REVIEW

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Severe acute hepatitis of unknown causes in children – Current findings, questions, opinions, and recommendations, a mini-review

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ABSTRACT

Since October 2021 in Alabama, the United States, and March 2022 in central Scotland, the United Kingdom, the number of cases of severe acute hepatitis of unknown etiology/causes in children was found to increase, and the total number of cases has reached 920 worldwide by June 22 this year, 45 cases (5%) required liver transplantation, and 18 cases (2%) died according to World Health Organization (WHO). To understand the basic characteristics of this disease/syndrome, a literature search was performed at PubMed, websites of WHO, UK Health Security Agency, and US and European Centers for Disease Control and Prevention, and more than 20 reports were enrolled as references for this review. The main clinical manifestations are anorexia, vomiting, fatigue, jaundice, and so forth. Most of the cases seemed to have a self-limited course of the disease, about 6% of cases may develop life-threatening acute liver failure. The disease seems to be transmissible from person to person. Human adenovirus was detected in up to 75% of cases, but this virus seems not to be the only and major etiologic agent, other cofactors probably are involved. Researchers proposed many hypotheses concerning the etiology and pathogenesis, and many important works and studies are ongoing. This mini-review is aimed at summarizing, reviewing, and further understanding the characteristics of the disease, raising some clinically relevant questions, and trying to discuss some questions that may be related to the treatment of the disease for consideration.

KEYWORDS

Acute liver failure, Children, Severe acute hepatitis of unknown causes

INTRODUCTION

Reports from the United Kingdom, World Health Organization (WHO), the US Centers for Disease Control and Prevention (US CDC), and Red Book Online on the sudden increase or outbreak of cases with severe acute hepatitis and pediatric acute liver failure of unknown cause/etiology (SAHUC and pALF) in children 10 or 16 years of age and younger have attracted much attention of pediatricians and child health care professionals as well as public,

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governments, and parents of children in China and rest of the world.[1–6] WHO reported that the total number of probable cases of June 22, 2022, worldwide was 920 from 33 countries.[7] At least 45 cases (5%) of the 920 probable cases required liver transplantation and 18 cases (2%) died. Most of the cases were reported from the UK (267) and the US (305).

There was a question if the total number of cases has truly increased as compared with the previous years. Interestingly, two reports published in *Euro Surveill* gave entirely different answers; one is "No",[8] the other is "Yes",[9] and the answer "Yes" was supported by results that 5/17 European and 1/7 non-European countries had an elevated number of cases compared to data of the previous 5 years.

This mini-review aimed to review and understand the major characteristics or findings of SAHUC, raise some questions and discuss some opinions and very preliminary recommendations that may be considered for further understanding and controlling the disease.

SOURCE OF INFORMATION

PubMed and websites of WHO, UK Health Security Agency and US CDC, European Centre for Disease Prevention and Control (ECDC) were searched using the terms: "acute hepatitis of unknown causes/etiology in children", "severe acute hepatitis of unknown causes/origin/etiology in children", "acute liver failure (ALF) in children"; the publication date was set starting from October 1, 2021. Very limited numbers (less than 30) of articles were retrieved and enrolled.

CURRENT FINDINGS

Case definition

The case definitions for SAHUC used by different organizations/institutions are rather different (Table 1), but the major points are similar: children at the age of 10 or 16 years and younger, having acute hepatitis since October 1, 2021, or since January 1, 2022, with viral hepatitis A–E excluded for confirmed cases or their tests were negative or not completed for possible causes, and liver enzymes (alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)) >500 IU/L in each case. The WHO definition for confirmed cases is "not applicable", probably because the etiologic agent or factor of this disease has not been determined yet.

Epidemiological findings

The time frame of the outbreak or the increase of the cases with SAHUC and pALF is between October 1, 2021, and May 2022. No seasonal cluster of cases was noted.

