PERSPECTIVE

Severe Acute Hepatitis: An Emerging Grave Illness in Children

Raghvendra Singh,[1] Akshay Kapoor[2]

[1]Department of Pediatrics, Maulana Azad Medical College (University of Delhi) and Lok Nayak Hospital, New Delhi, India.
[2]Sheffield Children's Hospital, Sheffield, United Kingdom.
Correspondence to: Dr Raghvendra Singh, Associate Professor, Department of Pediatrics, Maulana Azad Medical College, Bahadur Shah Zafar Marg, New Delhi 110 002. drraghvendrasingh@gmail.com

Acute hepatitis of unknown origin in children has been recently described in the literature, and a case definition has also been proposed for this condition. The exact etiology is unknown and exclusion of infectious, metabolic, autoimmune and toxin mediated injuries is essential. Management for this condition is supportive, but some may require liver transplantation. Infection prevention and control practices are important as the etiology remains unidentified.

Keywords: *Adenovirus, Pediatric acute liver failure, Liver transplantation.*

The Lancet child and adolescent health recently published an editorial on severe acute hepatitis in children [1]. World Health Organization (WHO) was first notified of 10 cases of severe acute hepatitis of unknown origin (AHUO) by International Health Regulations (IHR) of the United Kingdom in previously healthy young children on 5 April, 2022 [2]. Laboratory testing excluded Hepatotropic A, B, C, D and E cases, while SARS-CoV-2 and/or adenovirus (HAdVs) were detected in several cases. The proposed case definition of AHUO by the WHO is summarized in **Box I.** As of 8 July, 2022, five WHO regions comprising 35 countries had reported 1010 cases fulfilling the WHO case definition with 22 deaths [3]. The proposed case definition of AHUO by WHO is summarized in Table I.

Delta testing is not required, as it is only undertaken in persons who are HBsAg positive to establish the presence of coinfection.

Acute non-A-E hepatitis is a well-known entity for years and has been described earlier from Europe and India accounting for 5-10% of all acute hepatitis in children [4,5]. A retrospective German study over 30 years observed a rising incidence of non-A-E in their cohort from 2019 onwards with stable numbers for Hepatitis A-E [6]. However, the recent reports of increase in the number of severe acute hepatitis reported by some European countries and WHO was not substantiated by a question-naire based survey across several European countries conducted in April and May, 2022 [7,8]

A Mixed Basket

HAdVs are non-enveloped double-stranded DNA viruses with a worldwide distribution and usually cause self-limited infections in the healthy population. However, severe or disseminated HAdV infections may occur in some immunocompromised individuals. The transmission mode consists of fecal-oral spread, conjunctival inoculation or inhalation of aerosolized droplets. The polymerase chain reaction from respiratory material, stool, blood or urine samples is the most common method to establish the diagnosis. Symptoms often reported are related to respiratory tract infections (e.g., pharyngitis, coryza or pneumonia), keratoconjunctivitis, gastro-intestinal symptoms (diarrhea, abdominal pain and vomiting, notably with serotype 40 and 41, but possible as concomitant symptoms for all serotypes, particularly in young children) or genitourinary tract infections [9]. Approximately 60% of United Kingdom (UK) cases and 45% of tested samples in the United States were positive for HAdVs. The precise role of HAdV induced acute severe hepatitis in immunocompetent individuals remains elusive. HAdV41 has tissue tropism to invade the gastrointestinal tract with clinical symptoms of diarrhea, vomiting, and

Box I WHO Working Group Proposed Case Definition of Severe Acute Hepatitis of Unknown Origin

Confirmed: Not available at present.

Probable: A person presenting with acute hepatitis (non-hepatitis A-E)[a] with serum transaminase >500 IU/L (AST or ALT), who is 16 years and younger, since 1 October, 2021.

Epi-linked: A person presenting with acute hepatitis (non-hepatitis A-E)[a] of any age who has been in close contact with a probable case since 1 October, 2021.

