

Non-hepatotropic viral hepatitis and its causative pathogens: The ongoing need for monitoring in children with severe acute hepatitis of unknown etiology

Ran Wang^{1,2}  | Zhengde Xie² 

¹Beijing Key Laboratory of Pediatric Respiratory Infectious Diseases, Key Laboratory of Major Diseases in Children, Ministry of Education, National Clinical Research Center for Respiratory Diseases, Laboratory of Infection and Virology, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

²Research Unit of Critical Infection in Children, 2019RU016, Chinese Academy of Medical Sciences, Beijing, China

Correspondence

Zhengde Xie, Laboratory of Infection and Virology, Beijing Pediatric Research Institute, Beijing Children's Hospital, National Center for Children's Health, Capital Medical University, Beijing, China.

Email: xiezhengde@bch.com.cn

Funding source

CAMS Innovation Fund for Medical Sciences, Grant/Award Number: 2019-I2M-5-026; National Natural Science Foundation of China, Grant/Award Number: 82002130

Received: 2 July 2022; Accepted: 13 July 2022

ELEVATED INCIDENCE OF SEVERE ACUTE HEPATITIS OF UNKNOWN ETIOLOGY IN CHILDREN IN 2022

As of June 22, 2022, 920 probable cases of severe acute hepatitis of unknown etiology had been reported in 33 countries.¹ The numbers of reported cases were the highest in the United States and the United Kingdom. According to the World Health Organization, the criteria for a probable diagnosis of severe acute hepatitis of unknown etiology are: (1) onset after October 1, 2021; (2) aspartate aminotransferase (AST) level or alanine aminotransferase (ALT) level ≥ 500 IU/L; (3) age at onset ≤ 16 years; (4) exclusion of hepatitis A–E and absence of clear etiology.¹ Some affected children have developed acute liver failure (ALF), which requires more intensive care and liver transplants; some of these children have died.

Acute hepatitis of unknown etiology in children occurs every year, but some countries have reported elevated num-

bers of severe cases this year; the severity in these cases is greater than the typical severity in children with acute hepatitis.² It remains unclear the etiology of the affected patients. There is also no specific link or common feature among the reported cases. It has been suggested that the disease is caused by human adenovirus (HAdV) type 41 (or its variants), a novel variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or an unknown pathogen; it may also be associated with autoimmune hepatitis caused by mRNA vaccination against SARS-CoV-2 or enhanced by a previous SARS-CoV-2 infection or other cause.^{3,4}

KNOWLEDGE OF LIVER DYSFUNCTION CAUSED BY NON-HEPATOTROPIC VIRUS INFECTION

In addition to hepatitis viruses, many non-hepatotropic viruses can cause liver dysfunction in children. Acute hepatitis caused by these viruses usually manifests with or

DOI: 10.1002/ped4.12340

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 Chinese Medical Association. *Pediatric Investigation* published by John Wiley & Sons Australia, Ltd on behalf of Futang Research Center of Pediatric Development.

without jaundice, as well as minimally elevated levels of serum transaminases. Non-hepatotropic viral hepatitis is usually a component of the severe phenotype of the disease caused by corresponding viral infections; it results from immune-mediated injury or is directly caused by viral infection.

Here, we provide a summary of the etiologies and pathogens associated with non-hepatotropic viral hepatitis in children, with the aim of enhancing such knowledge among clinicians.

HERPESVIRUS

There are eight human herpesviruses, almost all of which can cause liver damage; however, the underlying mechanisms and clinical manifestations are different for each virus.⁵ Listed below are the five major herpesviruses that can cause liver damage.