Geographical distribution: Cases were reported from the UK, initially from central Scotland, but also from other parts of the UK and many other European countries, and the 25 US states. The number of cases reported in the UK on May 3 was 163, there were no deaths, and 11 (6.7%) of them required liver transplantation. On May 16, the number of UK cases increased to 197, and 180 of them were hospitalized, and 11 (6.1%) of them required a liver transplant, but no deaths occurred.[10,11] By May 11, 450 probable cases were reported worldwide, 31 required liver transplantation, and 11 cases died.[12] The countries that reported more than 10 cases include the UK (197), the US (180), Brazil (44), Italy (35), Spain (26), Mexico (21), Indonesia (14), Israel (12), Japan (12), Portugal (12), and Canada (11).[11,13] There were no clusters in rural or urban areas, no relation with parents' occupation, and so forth.

Race and ethnicity

In Alabama cases, all the 9 were white;[14] while in England cases, 87.5% were white.[15]

The patients had no clear history of toxic substances or potential food-borne or water-borne toxins or toxicants exposure. There was no history of hepatotoxic drugs (such as paracetamol, amoxicillin-clavulanate overdose. No evidence suggests that the current cases of SAHUC have any common source of infectious agents/pathogens, although adenovirus is highly considered to be related to the occurrence of the disease.

Most of the cases have not received vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and in England, only about 10%–14% of cases (13/123 and 14/100) had SARS-CoV-2 infection.[10,11]

Outcomes of the cases: By April 8, 74 cases were identified in the UK, six cases (8.1%) underwent liver transplantation, and no death was reported.[2] By April 27, 191 probable cases were reported, and 17 (8.9%) of them required liver transplantation.[15] There are different numbers of cases that required liver transplants or who had died because of differences in the time frame, regions, and case definition. The latest number of probable cases is 920, 45 (5%) required liver transplants, and 18 deaths.[7] All the nine Alabama cases recovered or were recovering, including two cases that received liver transplantation. By May 16, the number of UK cases increased to 197, and 180 of them were hospitalized, 11 (6.1%) of them required liver transplantation, and there were no deaths among the 180 cases.[15]

Clinical findings

The major symptoms and signs of the disease in the cases of England were jaundice and vomiting, seen in more than 70% of cases. More than half of the cases had pale stools,

TABLE 1 Case definitions reported by World Health Organization (WHO), the UK, and other sources

Reports	Type of case	Age of case (year)	Time since	Clinical and laboratory characteristics
WHO[7]	Confirmed	NA	NA	NA
	Probable	≤16	Oct 1, 2021	Acute hepatitis, non-viral hepatitis A–E, and ALT/AST > 500 IU/L
	Epi-linked	Any age	Oct 1, 2021	Acute hepatitis, non-viral hepatitis A–E, close contact of a probable case
England, Wales, North Ireland[2]	Confirmed	≤10	Jan 1, 2022	Acute hepatitis, non-viral hepatitis A–E, and serum ALT/AST > 500 IU/L
	Possible	11–16	Jan 1, 2022	Acute hepatitis, non-viral hepatitis A–E, and serum ALT/AST > 500 IU/L
	Epi-linked	Any age	Jan 1, 2022	Acute hepatitis, non-viral hepatitis A–E, close contact with a confirmed case
Acute Hepatitis Study Group[9]	Possible	≤16	ND	Acute hepatitis and serum ALT/AST > 500 IU/L, tests for viral hepatitis A–E were negative or undetectable or have not been completed
	Probable	≤16	ND	Acute hepatitis, with hepatitis A–E were excluded and serum ALT/AST > 500 IU/L
	Severe possible or probable case	ND	ND	A possible or probable case with acute liver failure (INR > 2.0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Epi-linked, epidemiological linked; INR, international normalized ratio; NA, not applicable; ND, not defined; WHO, World Health Organization.

less than half of cases had diarrhea and nausea, and around 50% of cases had lethargy. Fever was found in about 1/3 of patients, and respiratory symptoms were less common, seen in about 1/5 of cases. In Alabama cases ($n = 9$), more than half had vomiting and diarrhea, and less than half had upper respiratory symptoms before admission; 8/9 cases had scleral icterus, 7/9 had hepatomegaly, 1/9 had splenomegaly, and none had decreased liver size (not mentioned, acute liver atrophy might occur in very severe liver necrosis); six had jaundice, and one had encephalopathy.[4,14,15] Abdominal pain was reported to be present in a few cases. Upper respiratory symptoms (usually include nasal congestion, discharge, cough, sore throat, wheezing, and dyspnea) were present in 3/9 of cases.

