



COMMENTARY

Advances in Acute Severe Hepatitis of Unknown Etiology in Children

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Abstract

Since the International Health Regulations National Focal Point for the United Kingdom alerted the WHO of ten cases of acute severe hepatitis of unknown etiology in children on April 5, 2022, relevant cases have been reported worldwide. These patients had acute hepatitis (negative for hepatitis viruses A–E) and elevated aminotransferase (AST) or alanine aminase (ALT) exceeding 500 U/L. Furthermore, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and/or adenovirus type F41 have been detected in some cases. This unknown hepatitis has been hypothesized to be induced by a viral reservoir of novel coronavirus superantigen, which repeatedly stimulates the intestines and leads to a multisystem inflammatory syndrome in children (MIS-C), which causes immune abnormalities in the presence of human adenovirus. Although this hypothesis has not been confirmed by any in vivo experimental or clinical studies, it may provide ideas for possible intervention strategies.

Keywords: unknown hepatitis, adenovirus, SARS-CoV-2, co-infection, MIS-C

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INTRODUCTION

On April 5, 2022, the International Health Regulations National Focal Point for the United Kingdom alerted the World Health Organization (WHO) of ten cases of acute severe hepatitis of unknown etiology in children. These cases were spread across central Scotland, and were in children between 1 and 5 years of age who presented with clinical symptoms and signs of severe acute hepatitis, including jaundice; aminotransferase (AST) or alanine aminase (ALT) levels greater than 2,000 IU/L; and negativity for viral hepatitis types A, B, C, D and E. Some cases have shown gastrointestinal symptoms such as diarrhea and vomiting. Moreover, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and/or adenovirus have been detected in several cases. Whether these viruses are associated with

hepatitis of unknown etiology is uncertain, and no other epidemiological risk factors have been identified [1]. Related cases have since been reported worldwide.

Epidemiological reports

On April 8, the UK Health and Safety Agency published guidance requiring that after a child is found to have symptoms such as dark urine and/or pale fecal 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) exceeds 500 IU/L and is accompanied by symptoms of hepatitis, serum and EDTA blood samples, nose and throat swabs, and fecal and urine samples should be stored as soon as possible [2].

On April 15, 2022, this acute hepatitis of unknown etiology was defined by the

WHO. The cases are defined as those since January 1, 2022 in children 10 years of age or younger presenting with acute hepatitis (non-hepatitis viruses A, B, C, D or E) with AST or ALT exceeding 500 U/L. Possible cases are those in children who have laboratory test results identical to those in confirmed cases but are 11–16 years of age.

On April 19, 12 cases were detected in Israel: seven cases reported by the Schneider Children's Medical Center and five reported by the Shaare Zedek Medical Center. These cases were in different locations and did not show the characteristics of a cluster infection. Clinical symptoms and laboratory results were consistent with the definitions published by the WHO. Notably, all cases were in children infected with SARS-CoV-2 approximately 3.5 months before the hepatitis. However, no clear evidence indicates that this unknown hepatitis is associated with SARS-CoV-2 [3].

As of April 21, approximately 169 cases of acute hepatitis of unknown etiology had been reported in 12 countries. Notably, most SARS-CoV-2 positive cases (19 of 20) also tested positive for adenovirus, which was identified to be F type 41 in 18 cases [4]. On the same day, the United States Centers for Disease Control and Prevention issued a national health warning through the Health Alert Network, requiring doctors to observe and report all suspected cases of hepatitis of unknown origin to local health authorities. The first patient is believed to have been found in Alabama in October 2021. As of February of 2022, nine patients had been identified, including three patients with acute liver failure who also tested positive for adenovirus. These findings suggest potential correlations between adenovirus and acute severe hepatitis of unknown etiology in children. However, the clinical test results have indicated no viral inclusions on liver biopsy, and no evidence of viral infection was detected by immunohistochemistry or electron microscopy [5].

On April 23, the WHO published a modified definition of acute hepatitis of unknown etiology in children: the original confirmed definition was rescinded, and the age of probable cases was changed from 11–16 years of age to under 16 years of age. The definition also stated that although adenovirus is considered an underlying pathogenic factor, it does not adequately explain the current severe clinical symptoms. Additionally, most cases identified were in children not vaccinated against COVID-19; therefore, the hypothesis of adverse effects of the COVID-19 vaccine was not supported [4].

However, a rapid risk assessment report published by the European Centre for Disease Prevention and Control on April 28 noted that adenovirus and SARS-CoV-2 were the pathogens with the highest detection rates in children with unexplained acute hepatitis in Europe. As many as 50% of cases in Scotland and 75.5% of cases in England have tested positive for adenovirus. Subtype analysis of 11 cases in the UK has indicated that these adenoviruses were all type 41F, the same subtype found in several cases previously reported in the US. Therefore, the European Centre for Disease Prevention and Control has suggested the following

possible causes of this unknown hepatitis: a cofactor rendering normal mild adenoviral infections more severe or causing them to trigger immunopathology; a novel variant adenovirus or SARS-CoV-2; a drug, toxin or environmental exposure; or a novel pathogen acting either alone or through coinfection [6].