Human cytomegalovirus

Human cytomegalovirus (HCMV) is regarded as a weak pathogen that affects 40%–100% of the global population. It is not strongly pathogenic in immunocompetent individuals, and many infected individuals remain asymptomatic. HCMV infection-induced hepatitis (i.e., HCMV hepatitis) caused by primary infection mostly occurs in infants and young children; it manifests as a subclinical illness with mild to severe elevation of serum liver enzymes, and it is self-limiting in mild cases. HCMV hepatitis can also occur in patients with congenital systemic disseminated HCMV infection and post-transfusion syndrome. In immunocompromised patients, particularly liver transplant patients, an infectious mononucleosis-like syndrome with hepatic involvement occurs along with overt hepatitis. In contrast, immunocompetent patients (particularly patients aged < 7 years) develop anicteric hepatitis, but they rarely exhibit HCMV hepatitis requiring hospitalization.⁶ Overall, the degree of hepatic involvement caused by HCMV infection substantially varies according to the immune status of the host.

Epstein–Barr virus

Similar to HCMV, Epstein–Barr virus (EBV) can cause liver damage.⁷ However, unlike HCMV hepatitis, EBV-related liver damage is mainly the result of immune-mediated damage caused by infiltrating lymphocytes, rather than viral infection of hepatocytes, bile duct epithelial cells, and endothelial cells. Both primary and persistent EBV infections can cause liver damage. Primary EBV infection can manifest as infectious mononucleosis or be asymptomatic. Moderately elevated AST/ALT levels can be found in 80%–90% of patients with infectious mononucleosis.⁸ Liver dysfunction can also occur in

patients with persistent EBV infections such as chronic active EBV infection, autoimmune hepatitis, and EBV-associated hemophagocytic lymphohistiocytosis. Approximately 80% of patients with chronic active EBV infection have liver dysfunction; in such patients, chronic active hepatitis is diagnosed via biopsy. Liver damage in patients with EBV-associated hemophagocytic lymphohistiocytosis is a component of the disease spectrum. The proliferation of EBV-infected T/natural killer cells leads to the release of high levels of cytokines via signal amplification, which activates macrophages to phagocytose blood cells; subsequent lymphocyte infiltration into various organs causes liver dysfunction.

Human herpesvirus 6

Human herpesvirus (HHV)-6A and HHV-6B are considered distinct species. Primary HHV-6 infection mainly manifests as exanthema, which is caused by HHV-6B. Fulminant liver failure and acute decompensation of chronic liver disease associated with HHV-6B infection have been reported in children after primary infection or liver transplantation. The detection of HHV-6B DNA in plasma and liver tissue provided reasonable evidence to rule out chromosomal integration of HHV-6B.⁹

Herpes simplex virus

The clinical manifestations of herpes simplex virus (HSV) infection are mostly mild and self-limiting. Some neonates and immunocompromised patients can develop life-threatening systemic disseminated HSV infection, which involves organs such as the brain, liver, and lungs. HSV hepatitis is a rare but serious disease that constitutes <1% of viral hepatitis and 2% of virus-associated ALF.¹⁰ Overall, the chances of recovery and survival are significantly greater in children than in adults.^{9,11}

Varicella zoster virus

Varicella zoster virus (VZV) infection can manifest as two distinct diseases, namely chickenpox and shingles. Hepatitis after VZV infection in immunosuppressed patients is mostly mild; this occurs in patients with leukemia, transplant patients, patients with acquired immunodeficiency syndrome, and corticosteroid users. In contrast, disseminated VZV infection results in fulminant hepatitis and liver failure.¹²

In summary, herpesviruses are important pathogens associated with non-hepatotropic hepatitis. Similar to HCMV, DNA from EBV and HHV-6 is frequently detected in immunocompetent children with acute liver dysfunction. Therefore, polymerase chain reaction and serological assessments are both necessary for the accurate diagnosis

and treatment of children with acute hepatic insufficiency caused by primary herpesvirus infection.

HUMAN ADENOVIRUS

There are seven subgenera (A–G) and at least 113 types of HAdV, among which only HAdV-41, -40, and -52 cause gastrointestinal symptoms.¹³ HAdV usually causes mild, self-limiting respiratory or digestive tract infections in young children; liver dysfunction can occur during severe respiratory HAdV infections, even in healthy children. However, in immunocompromised hosts (e.g., organ or bone marrow transplant patients and patients with malignant tumors), HAdV infection can trigger other severe symptoms such as fulminant HAdV hepatitis. Histopathology analyses have shown that non-zonal coagulative hepatocyte necrosis and characteristic intranuclear inclusions are features of HAdV hepatitis.¹⁴ However, the association between severe acute hepatitis of unknown etiology and HAdV infection requires further exploration.