Questions

Are all pediatricians, including those working at the community clinics, familiar with the diagnostic criteria of ALF and thus require liver transplantation? If the answer is "No", efforts need to be made to let every pediatrician know the criteria, since many of them may have a chance to see a patient in that situation and need quick and correct management. See the diagnostic criteria for ALF in the later section.

Laboratory findings for diagnosis and differential diagnosis

Tests related to acute liver injuries

Liver enzymes of the cases were at very high levels, much higher than 400 or 500 IU/L; serum bilirubin was found significantly elevated (total and direct/indirect). No descriptions about tests on blood coagulation, prothrombin time, international normalized ratio (INR), and tests for encephalopathy and ammonia were found.

Of the nine Alabama cases, six received liver biopsy,[14] which showed various degrees of liver inflammation without viral inclusions; there was neither immunohistochemical evidence of human adenovirus (HAdV) nor electron microscopic findings of viral particles. No further descriptions in this regard were available. Description of liver biopsy findings is also available from the UK cases.[10] The liver specimens included those from six explanted (removed) livers and liver biopsy material from eight cases from England and Scotland. The histopathological findings on H & E stained tissue slices included variable severity of liver inflammation (from mild hepatocellular injury to massive hepatic necrosis). The overall pathologic changes were non-specific, and no clearly identifiable cause was found.

Questions

A liver biopsy is extremely important for finding out the major pathological changes and possible pathogenic agents. Is the routine percutaneous approach for liver biopsy safe enough? Is there any safer approach? Was immune electron microscopy performed in addition to the routine transmission electron microscopy?

Tests related to possible pathogenic agents or pathogenesis of the disease

Viral hepatitis A–E was excluded for each of the cases reported so far. HAdV has been detected in more than half of the cases reported from different regions/countries. In Alabama cases of the US, all the nine cases were positive (in whole blood specimens) for HAdV by real-time polymerase chain reaction, and for five of them, Hexon gene hypervariable region sequencing showed that all these 5 cases were infected with HAdV type 41.[12]

Adenovirus has been the most frequently detected viral pathogen. However, the role of this virus in the pathogenesis of SAHUC is not clear. It is hypothesized that other cofactors are probably involved in the development of the SAHUC and ALF through some unknown interaction. The number of cases in the UK increased to 197 by May 16, and 170 of them were tested for HAdV, and 116 (68.2%) were positive,[1] the tests for most of the cases were performed on whole blood specimens, which were found to have higher detection rate as compared with serum or plasma specimens. In another report, the detection rate was even higher, 75.5%, in England patients, and molecular subtyping showed that 18 cases were positive for HAdV F type 41.[15] Coinfection of HAdV with SARS-CoV-2 was found in 19 of 20 cases. Adenovirus immunohistochemistry was performed on nine of 14 liver specimens, which showed immunoreactivity in the intrasinusoidal lumen but not in residual liver cells, this was considered to be a non-specific finding.[10] SARS-CoV-2 was positive in 14 (including three cases who were positive 8 weeks prior to admission) of 97 (14.4%) cases.

In addition to HAdV and SARS-CoV-2, the following viruses were also detected in very low proportions of cases: Epstein-Barr virus, enterovirus, human herpesvirus 6 and 7, cytomegalovirus, respiratory syncytial virus, and metapneumovirus. Adeno-associated virus-2 (AAV-2) was detected in the metagenomic analysis of serum from five Scotland cases. There are a few hypotheses about the detection of AAV-2, including an undetermined role in the pathogenesis of the SAHUC.

