



Severe Acute Hepatitis in Children

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ABSTRACT

Viral infections affecting the liver had a serious impact on humanity, as they have led to significant morbidity and mortality in patients with acute and chronic infections. The discovery of the viral agents of severe acute hepatitis in children triggered interest of the scientific community to establish the pathogenesis and diagnostic techniques to identify the affected population. But, WHO, together with scientists in various affected countries, are working to understand the cause of this infection that does not appear to belong to any of the known five types of hepatitis viruses: A, B, C, D and E. Many cases of severe acute hepatitis of unknown origin in children <10 years of age were reported by the International Health Regulations (IHR) was mainly by adenovirus infection, HAdV-41. Although most acute infections cause mild disease and even go undetected, some can lead to complications and turn fatal. With the rapid scientific and technological advances in the last centuries, controlling and even curing the infections became a possibility, with a large focus on preventive medicine through vaccination. The review article describes the epidemiology, pathogenesis, clinical presentation, diagnostic tools and current medication regimens for severe acute hepatitis of unknown origin in children.

Keywords: Hepatitis, WHO, liver cirrhosis, jaundice, Liver function test, HAdV-41.

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INTRODUCTION

Viral infections are the most common cause of hepatitis but there are other possible causes of hepatitis like alcohol consumption, several health conditions, and some medications can all cause this condition. Autoimmune hepatitis is a disease that occurs when your body makes antibodies against your liver tissue. The five main viral classifications of hepatitis are hepatitis A, B, C, D, and E. A different virus is responsible for each type of viral hepatitis. The World Health Organization (WHO) estimates that 354 million trusted source people currently live with chronic hepatitis B and C globally¹. WHO, announced that every 30 seconds, someone dies from hepatitis-related diseases, including liver failure, cirrhosis and cancer². The UN health agency, with the goal of eliminating hepatitis by 2030, has called on countries to reach four specific targets. It aims to reduce new infections of hepatitis B and C by 90 per cent; reduce hepatitis-related deaths from liver cirrhosis and cancer by 65 per cent; ensure that at least 90 per cent of people with hepatitis B and C virus are diagnosed; and at least 80 per cent of those eligible, receive appropriate treatment³.

Hepatitis A

The Hepatitis A virus (HAV) causes Hepatitis A. This type of hepatitis is an acute, short-term disease^{4,5}.

Hepatitis B

The Hepatitis B virus (HBV) causes Hepatitis B. This is often an ongoing, chronic condition. The Centers for Disease Control and Prevention (CDC) estimates that around 257 million people are living with chronic hepatitis B in around worldwide⁶.

Hepatitis C

Hepatitis C is caused by Hepatitis C virus (HCV). HCV is among the most common blood borne viral infections and typically presents as a long-term condition. According to the CDC, approximately 2.4 million people are currently living with a chronic form of this infection⁷.

Hepatitis D

This is a rare form of hepatitis that only occurs in conjunction with hepatitis B infection. The hepatitis D virus (HDV) causes liver inflammation like other strains, but a person cannot contract HDV without an existing hepatitis B infection. Globally, HDV affects almost 5 percent of people with chronic hepatitis B⁸.

Hepatitis E

Hepatitis E is a waterborne disease that results from exposure to the hepatitis E virus (HEV). It is mainly found in areas with poor sanitation and typically results from ingesting fecal matter that contaminates the water supply. Hepatitis E is usually acute but can be particularly dangerous in pregnant women⁹.



Causes of non-infectious hepatitis

Although hepatitis is most commonly the result of an infection, other factors can cause the condition.

Alcohol and other toxins

Excess alcohol consumption can cause liver damage and inflammation. This may also be referred to as alcoholic hepatitis. The alcohol directly injures the cells of your liver. Over time, it can cause permanent damage and lead to thickening or scarring of liver tissue (cirrhosis) and liver failure. Other toxic causes of hepatitis include misuse of medications and exposure to toxins.

Autoimmune system response

Autoimmune hepatitis is a disease that occurs when your body makes antibodies against your liver tissue. This causes ongoing inflammation that can range from mild to severe, often hindering liver function. It's three times more common in women than in men.

Symptoms of Hepatitis

Common symptoms of infectious hepatitis include:

- Fatigue
- Flu-like symptoms
- Dark urine
- Pale stool
- Abdominal pain
- Loss of appetite
- Unexplained weight loss
- Yellow skin and eyes, which may be signs of jaundice

Diagnosis¹¹

During a physical examination, doctor may press down gently on your abdomen to see if there's pain or tenderness. They may also check for any swelling of the liver and any yellow discoloration in your eyes or skin.

Liver function tests

Blood samples is used to determine how efficiently liver works. Abnormal results of these tests and high liver enzyme levels may indicate that liver is stressed, damaged, or not functioning correctly.

Other blood tests

Liver function tests are abnormal; doctor will likely order other blood tests to detect the source of the problem. These tests can the presence of hepatitis viruses or antibodies your body produces to combat them. Doctors may also use blood tests to check for any signs of autoimmune hepatitis.

Liver biopsy

The liver biopsy is a procedure that involves taking a sample of tissue from liver. A medical professional may take this sample through your skin with a needle, meaning there is no need for surgery. They will typically use an ultrasound scan for guidance during this procedure. This

test allows determining how infection or inflammation has affected liver.

Ultrasound

In abdominal ultrasound, ultrasound waves to create an image of the organs within your abdomen. This test allows to take a close look at liver and nearby organs. This can be a useful test in determining the cause of your abnormal liver function. It can reveal:

- Fluid in your abdomen
- Liver damage or enlargement
- Liver tumors
- Abnormalities of your gallbladder.