HUMAN ENTEROVIRUS

There are 12 groups (A–L) of human enterovirus (HEV), among which groups A–D can infect humans. HEV infection is a rare but relevant cause of ALF in neonates. Coxsackie virus groups A (CVA) and B (CVB), as well as echoviruses, belong to the genus *Enterovirus*; infections with such viruses manifest as multisystem diseases including myocarditis, meningoencephalitis, and (rarely) fulminant ALF. Neonates and infants are at risk of disseminated CVB and echovirus infections. CVA4, CVA9, CVB5, and some types of echoviruses are the most common HEVs associated with hepatitis. Symptoms of hepatitis caused by HEV infection are mild, with rare instances of severe jaundice or elevated levels of ALT, AST, and bilirubin; affected patients generally have a good prognosis.¹⁵ The natural course of the disease may be prolonged in immunocompromised hosts. Thus, there is a need to carefully monitor the indicators of HEV infection, considering its involvement in neonatal ALF or hepatitis, to enable a more rational diagnosis and management.

MEASLES VIRUS

Hepatitis is a rare and transient complication of measles in childhood. The diagnosis of measles virus-related liver damage is based on clinical features and a fourfold increase in the hemagglutination inhibiting antibody titer, as well as increases in liver enzymes. Hepatic involvement in children with measles is subclinical and resolves rapidly; it is not associated with the duration and severity of fever or the coexistence of other complications, although such involve-

ment can be severe in children with measles who receive hepatotoxic drugs.¹⁶

HANTAVIRUS

In parts of China and Japan, hantavirus (HV) antibodies have been detected in serum samples from some patients with hepatitis of unknown etiology, suggesting that HV may be the causative pathogen in numerous cases of acute hepatitis without concurrent hepatitis virus A–E infection, at least in these locations.^{17,18} Although the relationship between HV and hepatitis has not been confirmed, clinicians should not ignore cases of HV infection in patients with clinical manifestations of acute hepatitis who lack features suggestive of either hemorrhagic fever with renal syndrome or hantavirus pulmonary syndrome.

ROTAVIRUS

Rotavirus infection is a major cause of gastroenteritis; mild hepatic dysfunction has been reported in affected patients, although it is rare and transient. Symptoms in affected patients may include hypoglycemia, hepatomegaly, and increased levels of serum transaminases and creatinine kinases; these findings suggest the presence of steatosis leading to liver dysfunction.¹⁹

FLAVIVIRUS

Yellow fever virus

Severe liver injury is associated with yellow fever virus infection; such injury is characterized by widespread apoptosis-induced hepatocyte death, partially because of lytic necrosis.²⁰ Acinar lesions in the midzone region are associated with mild to moderate inflammatory infiltrates, which mainly consist of monocytes. Infiltration by CD4⁺ and CD8⁺ T cells was observed in the liver parenchyma, similar to findings in other hepatotropic viral infections, where these cells are involved in viral clearance.²¹

Dengue virus

Dengue fever caused by dengue virus infection is a potentially life-threatening disease with an increased risk of severity in children.²² Hepatic involvement is characterized by numerous clinical manifestations, ranging from asymptomatic elevations in serum transaminases to ALF.²³ Although the pathogenesis of liver injury secondary to dengue virus infection remains unclear, potential mechanisms include apoptosis in hepatocytes and Kupffer cells, immune-mediated hepatocyte injury, and shock-induced ischemic hepatitis.²⁴ Currently, there is no specific treatment for dengue-associated ALF; affected patients receive supportive care and measures to prevent further complications.