[a]*If hepatitis A-E serology results are awaited, but other criteria are met, these can be reported and classified as "pending classification." Cases with other explanations for their clinical*

fever [10]. However, HAdV41 is not known to cause acute liver failure in immunocompetent children. Enhanced HAdV surveillance in pediatric hepatitis cases as well as in animals and environments combined with specific laboratory and clinical investigations are urgently required to improve our knowledge of the impact and the spread of this new human threat [11]

CLINICAL PRESENTATION

Acute Hepatitis of Unknown Origin

Kelgeri, et al. [12] described the Birmingham liver transplantation (LT) unit, United Kingdom, experience in 44 children with acute hepatitis of unknown cause. The confirmed case definition for AHUO by the UK Health Security Agency (UKHSA) was utilized, i.e., acute hepatitis that is not due to hepatitis A through E viruses or a metabolic, inherited or genetic, congenital, or mechanical cause, with a serum aminotransferase level >500 IU per liter in a child who is ≤10 years of age presenting after 1 January, 2022 [13]. Most children were healthy before the illness, and only 3 had unrelated chronic health conditions. Jaundice in 93% was the most common condition, followed by vomiting in 54%, diarrhea in 32%, abdominal pain in 27%, and lethargy in 23%. The peak ALT levels ranged from 603-6279U/L (Normal 0-41U/L). The liver biopsy was performed in 9 children, but none had viral inclusions and immunohistochemical tests positivity for human adenovirus. Of these 44 children, 38 survived with the native liver; however, 6 (14%) children required liver transplantation [12].

Acute Hepatitis With Human Adenovirus Viremia

Gutierrez, et al. [14], in 2022, reported a case series of acute hepatitis in 15 children from United States, of whom 9 (60%) had no identifiable cause. Of these 9 non-identified cases, 8 were positive for HAdV infection. All nine children had been previously healthy. The symptoms began days to weeks before admission. The symptoms at admission in decreasing order were emesis, diarrhea, fever, fatigue, upper respiratory symptoms, poor appetite, and dark urine. The physical findings in 9 children included scleral icterus in 8, hepatomegaly in 7, hepatic encephalopathy, and splenomegaly in one each. The clinical symptomatology was similar to the above mentioned UK study. ALTs and ASTs ranged from 602-4696U/L and 447-4000U/L, respectively. The liver biopsy in six children revealed degrees of chronic and acute portal and lobular hepatitis characterized by mixed inflammation, consisting of lymphocytes, histiocytes, and neutrophils with interface activity in the majority of cases. Inflammation in the lobules was associated with extensive hepatocyte damage and foci of apoptosis. 3 of these 6 samples were positive for HAdVs by PCR, but none tested positive for immunohistochemical tests and viral inclusions for HAdVs. The INR ranged from 1.0-7.3, and three children met the criterion for pediatric acute liver failure (PALF). Two children with PALF required liver transplantation, and one recovered spontaneously. The remaining six children recovered with supportive treatment.

SARS-CoV-2 and Hepatic Involvement

Gastrointestinal tract involvement in severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection has been described in adults and children. However, children with chronic liver disease, including autoimmune liver disease and liver transplant, do not fare poorly in the course of SARS-CoV-2 infection. A case series described severe hepatitis as a primary manifestation of SARS-CoV-2 infection, with two children out of four fulfilling the clinical definition for PALF [15]. The WHO also mentioned 78 cumulative SARS-CoV-2 positivity by PCR in severe hepatitis cases, with many having HAdV coinfection [2].

POSSIBLE HYPOTHESES

Several working putative mechanisms have been suggested for this enigmatic entity. The first multipronged hypotheses were suggested by the UKHSA [13] and endorsed by the ESPGHAN working group [16]. The working mechanisms proposed are a typical HAdV infection with abnormal susceptibility or host response which allows adenovirus infection to progress more frequently to hepatitis, a considerable number of typical adenovirus infections, uncovering a very rare or under-recognized complication, abnormal susceptibility or host response to adenovirus due to priming by prior infection or coinfection with SARS-CoV-2 (including Omicron restricted) or another infection or abnormal host response to a toxin, drug or an environmental agent. Other hypo-theses suggested by the same bodies include a novel variant adenovirus, with or without a contribution from a cofactor, a post-infectious SARS-CoV-2 syndrome (inclu-ding an Omicron restricted effect), drug, toxin or environ-mental exposure, a novel pathogen either acting alone or as a coinfection and new variant of SARS-CoV-2. Toxico-logic investigations have not revealed any specific toxico-logical or other environmental factors as the cause of the severe acute hepatitis in children detected in multiple countries, but public health investigations are ongoing.

Another interesting proposed hypothesis is that the SARS-CoV-2 infection can lead to a viral reservoir in the gastrointestinal tract and the repeated release of viral proteins can lead to immune activation. Immune activation might, in turn, be initiated by a superantigen motif within the SARS-CoV-2 spike protein that bears a resemblance to

staphylococcal enterotoxin B, triggering broad and non-specific T-cell activation. Adenovirus-induced type-1 immune skewing, which, upon subsequent staphylococcal enterotoxin B administration, led to excessive IFN-γ production and IFN-γ-mediated apoptosis of hepatocytes in mouse models [17]. Fortunately, no link with COVID-19 vaccination has been found as most children were unvaccinated.