Toxicological investigations are continuing; 75% of cases had taken paracetamol, but there was no overdose use. On the other hand, paracetamol or its metabolites were detected in 12 cases and one control, but the levels are related to normal therapeutic use. Small numbers of urine and whole blood samples were tested for metal toxicants of interest, and no elevated levels were found.[11]

Questions

The target of the tests for HAdV must have been viral nucleic acids. How were the tests for antibodies, especially IgM antibodies against the HAdV? Was dual sera (2-week apart) IgG or total antibody titers tested? Such information may be helpful for consideration of etiology.

Other examinations, such as ultrasound and other imaging

No description of liver and biliary or abdominal ultrasound and other imaging was found.

Hypotheses for possible etiologic agents/factors

Although HAdV was detected in most (as high as 75%) of the reported cases with SAHUC, there is no direct or indirect evidence that adenovirus is the only or major etiologic agent for this disease. This is because i) HAdV, including the subtype F41, are all well-known for their organ/system tropism, which is respiratory and gastrointestinal (GI), instead of hepatic, though GI has close links to the hepatobiliary system; ii) in immunocompetent children, adenovirus infections cause self-limited diseases, and severe hepatitis and disseminated infections and liver failure caused by HAdV were reported for immunocompromised children[16,17]; iii) immunohistochemical and electron microscopy failed to demonstrate the presence of adenoviral antigens or viral particles in liver biopsy specimens (further studies in this term are warranted).[10] But this does not mean that adenovirus is excluded from the possible etiologic agents.

Various hypotheses have been proposed for possible etiologic factors, their interactions, and their mechanism.[10,12,18] However, each of the hypotheses needs further studies and solid evidence.

(1) Adenovirus altered by a cofactor. The cofactor can be an unidentified or even an unrecognized pathogen, another virus, another type of microorganism, a toxic substance, a bioproduct or cytokine that formed in the body as a result of an immune reaction. The cofactor could have changed in some way the organ tropism of HAdV to target liver cells, which may increase the virulence of the HAdV. The cofactor or its interaction with the virus may have changed the cell/organ tropism of HAdV and may have also changed the virulence of the virus.

(2) The hypothesis on host response is altered by a cofactor. Host response to a viral infection can be overactivated by some intrinsic or environmental cofactors and result in massive lysis and necrosis of hepatocytes. On the other hand, some of the cofactors may have inhibitory effects on the immune system, which may lead to reduced immunity against a virus and the virus may cause overwhelming infection and liver failure. To test the above-mentioned two hypotheses, animal model studies may be needed.
(3) Hypothesis on immune deficit caused by coronavirus disease 2019 (COVID-19) pandemic. Lack of exposure to certain pathogens for some time (such as during the pandemic of COVID-19) may lead to increased susceptibility of children to the pathogens. To confirm or test this hypothesis, immune reactivity (humoral and cellular, specific and nonspecific) of the patients and matched controls should be detected and compared.[18]
(4) Hypothesis on superantigen-mediated immune activation: Previous SARS-CoV-2 infection may lead to the formation of a viral reservoir, that is, the persistence of the virus in the GI tract may result in repeated release of viral protein, which may cause immune activation. Such activation may be mediated by a superantigen motif within the spike protein of the SARS-CoV-2, which triggers broad and non-specific T-cell activation and finally cause liver failure and death. To test this hypothesis, the following studies should be carried out: in SAHUC cases: persistence of SARS-CoV-2 in stool, T-cell receptor skewing, and upregulation of IFN-γ should be confirmed. Such study may lead to the emergence of immunomodulatory therapies against the SAHUC.[19]
(5) Other hypotheses may include: i) post-infectious SARS-CoV-2 syndrome, ii) new variant of adenovirus, iii) non-infectious causes such as a novel pathogenic agent or toxicant, and iv) new variant of SARS-CoV-2.[12]

There are many more hypotheses concerning the etiology of SAHUC, and for any of the hypotheses, corresponding studies and relevant surveillance are needed.