OTHER VIRUSES

In addition to the above viruses, infections with viruses such as parvovirus B19, human bocavirus, and respiratory syncytial virus have been reported to cause liver dysfunction or ALF in immunocompetent or immunodeficient children; such manifestations may be a rare but common clinical outcome of disseminated viremia.^{25,26}

INITIATIVES

There is a need for greater attention toward non-hepatotropic virus-induced acute liver injury and ALF in both immunosuppressed children and immunocompetent children. Thus, we propose intensive surveillance to determine the etiology of non-hepatotropic viral hepatitis in children, based on the best available detection technology and sample type (needle biopsy if necessary). Additionally, the collaborations of experts from multiple disciplines (e.g., clinical medicine, virology, and immunology) will help to protect the health of affected children.

CONFLICT OF INTEREST

None.

REFERENCES

- World Health Organization. Severe acute hepatitis of unknown aetiology in children - Multi-country. <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON394>. Accessed July 5, 2022.
- Marsh K, Tayler R, Pollock L, Roy K, Lakha F, Ho A, et al. Investigation into cases of hepatitis of unknown aetiology among young children, Scotland, 1 January 2022 to 12 April 2022. *Euro Surveill*. 2022;27:2200318. DOI: 10.2807/1560-7917.ES.2022.27.15.2200318
- European Centre for Disease Prevention and Control. Increase in severe acute hepatitis cases of unknown aetiology in children. <https://www.ecdc.europa.eu/en/publications-data/increase-severe-acute-hepatitis-cases-unknown-aetiology-children>. Accessed July 5, 2022.
- Boettler T, Csernalabics B, Salié H, Luxenburger H, Wischer L, Salimi Alizei E, et al. SARS-CoV-2 vaccination can elicit a CD8 T-cell dominant hepatitis. *J Hepatol*. 2022;S0168-8278(22)00234-3. DOI: 10.1016/j.jhep.2022.03.040
- Fingerth JD. Herpesvirus infection of the liver. *Infect Dis Clin North Am*. 2000;14:689-719. DOI: 10.1016/s0891-5520(05)70127-6
- Da Cunha T, Wu GY. Cytomegalovirus hepatitis in immunocompetent and immunocompromised hosts. *J Clin Transl Hepatol*. 2021;9:106-115. DOI: 10.14218/JCTH.2020.00088
- Liu M, Wang X, Zhang L, Feng G, Zeng Y, Wang R, et al. Epidemiological characteristics and disease burden of infectious mononucleosis in hospitalized children in the mainland of China: a nationwide retrospective study. *Virol Sin*. 2022;12:S1995-820X(22)00121-3. DOI: 10.1016/j.virs.2022.07.007
- Macswain KF, Crawford DH. Epstein-Barr virus-recent advances. *Lancet Infect Dis*. 2003;3:131-140. DOI: 10.1016/s1473-3099(03)00543-7
- Hill JA, Myerson D, Sedlak RH, Jerome KR, Zerr DM. Hepatitis due to human herpesvirus 6B after hematopoietic cell transplantation and a review of the literature. *Transpl Infect Dis*. 2014;16:477-483. DOI: 10.1111/tid.12208
- Schiødt FV, Davern TJ, Shakil AO, McGuire B, Samuel G, Lee WM. Viral hepatitis-related acute liver failure. *Am J Gastroenterol*. 2003;98:448-453. DOI: 10.1111/j.1572-0241.2003.t01-1-07223.x
- Moldovan B, Mentha G, Majno P, Berney T, Morard I, Giostra E, et al. Demographics and outcomes of severe herpes simplex virus hepatitis: a registry-based study. *J Hepatol*. 2011;55:1222-1226. DOI: 10.1016/j.jhep.2011.02.029
- Han SB, Seo YE, Kim SK, Lee JW, Lee DG, Chung NG, et al. Varicella with rapidly progressive hepatitis presenting with multiple hepatic nodules in a child with acute leukemia. *J Infect Chemother*. 2016;22:822-825. DOI: 10.1016/j.jiac.2016.07.005
- Ghebremedhin B. Human adenovirus: Viral pathogen with increasing importance. *Eur J Microbiol Immunol (Bp)*. 2014;4:26-33. DOI: 10.1556/EuJMI.4.2014.1.2
- Schaberg KB, Kambham N, Sibley RK, Higgins J. Adenovirus hepatitis: Clinicopathologic analysis of 12 consecutive cases from a single institution. *Am J Surg Pathol*. 2017;41:810-819. DOI: 10.1097/PAS.0000000000000834
- Yen FB, Chang LY, Kao CL, Lee PI, Chen CM, Lee CY, et al. Coxsackieviruses infection in northern Taiwan—epidemiology and clinical characteristics. *J Microbiol Immunol Infect*. 2009;42:38-46.
- Papadopoulou A, Theodoridou M, Syriopoulou V, Mostrou G, Kattamis CH. Hepatitis in children hospitalized with measles: the experience acquired after a Greek epidemic. *J Paediatr Child Health*. 2001;37:55-57. DOI: 10.1046/j.1440-1754.2001.00580.x
- Meng G, Lan Y, Nakagawa M, Maehara T, Mitani K, Tomiyama T, et al. High prevalence of hantavirus infection in a group of Chinese patients with acute hepatitis of unknown aetiology. *J Viral Hepat*. 1997;4:231-234. DOI: 10.1046/j.1365-2893.1997.00140.x
- Kariwa H, Yoshimatsu K, Araki K, Chayama K, Kumada H, Ogino M, et al. Detection of hantaviral antibodies among patients with hepatitis of unknown etiology in Japan. *Microbiol Immunol*. 2000;44:357-362. DOI: 10.1111/j.1348-0421.2000.tb02506.x
- Ishige M, Fuchigami T, Furukawa M, Kobayashi H, Fujiki R, Ogawa E, et al. Primary carnitine deficiency with severe acute hepatitis following rotavirus gastroenteritis. *J Infect Chemother*. 2019;25:913-916. DOI: 10.1016/j.jiac.2019.04.020
- Quaresma JA, Barros VL, Pagliari C, Fernandes ER, Andrade HF Jr, Vasconcelos PF, et al. Hepatocyte lesions and cellular immune response in yellow fever infection. *Trans R Soc Trop Med Hyg*. 2007;101:161-168. DOI: 10.1016/j.trstmh.2006.02.019