MANAGEMENT

As the etiology of this condition is still not understood fully, the mainstay of therapy for severe acute hepatitis of unknown etiology in children is supportive. Patient consciousness, volume status, urine volume, blood electrolytes, liver function, and coagulation function should be closely monitored during the entire treatment period, as should maintenance of water, electrolyte and acid-base balance [18]. Approximately 6-10% of children require liver transplantation and liver transplantation is necessary for children with ALF who fail to improve with supportive measures. There are no well-defined and universally consistent indications for liver transplantation in ALF children. Treatment with cidofovir in HAdV infection has also been described in [19]. The role of steroids in treating this condition needs to be studied by clinical trials in the future [20].

Prevention

WHO advises general infection prevention and control (IPC) practices as the etiology is unknown. These include hand hygiene, physical distancing, good ventilation when indoors, use of masks, adopting safe and hygienic food measures and home isolation when unwell. Health facilities should adopt droplet precautions for suspected and probable cases [3].

RESEARCH AGENDA FOR SEVERE ACUTE HEPATITIS

The ESPGHAN Hepatology Committee has set a research agenda for this condition [16]. It stresses the need for running prospective, multicenter studies to collect data on the incidence of this cluster of acute hepatitis and acute hepatitis in general. It also recommends advanced virological, including metagenomic (from blood, serum, urine, stool, respiratory and liver samples) and toxicology (including environmental and food toxicity) testing should be undertaken. Ideally, DNA, blood samples, nasal and throat swabs and fecal samples should be stored for future centralized testing. It suggests a battery of investigations for the work up for infectious diseases of children with acute hepatitis as summarized in **Table I**.

Concurrently, excluding non-infectious etiologies, including autoimmune, metabolic and drug-related causes of severe acute hepatitis, is also essential. Histopathology results from a larger patient cohort would provide additional insights into the possible viral origin. Finally, there is a need to investigate the underlying susceptibility of a dysregulated immune response. The high cost of the detailed workup is the main limiting factor especially in lower-middle income countries (LMICs).

Table I Infectious Disease Investigations Suggested for Children With Acute Hepatitis

Sample type	*Test*	*Pathogen*
Blood	PCR	Adenovirus, enterovirus, CMV, EBV, HSV, hepatitis A, hepatitis C, hepatitis E, HHV6 and 7
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
Nasal/throat swab	PCR	Respiratory virus panel (including adenovirus/enterovirus/influenza, SARS-CoV-2)
Stool	PCR, stool culture	Adenovirus, sapovirus, norovirus, enterovirus

PCR: polymerase chain reaction, CMV: cytomegalovirus, EBV: Epstein-Barr virus, HSV: herpes simplex virus, HHV: human herpes virus.

Whether this entity is a new disease condition or a rediscovery of an already existing condition due to heightened surveillance and diagnostic measure is not known at present. Non-Hep-A-E were described in Indian children in earlier hospital based case series and its proportion ranged from 3.5-22 % [5,21-23]. The overall mortality ranged from 39-64% in two of these earlier series with fulminant hepatic failure but the unidentified causes constituted a smaller proportion in these series [22,23]. In a recently published study on 125 children with PALF, no cause could be identified in 23% of cases and mortality/LT was required in 41.4% of these indeterminate cases. However, the mortality/LT rates in indeterminate and infectious causes were comparable [24].

CONCLUSIONS

Severe acute hepatitis of unknown origin is an emerging entity with high risks to children afflicted with this disease. Human adenovirus infection has been found in high proportions of children, but this agent's direct cytopathic effect seems less likely. COVID-19 infection with immune dysregulation coupled with antigenic stimulation by HAdV or another infectious agent is another possibility. The majority of children recover with conservative measures but a liver transplant is required in the rest. Globally

coordinated multi-centric research with extensive tests for infectious agents and immunological mechanisms is the need of the hour.

Contributors: RS: wrote the initial draft; AK: reviewed the manuscript and provided critical inputs. Both authors have read and approved the final version.

Funding: None; *Competing interests*: None stated.

