Diagnosis and Clinical Management of Acute Severe Hepatitis of Unknown Origin: Operational Recommendation of Peking Union Medical College Hospital

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Abstract

Around 450 cases of acute severe hepatitis of unknown origin in children have been reported in 21 countries and region globally since April 2022, which has exceeded the past annual incidences of related regions, and has aroused wide concern. Affected patients were predominantly children under 16 years of age, presented with symptoms of acute hepatitis with markedly elevated liver enzymes, and had been ruled out of common viral infections such as hepatitis A, B, C, D, and E. Similar cases have not been reported in China yet. However, considering that the severe acute hepatitis has involved worldwide areas, still with unknown origin, and incidences of severity is relatively high, we formulated this recommendation to standardize diagnosis and treatment of acute severe hepatitis of unknown origin in Peking Union Medical College Hospital, to get fully prepared to the possible public health events.

Keywords: Child; Acute severe hepatitis of unknown origin; Diagnosis; Treatment

Epidemic overview

In April 2022, the UK National focal point of the International Health Regulations reported to the World Health Organization (WHO) 10 cases of severe acute hepatitis of unknown origin in children aged < 10 years who had been identified in Scotland since January 2022. The affected children mainly presented with acute hepatitis with markedly elevated liver enzymes, without confirmed evidence of hepatitis A, B, C, D, or E. Later, cases of severe acute hepatitis of unknown origin surged in many European and American countries, which exceeded the past annual incidence in these regions and raised global concern.10 As of May 10, a total of approximately 450 pediatric cases of severe acute hepatitis of unknown origin have been reported from 21 countries and regions around the world, among which at least 18 cases required liver transplantation.15 Currently, no similar case has been reported in China. However, new cases of severe acute hepatitis of unknown origin have emerged in a large geographical area, and a high proportion of patients required critical care. Therefore, we specially formulated the following recommendations to standardize and guide the diagnosis and treatment of severe acute hepatitis of unknown origin at Peking Union Medical College Hospital, to get fully prepared for possible public-health events.

Of note, since no similar cases have been reported in China since January 2022, the following recommendations are mainly formulated based on current reports combined with previous clinical experience with similar patients. The working group will pay close attention to international and domestic trends to keep the recommendation updated timely.
aged 1 to 5 years were predominantly affected. Onset of similar cases occurred in a relatively limited period, though quite sporadic without clear epidemiological association. The current data suggested a peak incidence in March 2022.

Currently, the etiology of severe acute hepatitis remains unclear. However, human adenovirus (HAdV) has been detected in serum samples of >50% of patients, and HAdV-41 Type F was detected in at least 18 cases.[1,3] In addition, some patients had concurrent coronavirus disease 2019 (COVID-19), but there is no evidence indicating its definite association with severe acute hepatitis of unknown origin.

**Diagnostic process of severe acute hepatitis of unknown origin**

**Screening criteria[1]**

1. Suspected cases: Patients showing signs of acute hepatitis, with (1) serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >500 U/L, with or without elevated bilirubin levels, and (2) exclusion of hepatitis A–E virus infections following preliminary screening; (3) Focus on children and adolescents aged ≤16 while taking adults into account as well.

2. Epidemiologically-related cases: Patients with acute hepatitis (not hepatitis caused by viruses A–E) of any age who have been close contacts with suspected cases.

3. Currently, there are no practical diagnostic criteria for this disease. However, if recommended screening criteria 1 or 2 are met, the case should be reported and the following diagnosis and treatment process should be initiated.

**Clinical assessment**

1. Epidemiological history:
   (1) History of exposure to drugs or toxins within 3 months before the disease onset.
   (2) History of contact with animals or special food.
   (3) History of vaccination against and infection with the severe acute respiratory syndrome coronavirus 2. History of other infections within 3 months.
   (4) History of contact with similar cases.

2. Clinical manifestations:
   The disease has an acute onset, with the most common clinical manifestations being jaundice, nausea, or vomiting, and loss of appetite. Concurrent abdominal pain or diarrhea may be observed in some patients, in addition to systemic symptoms such as fever, fatigue, and drowsiness. However, respiratory symptoms are rarely observed. Progressive disease status may be associated with increased risks of abnormal bleeding and alteration in consciousness. Patients who have progressed to liver failure may develop hepatorenal syndrome, and present with oliguria, edema, etc.

   Acute liver failure should be considered, when jaundice develops rapidly within 2 weeks of onset (daily bilirubin increase ≥17.1 μmol/L or bilirubin level >10 times the upper limit of the normal values) and progressive shrinkage of the liver is observed with or without varying degrees of kidney damage, hemorrhage, and symptoms of hepatic encephalopathy.

3. Family history:
   Explore the family history of possible liver diseases and autoimmune diseases.

**Laboratory workup [Figure 1]**

The most prominent abnormality in laboratory results is abnormal liver function, including the elevation of transaminase (ALT or AST) and bilirubin levels. Disease progression may be associated with prolonged prothrombin time and hyperammonemia.

1. In all cases showing signs of severe acute hepatitis, the following tests should be performed:
   (1) Complete blood counts; urine analysis; fecal analysis; liver and kidney function tests (including albumin and globulin); ammonia level; blood lipids, and coagulation functions.
   (2) Anti-HAV-IgM, HBsAg (if positive, perform the HBV-DNA test), anti-HCV-Ab (if positive, perform the HCV-RNA test), and anti-HEV-IgM.
   (3) Abdominal ultrasound examination.