21. Quaresma JA, Barros VL, Fernandes ER, Pagliari C, Takakura C, da Costa, et al. Reconsideration of histopathology and ultrastructural aspects of the human liver in yellow fever. *Acta Trop*. 2005;94:116-127. DOI: 10.1016/j.actatropica.2005.03.003
22. Wang R, Wang X, Zhang L, Feng G, Liu M, Zeng Y, et al. The epidemiology and disease burden of children hospitalized for viral infections within the family Flaviviridae in China: A national cross-sectional study. *PLoS Negl Trop Dis*. 2022;7:e0010562. DOI: 10.1371/journal.pntd.0010562
23. Jagadishkumar K, Jain P, Manjunath VG, Umesh L. Hepatic involvement in dengue Fever in children. *Iran J Pediatr*. 2012;22:231-236.
24. Sriphongphankul H, Liabsuetrakul T, Osatakul S. Clinical outcomes of children diagnosed dengue-associated acute liver failure with or without N-acetylcysteine treatment: A retrospective cohort study. *J Trop Pediatr*. 2021;67:fmab039. DOI: 10.1093/tropej/fmab039
25. Leon L, Alves A, Garcia R, Melgaço JG, de Paula VS, Pinto MA. Parvovirus B19 infection in a fatal case of acute liver failure. *Pediatr Infect Dis J*. 2017;36:e355-355:e358. DOI: 10.1097/INF.0000000000001731
26. Haytoğlu Z, Canan O. Bocavirus viremia and hepatitis in an immunocompetent child. *Balkan Med J*. 2017;34:281-283. DOI: 10.4274/balkanmedj.2015.1492

How to cite this article: Wang R, Xie Z. Non-hepatotropic viral hepatitis and its causative pathogens: The ongoing need for monitoring in children with severe acute hepatitis of unknown etiology. *Pediatr Investig*. 2022;6:151–155. <https://doi.org/10.1002/ped4.12340>