DISCUSSION

Case definition

Is it possible for all countries to use a single unified case definition, for example, the WHO definition? It should be possible if a consensus is reached among the experts and authorities of WHO and countries closely involved in this disease, such as the UK, US, and others. As listed in Table 1, case definition also had a type of case "Severe possible or probable case", this defines the severity of cases, and if the severity is included in the case definition, there should also be words like "mild", "moderate", and so forth, and those are not necessary. A unified, simple, and easy-to-use definition like "confirmed, probable, Epi-linked" case definition would be facilitative enough for classification and statistics, and so forth.

Diagnostic criteria of ALF

The indications for liver transplantation are very important, and the pediatricians in the ward of hepatology or intensive care unit and even those working at community clinics should also be familiar with the basic indications for the transplant so that they would not miss the best period of time for the preparation and implementing the liver transplant surgery. The pALF is defined as acute liver injury confirmed by biochemical evidence with at least one of the following two: INR > 1.5 could not be corrected with supplementary vitamin K with encephalopathy; INR > 2.0 could not be corrected with supplementary vitamin K without encephalopathy. The biochemical evidence for acute liver injury may include AST, ALT, γ-glutamic transpeptidase, alkaline phosphatase, total and fractionated bilirubin, albumin, and total protein.[20]

For diagnosis and differential diagnosis of the disease, it is good to have various sophisticated modern techniques; however, careful clinical observation and physical examinations are still important for the care of patients. For example, for finding out jaundice at the early stage of the disease, the illumination of the place should be good enough, and the use of an old type of filament light should be avoided. For abdominal pain (in older children), the type of pain (dull? or mild?) should be asked. Such information would be useful for diagnosis and differential diagnosis.

Need for ultrasound and other imaging examinations

Are imaging studies like computed tomography (CT) and ultrasound of the liver and biliary system important for SAHUC cases? The answer should be "Yes, they are". As long as the patients' condition allows, or bedside equipment is available, at least liver and biliary Doppler ultrasonography should be performed, and if required, even CT, magnetic resonance imaging, and even magnetic resonance cholangiopancreatography should be considered.[20] Absence of hepatomegaly cannot rule out SAHUC since there is the possibility that in cases with massive liver necrosis the size of the liver may not increase, instead, even shrink (acute liver atrophy). Therefore, an abdominal ultrasound is indicated, which may also provide some more information for diagnosis and differential diagnosis. A liver biopsy may be necessary, and a trans-jugular approach is advised for the prevention of complications.

Treatment of SAHUC and ALF

The etiology of the SAHUC and ALF is unknown, the treatment of patients without liver failure is supportive, and for those who already have liver failure, the only treatment available and effective is liver transplantation. However, according to de Kleine et al.,[8] at least 3 patients died before a donor's liver was available. Caregivers and clinical researchers need to think about if there are some alternative therapeutic approaches that can mitigate or slow down the progression of the disease.

(1) Antiviral treatment against HAdV: It has been pointed out that there are no indications for antiviral treatment for adenovirus infection.[15,21] The major reasons include: i) HAdV usually does not cause severe hepatitis in immunocompetent children, but this is not absolute; ii) in liver biopsy studies, no evidence of viral inclusions and particles were found. Further studies with more sensitive methods may be ongoing. At present, there is no clear evidence to exclude HAdV from etiologic agents of SAHUC. There is a small number of reports showing that HAdV may induce hepatitis and even liver failure in immunocompetent children.[21] Therefore, antiviral treatment against adenovirus should be considered for at least a part of the patients, for example, the cases with higher viral load. Some of the consensus/recommendations already suggested that cidofovir or ribavirin should be considered. The selection of antiviral therapy for a viral infection should be based on better-designed studies and observations.