2. Complete the following if severe acute hepatitis of unknown origin is suspected (completed separately in batches as appropriate in infants and children):
   (1) Anti-HSV1/2-IgM/IgG, CMV-DNA, EBV-DNA, anti-parvovirus B19-IgM/IgG, adenovirus typing, antibodies against Legionella pneumophila – IgM/IgG, antibodies against Mycoplasma pneumoniae and Chlamydia, Widal and Weil-Felix tests, stool culture, stool adenovirus and norovirus testing, and metagenomic sequencing of the peripheral blood.
   (2) C-reactive protein, creatine kinase, and cardiac enzymes; lymphocyte subsets, immunoglobulins and complements may be tested as appropriate.
   (3) Anti-nuclear antibody, autoimmune hepatitis antibodies (anti-smooth muscle antibody, anti-mitochondrial antibody, anti-liver-kidney microsome antibody type I, and anti-liver cytosol antibody type-I, etc.); ceruloplasmin.
   (4) Screening for heavy metals and toxins.
   (5) Imaging examinations: electrocardiogram and ultrasound of the inferior vena cava and portal vein. Magnetic resonance imaging or computed tomography may be performed when deemed necessary based on clinical judgment;
   (6) Ophthalmological consultation to determine the presence of Kayser–Fleischer (K-F) rings.

3. For patients in whom a clear diagnosis cannot be made after the above screening:
   (1) Collect peripheral blood samples; nasal pharyngeal swabs; and vomits, urine, and stool specimens for further etiology exploration.
   (2) If possible, liver biopsy should be performed. Biopsy specimens should be sent for routine smear examination, pathogen culture, metagenomic sequencing, and pathological examination.

4. Dynamic monitoring:
   The changes in the clinical conditions of newly identified patients should be closely monitored, and the frequency of indicator monitoring should be determined according to the clinical situation of the patient. For all newly identified patients, we recommend a daily repeat of complete blood counts, liver function tests and coagulation function tests for 3 consecutive days following the first visit. Thereafter, the frequency of re-examination should be determined according to the changes in clinical conditions.
Treatment

As the cause of this disease remains unclear, quarantine of suspected cases is recommended during diagnosis and treatment. Objects contaminated by the feces, secretions, excrements, and blood of the patient should be thoroughly disinfected.

Once a suspected case is observed after initial assessment, the Office of Medical Administration should be informed, and diagnosis and treatment of severe hepatitis of unknown origin by a multidisciplinary team consisting of physicians from the departments of infectious diseases, pediatrics, emergency medicine, and intensive care medicine should be initiated.

1. General treatment:
   - Bed rest to reduce physical exertion and liver burden. Energy supply should be guaranteed, with enteral nutrition as the main supply method to provide a diet with high carbohydrate, low fat, and moderate protein. For patients with insufficient oral intake, calories, fluids, vitamins, and trace elements should be supplied daily intravenously. Hypoalbuminemia should be corrected. Clinical conditions and changes in laboratory indicators such as liver function test results, electrolyte levels, acid-base equilibrium, and coagulation indicators should be closely monitored.

2. Treatment of liver injury and jaundice:
   - Choose liver-protecting anti-inflammatory and detoxifying drugs, liver cell membrane protectors, and choleretics as appropriate according to the clinical conditions.
   - Correction of abnormal blood coagulation functions:
     - Vitamin K1 should be supplemented intravenously when necessary (precautions should be taken to avoid allergic reactions). Blood plasma and coagulation factors should be supplemented as appropriate according to the bleeding status.
   - Prevention and treatment of hepatic encephalopathy:
     - Appropriate protein diet should be administered to maintain free bowel movement. Lactulose and probiotics may be routinely used, and branched-chain amino acids may be supplemented as appropriate.
   - Prevention and treatment of hepatorenal syndrome:
     - Correct the status of hypovolemia, actively monitor and prompt control the potential infections, and carefully avoid nephrotoxic drugs. Hepatorenal syndrome should be considered in patients who fail to respond to the conventional combination therapy, and vasoconstrictors (terepressin or norepinephrine) infused with albumin can be used to improve the syndrome.
   - Bioartificial liver:
     - Could be used to temporarily perform part of the liver function so that liver cells may be regenerated in acute or subacute liver failure. Bioartificial liver may also buy time for liver transplantation for patients in whom cell regeneration is impossible.
not possible. Non-biological artificial liver technologies including blood perfusion, plasma adsorption, and plasma exchange can be used according to clinical evaluation.

7. Liver transplantation:
   For critically ill patients with poor response to internal medical treatment, liver transplantation may be considered, provided there are no contraindications.

8. Prevention and treatment of secondary infections:
   Attention should be paid to secondary hepatobiliary infection or spontaneous bacterial peritonitis. Based on clinical indications, empirical regimen covering Gram-negative bacilli and anaerobic bacteria may be administered, and targeted regimen should be used when further tests reveal specific pathogen evidence.

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Conflicts of Interest
None.

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References
[1] World Health Organization. Multi-country–acute, severe hepatitis of unknown origin in children. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON376. Accessed May 11, 2022.
[2] European Centre for Disease Prevention and Control. Epidemiological update: hepatitis of unknown etiology in children. Available from: https://www.ecdc.europa.eu/en/news-events/epidemiological-update-hepatitis-unknown-aeetiology-children. Accessed May 12, 2022.
[3] Baker JM, Buchfellner M, Britt W, et al. Acute hepatitis and adenovirus infection among children-Alabama, October 2021–February 2022. MMWR Morb Mortal Weekly Rep 2022;71 (18):638–640. doi: 10.15585/mmwr.mm7118e1.
[4] Liver Failure and Artificial Liver Group, Chinese Society of Infectious Diseases, Chinese Medical Association, Severe Liver Disease and Artificial Liver Group, Chinese Society of Hepatology, Chinese Medical Association. [Guideline for diagnosis and treatment of liver failure]. Zhonghua Gan Zang Bing Za Zhi 2019;27 (1):18–26. doi: 10.3760/cma.j.issn.1007-3418.2019.01.006.

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