REFERENCES

1. The Lancet Child Adolescent Health. Severe acute hepatitis in children. Lancet Child Adolesc Health. 2022;6:593.
2. World Health Organization. Disease outbreak news: acute hepatitis of unknown aetiology- the United Kingdom of Great Britain and Northern Ireland. 15 April, 2022. Accessed Sept 5, 2022. Available from: *https://www.who.int/emergencies/disease-outbreak-news/item/acute-hepatitis-of-unknown-aetiology – the-united-kingdom-of-great-britain-and-northern-ireland*
3. World Health Organization. Disease outbreak news: Severe acute hepatitis of unknown etiology in children-Multi-country. Accessed Jul 12, 2022. Available from: *https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON400*
4. Braccio S, Irwin A, Riordan A, et al. Acute infectious hepatitis in hospitalized children: A British Paediatric Surveillance Unit study. Arch Dis Child. 2017;102:624-28.
5. Poddar U, Thapa BR, Prasad A, Singh K. Changing spectrum of sporadic acute viral hepatitis in Indian children. J Trop Pediatr. 2002;48:210-3.
6. Leiskau C, Tsaka S, Meyer-Ruhnke L, et al. Acute severe non-AE-hepatitis of unknown origin in children–a 30-year retrospective observational study from north-west Germany. J Hepatol. 2022:SO168-8278 (22) 03464-X. E-pub ahead of print.
7. de Kleine RH, Lexmond WS, Buescher G, et al. Severe acute hepatitis and acute liver failure of unknown origin in children: a questionnaire-based study within 34 paediatric liver centres in 22 European countries and Israel, April 2022. Euro Surveill. 2022;27:2200369.
8. van Beek J, Fraaij P, Giaquinto C, et al. Case numbers of acute hepatitis of unknown aetiology among children in 24 countries up to 18 April 2022 compared to the previous 5 years. Euro Surveill. 2022;27:2200370.
9. Lynch JP III, Kajon AE. Adenovirus: epidemiology, global spread of novel serotypes, and advances in treatment and prevention. Semin Respir Crit Care Med. 2016;37:586-602.
10. Mücke MM, Zeuzem S. The recent outbreak of acute severe hepatitis in children of unknown origin - what is known so far. J Hepatol. 2022;77:237-42.
11. Hakim MS. The recent outbreak of acute and severe hepatitis of unknown etiology in children: A possible role of human adenovirus infection? J Med Virol. 2022;94:4065-8.
12. Kelgeri C, Couper M, Gupte GL, et al. Clinical spectrum of children with acute hepatitis of unknown cause. New Engl J Med. 2022;387:611-9.
13. U.K. Health Security Agency. Investigation into acute hepatitis of unknown aetiology in children in England. Technical Briefing 3. 2022. Accessed Sep 5, 2022. Available from: *https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/fle/1077027/acute-hepatitis-technical-briefing_3.pdf*
14. Gutierrez Sanchez LH, Shiau H, Baker JM, et al. A case series of children with acute hepatitis and human adenovirus infection. New Engl J Med. 2022;87:620-30.
15. Antala S, Diamond T, Kociolek LK, et al. Severe hepatitis in pediatric COVID-19. J Pediatr Gastroenterol Nutr. 2022; 387:611-9.
16. Indolfi G, Czubkowski P, Fitzpatrick E, Gonzales E, et al. Acute hepatitis of unknown aetiology among young children: Research agenda by the ESPGHAN hepatology committee. J Pediatr Gastroenterol Nutr. 2022;75:543-8.
17. Brodin P, Arditi M. Severe acute hepatitis in children: Investigate SARS-CoV-2 superantigens. Lancet Gastroenterol Hepatol. 2022;7:594-5.
18. Chen J, Shu Q, Zhao ZY. Response to the outbreak of severe acute hepatitis of unknown origin in children. World Journal of Pediatrics. 2022;23:1-4.
19. Verma A, Vimalesvaran S, Lampejo T, et al. Use of cidofovir in recent outbreak of adenovirus-associated acute liver failure in children. Lancet Gastroenterol Hepatol. 2022;7:700-2.
20. Kelly DA, Stamataki Z. Sudden onset hepatitis in children. Nat Rev Gastroenterol Hepatol. 2022;19:553-54.
21. Bendre SV, Bavdekar AR, Bhave SA, et al. Fulminant hepatic failure: Etiology, viral markers and outcome. Indian Pediatr. 1999;36:1107-12.
22. Arora NK, Nanda SK, Gulati S, et al. Acute viral hepatitis types E, A, and B singly and in combination in acute liver failure in children in north India. J Med Virol. 1996;48:215-21.
23. Poddar U, Thapa BR, Prasad A, et al. Natural history and risk factors in fulminant hepatic failure. Arch Dis Child. 2002;87:54-6.
24. Amatya P, Kapalavai SK, Deep A, et al. Pediatric acute liver failure: An experience of a pediatric intensive care unit from resource limited settings. Front Pediatr. 2022;10:956699.