Cidofovir: A few case series reports showed that cidofovir treatment was effective and safe in the treatment of severe adenovirus infection. Muller et al.[16] reported that of 10 pediatric cases of post-hematopoietic stem cell transplantation (HSCT) with severe HAdV infection diagnosed via specific viral antigen detection, eight had clinical improvement and in 12 clinical isolates of the adenovirus, susceptibility to cidofovir was demonstrated. In another report of 57 post-HSCT cases, cidofovir treatment achieved complete resolution of clinical symptoms and viral clearance in 56 of the cases (98%) although one patient died of pneumonia.[17] No randomized controlled clinical trial report on cidofovir treatment of adenovirus infection could be found.

Ribavirin: Should ribavirin be recommended for antiviral treatment of adenovirus infection in cases with SAHUC? The answer should be "No" based on the literature. The officially approved indications for ribavirin in some developed countries are the only treatment of chronic hepatitis C in combination with interferon-α and nebulized inhalation treatment of acute lower respiratory tract infection caused by a respiratory syncytial virus in infants and young children. The efficacy of the latter has not been well established, therefore the therapy for this indication is largely given up although it was reported to be effective in the treatment of Lassa fever virus infection. A review of history and studies by Crotty et al.[22] demonstrated that the drug is an RNA virus mutagen and ribavirin's primary antiviral mechanism of action against a model RNA virus is via lethal mutagenesis of the RNA virus genomes. The above-mentioned three viruses are all RNA viruses. Ribavirin is not regarded as a major antiviral agent against DNA viruses such as adenovirus or herpesviruses, although there are reports in favor of treating adenovirus infection. In the report of Gavin et al.[23] of the five immunocompromised children with severe HAdV infection treated with intravenous ribavirin and intravenous immunoglobulin, three died, and two recovered. Ronchi et al.[24] reported that in 26 neonates with HAdV infection, ribavirin treatment could not improve the patients' outcomes.

(2) Liver-protective therapies: In the clinical practice of more than 5 decades in the treatment of acute and chronic viral hepatitis, Chinese physicians and pediatricians have achieved some experience in the treatment of acute and chronic liver injuries which they call "liver-protective therapies" using both western medicines and traditional Chinese medicines (TCM). At a recent symposium held online in China specifically for SAHUC and ALF, experts from both western and TCM hospitals had discussions and exchanges on the treatment of SAHUC and ALF.[25] The experts believe that combined western and TCM approaches may have good therapeutic effects. On the other hand, some of the alternative treatments like extracorporeal biological and non-biological liver support methods, plasmapheresis, and blood-purification treatments have achieved preliminary results showing that some of such treatments could be effective and safe.[26–28]

(3) Treatment of disseminated intravascular coagulation (DIC): Patients with severe liver injury and massive hepatocyte necrosis may progress into liver failure and multiorgan failure and may develop DIC, which at the early stage may have hypercoagulation status, which needs quick and appropriate heparin treatment, and at the later stage, widespread fibrinolysis would occur, and at this stage anti-fibrinolytic treatment with aminocaproic acid may be needed.[29,30]

(4) Possibility of conducting randomized controlled clinical trials: If the number of SAHUC cases continues to increase, it should be possible to design and conduct prospective randomized controlled clinical trials focusing on different therapeutic approaches, for example, antiviral therapy with cidofovir, for instance, if a study team considers it is required and worthy of testing and

approved. Other trials may be designed for liver protective approaches, including western medicine as well as TCM or combined approaches, and immunomodulatory treatments. But for any kind of antiviral therapy, the treatment should start early after the onset of the symptoms, preferably within 3 to 5 days after onset as lessons from the trials for COVID-19 provided,[31] and there should be virological outcomes and placebo or standard treatment plus placebo control cases.

In summary, SAHUC is a disease or syndrome of unknown etiology in younger children with about 6% of the cases that may progress to life-threatening ALF and 1% mortality. Diagnosis and differential diagnosis may not be difficult, but need to rule out infections caused by many viruses, including hepatitis viruses A–E and some other viruses and other known factors. Treatment of the disease at present is mainly supportive and symptomatic. Pediatricians and other care providers expect early clarification of the etiology and availability of specific, effective, and safe therapeutic and preventive approaches.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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