Causative analysis

Human adenovirus is a non-enveloped, double-stranded DNA virus with an icosahedral protein capsid, of the family Adenoviridae, which consists of 11 different structural proteins. More than 100 types of human adenoviruses have been identified (types 1–51 are sera type, and types 52–103 are gene type) and divided into seven species termed A–G, many of which have well-characterized tropisms for specific tissues [7]. Human adenoviral infection usually causes upper respiratory, gastrointestinal or conjunctival lesions. Most patients are self-limited and generally heal within several weeks; therefore, fatal and disseminated infections are uncommon. In addition, the clinical manifestations in patients infected with types 40/41 (species F) include fever, vomiting, diarrhea and occasionally persistent and acute gastroenteritis in young children [8]. Thus, single human adenovirus infection appears not to be associated with acute severe hepatitis of unknown etiology in children. The WHO and the Pan-American Health Organization issued a new relevant technical note on May 10 indicating that although adenovirus had been detected in the blood or plasma of multiple children, the viral titers were low, and no adenovirus was detected in the liver tissue. Presumably, adenoviral infection is a coincidental factor [9].

Is this unknown hepatitis caused by SARS-CoV-2? The SARS-CoV-2 virus invades cells by binding the host cell receptor angiotensin converting enzyme 2 (ACE2) through its spike glycoprotein. Although respiratory symptoms are the most typical clinical manifestation of SARS-CoV-2 infection, ACE2 does not have lung tissue specificity but is also highly expressed in multiple human organs, such as the colon, biliary tract and liver [10]. Moreover, an excessive inflammatory state is caused by elevated cytokine production after SARS-CoV-2 infection, in a condition known as cytokine storm syndrome. Accompanied by substantial 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 findings provide a theoretical basis for the emergence of liver lesions after SARS-CoV-2 infection. Several studies have indicated 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 approximately 58%–78% [13]. Liver biopsies in patients with COVID-19 have shown a large increase in ballooned hepatocytes and liver lobular inflammation, which are considered evidence of viral injury [14]. Therefore, this unknown hepatitis may be a long-term symptom of COVID-19.

On May 13, The Lancet Gastroenterology & Hepatology presented a new opinion suggesting that SARS-CoV-2 superantigen may be the cause of acute hepatitis of unknown etiology in children. The literature has reported that the SARS-CoV-2 virus remains in the gastrointestinal tract after infection, thus forming a viral reservoir that releases viral proteins in enterocytes and stimulates 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]. Therefore, MIS-C is considered a new clinical manifestation associated with SARS-CoV-2 infection, which affects multiple organ systems. During the onset of MIS-C, shock, gastrointestinal symptoms, hypercoagulability and disseminated intravascular thrombosis have been described in patients [16]. Notably, several clinical features of MIS-C are similar to those of toxic shock syndrome and Kawasaki disease; therefore, more attention must be paid to their clinical symptoms differences during diagnosis and therapy. In general, most patients with MIS-C have symptoms of abdominal pain, diarrhea or vomiting, which are relatively uncommon in Kawasaki disease [17]. To date, the pathogenesis of MIS-C remains unknown. The cause of MIS-C has been proposed to be an uncontrolled cytokine storm involving high levels of inflammatory markers, or a superantigen-like motif in the spike protein of SARS-CoV-2 [18]. If such a SARS-CoV-2 viral reservoir is present in children who are subsequently coinfecting with adenovirus, superantigen-mediated effects may be more pronounced and lead to immune abnormalities, thus resulting in 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 may provide research directions and possible intervention strategies. Perhaps in treating this unknown hepatitis, we should also focus on whether other organs are affected. Further revelations may be gained from lessons in treating diseases in which viral reservoirs can form, such as AIDS. On the one hand, attention should be paid to the clearance of the viral reservoir. On the other hand, factors that may reactivate the viral reservoir—such as co-infection of other viruses and immune system disorders—should also be prevented.

Current situation

As of May 27, 650 cases of acute severe hepatitis of unknown etiology in children have been reported in 33 countries. More recent cases have shown more severe clinical symptoms and a higher proportion of acute liver failure: at least 38 children (6%) have required liver transplants, and nine (1%) deaths have been reported. Consequently, the WHO considers the risk of this unknown hepatitis at the global level to be moderate [19]. At present, no related cases have been found in China, and health authorities and medical institutions are paying close attention to, and continually monitoring, the situation of hepatitis of unknown etiology.

Prevention recommendations

The main preventive measures involve having children avoid going to crowded public places without air circulation, avoiding droplet contact and fecal-oral transmission routes, ensuring adequate child sleep and nutrition, washing hands frequently, wearing masks and maintaining social distancing. If children show signs of jaundice, or digestive tract and other hepatitis disease symptoms, they must seek medical treatment as quickly as possible.

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CONFLICTS OF INTEREST

All authors declare that they do not have any conflicts of interest.

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