, in China, data on the prevalence of severe acute hepatitis of unknown etiology in children are lacking. Is the pre-COVID-19 prevalence significantly different from the current prevalence? If the incidence of this disease continues to increase, pediatric professionals should be trained to address this issue in the clinical setting.
Conflicts of Interest

None.

Editor note: Fu-Sheng Wang is the editor of Infectious Diseases & Immunity. The article was subject to the journal’s standard procedures, with peer review handled independently by this editor and his research group.

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