SEVERE ACUTE HEPATITIS OF UNKNOWN ORIGIN IN CHILDREN

Adenovirus infection

But, WHO, together with scientists and in various affected countries, are working to understand the cause of this infection that does not appear to belong to any of the known five types of hepatitis viruses: A, B, C, D, and E. Many cases of severe acute hepatitis of unknown origin in children <10 years of age were reported by the International Health Regulations (IHR) National Focal Point (NFP) for the United Kingdom across central Scotland On 5 April 2022. Adenovirus infection, HAdV was detected in 72% (91/126) of the UK cases, with 18 identified as HAdV-41¹². 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.¹³

SARS-CoV-2 infection

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 tract¹⁴. 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. Adenovirus 41 drives a type I immune response and amplifies SEB-mediated hyperimmune pathology. These conclusions are speculative, without scientific conclusions, which need to be confirmed further¹⁵.



Symptoms

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 admission¹⁶.

Diagnosis

Tests for hepatitis viruses A–E have been universally negative. The 91 of the 126 children (72%) tested for adenovirus had positive results, and adenovirus type 41f was identified in blood samples from all 18 children with successful subtype analysis. Adenovirus was also identified in 44% of stool samples and 29% of respiratory samples. Based on the characteristics of the reported cases and our experiences in managing hepatitis in children. We recommend using the following modalities for diagnosis.

Recommended laboratory tests in suspected cases of severe acute hepatitis in children

Sample type	Test	Pathogen
Blood*	PCR	Adenovirus, Enterovirus, CMV, EBV, HSV, Hepatitis A, Hepatitis C, Hepatitis E, HHV6 and HHV7
Blood*	Serology	Hepatitis A, B, C, E, CMV, EBV, SARS-CoV-2 anti-S, SARS-CoV-2 anti-N (only if locally available)
Blood	Culture	Standard culture for bacteria/fungi (only if clinically indicated i.e. fever)
Throat swab*	PCR	Respiratory virus panel (including adenovirus/enterovirus/influenza, SARS-CoV-2)
Stool*	PCR	Adenovirus, sapovirus, norovirus, enterovirus. Standard bacterial stool pathogen panel to include <i>Salmonella</i> spp. (or stool culture depending on local test availability)
Blood* (whole blood in EDTA and plasma separated specimen)	Toxicology	Local investigations according to history
Urine*	Toxicology	Local investigations according to history

Laboratory tests

Whole blood, serum, respiratory secretions, feces, urine or other body fluid samples can be sampled according to pathogens, and metagenomic sequencing can be performed if available. Blood ALT, AST, total bilirubin,

direct bilirubin, albumin, glutamyltransferase, prothrombin time, activated partial thrombin time, international standardized ratio (INR), fibrinogen and serum ammonia might be tested to assess the severity. C-reactive protein, procalcitonin, blood gas electrolytes, cytokines, serum ferritin, blood glucose, renal function and myocardial enzymes are helpful for evaluating related complications.^{17,18}

Treatment

Treatment for severe acute hepatitis of unknown etiology in children is supporting therapy, including adequate rest, avoiding excessive protein intake, and preventing complications. Patient consciousness, volume status, urine volume, blood electrolytes, liver function and coagulation function should be closely monitored during the entire treatment period, as should maintaining water, electrolyte and acid–base balance. Subsequent symptoms, such as hypovolemia, hypoproteinemia, gastrointestinal bleeding, infection, electrolyte imbalance, hypoglycemia, and constipation, should be actively treated to prevent serious complications, such as hepatic encephalopathy and hepatorenal syndrome.¹⁹ Various transplantation techniques should be applied to shorten the waiting time as much as possible in cases of ALF.¹⁴ World Health Organization. Disease outbreak news; multicountry acute, severe hepatitis of unknown origin in children. The etiology of severe acute hepatitis in children is still under investigation. For those positive for adenovirus infection, supportive care is mainly recommended. Although cidofovir has been reported to be effective against adenovirus in solid organ transplant recipients and children with severe viremia²⁰. More studies are required to approve the benefits in immunocompetent individuals. Only case reports indicated the efficacy of ribavirin for adenovirus infection^{21,22}.

Prevention

The etiology of severe acute hepatitis in children is unknown. At present, it is recommended to adopt routine prevention methods for adenovirus and respiratory viruses, such as hand hygiene and respiratory hygiene²³. Clinicians are asked to be alert to children presenting with signs and symptoms of hepatitis that may require serum transaminase testing and are encouraged to diagnose, investigate and report potential cases²⁴.

CONCLUSION

The recognition of the epidemiological and clinical features of severe acute hepatitis of unknown origin among children is crucial. Fortunately, the medical advances in the last centuries have allowed to effectively diagnose them and comprehensively establish its multisystemic impact in this population. With the advent of new therapies, the possibility of achieving control of the disease is a reality. Children with jaundice or gastrointestinal symptoms seek medical treatment, clinicians should consider prompt laboratory evaluation with LFTs and coagulation markers (prothrombin time/INR) to facilitate timely identification



of potential cases of acute hepatitis of unknown origin. Clinicians must report public health authorities about cases of acute non-A–E hepatitis of unknown origin. Although no evidence-based therapies have been established in the management of acute hepatitis of unknown origin during the 2022 outbreak, supportive measures and close clinical and laboratory monitoring are very much needed, including hospitalization for those with evidence of hepatitis or acute liver failure.

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