New Microbes and New Infections 56 (2024) 101203

Contents lists available at ScienceDirect

New Microbes and New Infections

journal homepage: www.journals.elsevier.com/new-microbes-and-new-infections

Original Article

Clinicopathological characteristics of 3 probable pediatric cases with acute severe hepatitis of unknown aetiology

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ARTICLE INFO

Handling Editor: Patricia Schlagenhauf

Keywords:
Acute severe hepatitis
Unknown aetiology
Children
Clinicopathological characteristics

ABSTRACT

Background: Acute severe hepatitis with unknown aetiology in children (ASHep-UA) has become a global health alert. This article reported clinicopathological characteristics of 3 probable ASHep-UA cases.
Methods: We respectively collected serological data and liver biopsies of 3 suspected cases of ASHep-UA. Neutralizing antibodies titer for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variants were determined by virus neutralization test (VNT). Histological assessment, immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) for cytomegalovirus (CMV), Epstein-Barr virus (EBV), human adenoviruses (HAdV), adeno-associated virus (AAV2), human herpes virus type 6 (HHV-6) were performed to identify possible aetiologies.
Results: Remarkable elevation of transaminase (median ALT level, 1100 IU/liter; median AST level, 500 IU/liter) were revealed with undetectable hepatitis A-E and non-hepatotropic virus in both sera and tissues. Weakness, jaundice, pale stools and splenomegaly were observed. Interestingly, two individuals had SARS-CoV-2 Omicron variants infection. Histologically, moderate or severe lobular necroinflammation, active interface hepatitis and portal inflammatory infiltrate with lymphocytic, plasma cells, neutrophils and eosinophilic cells were noted.
Conclusions: The exact aetiology of ASHep-UA was still unknown. By reporting the 3 probable cases, we expect to enrich the clinical experience in diagnosis and treatment of ASHep-UA as well as the pathological characteristics.

1. Introduction

As of November 2022, at least 1121 cases of ASHep-UA had been reported worldwide, including 27 (2.41%) deaths [1,2]. The cases are notified in 36 countries. The United Kingdom and the United States of America have the largest number of cases, with 280 and 358 respectively [1–4]. The case definitions used by different institutions 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 hepatitis A–E virus excluded, and liver enzymes (ALT and/or AST) > 500 IU/L in each case (Table 1) [1,5,6]. The most common clinical manifestations in patients were gastrointestinal symptoms, including vomiting, abdominal pain and diarrhea, while a proportion of cases had fever or respiratory symptoms. The cases were identified in different countries or different regions of the same country, without defined epidemiological association. The age of patients ranged from 1 month old to 16 years old. Majority (75.5%) of these patients were ≤five years old, especially in Europe [1].

Although multiple hypotheses had been proposed, the true aetiology of ASHep-UA remained unknown. The most commonly detectable pathogens were HAdV and SARS-CoV-2. HAdV was detected in 52% cases in Europe and 66% in the United Kingdom, whereas SARS-CoV-2 was positive in 10.2% patients according to the report from ECDC [1, 3]. Therefore, HAdV and SARS-CoV-2 were supposed to be the major causes of ASHep-UA. Other pathogens, such as AAV2, HHV-6, had been identified in the UK cases, suggesting the association between the two virus and ASHep-UA. In order to provide more information to enrich the clinical experience in diagnosis and treatment of ASHep-UA, we

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https://doi.org/10.1016/j.nmni.2023.101203
Received 18 August 2023; Received in revised form 13 November 2023; Accepted 22 November 2023
Available online 1 December 2023

Table 1
Case definitions used by different institutions.

Case definition	Description
Current WHO and ECDC case definition	
Confirmed	N/A at present
Probable/ Possible	A person presenting with an acute hepatitis (non-hepatitis viruses A–E) with serum aminotransferase >500 IU/L (AST or ALT), who is 16 years or younger, since 1 October 2021.
Epi-linked	A person presenting with an acute hepatitis (non-hepatitis viruses A–E) of any age who is a close-contact of a probable case, since 1 October 2021.
England, Wales, Northern Ireland case definitions	
Confirmed	A person presenting since 1 January 2022 with an acute hepatitis which is not due to hepatitis A-E viruses, or an expected presentation of metabolic, inherited, or genetic, congenital, or mechanical cause with serum transaminase greater than 500 IU/L (Aspartate Transaminase AST or Alanine Transaminase -ALT), who is 10 years old and under.
Probable/ Possible	A person presenting with an acute hepatitis since 1 January 2022 with an acute hepatitis which is not due to hepatitis A-E viruses or an expected presentation of metabolic, inherited or genetic, congenital or mechanical cause with serum transaminase greater than 500 IU/L (AST or ALT), who is 11–15 years old.
Epi-linked	A person presenting since 1 January 2022 with an acute hepatitis (non-hepatitis A to E) who is a close contact of a confirmed case.
Scotland case definition	
Confirmed	A person presenting with a serum transaminase greater than 500 IU/L (AST or ALT) without any known cause, who is 10 years of age and under or a contact of any age of a confirmed case, since 1 January 2022.

collected clinical data including serological parameters and liver biopsy specimens of 3 suspected cases, simultaneously carried out relevant study to analyze the clinical pathological characteristics.

2. Materials and methods

2.1. Patients

We conducted a retrospective study which consecutively enrolled 20 children with hepatitis of unknown cause, who were hospitalized in the Fifth Medical Center of the PLA General Hospital from November 18, 2019 to September 29, 2022. According to the criteria of WHO and the National Health Commission of China, the admission time of 13 patients was before January 1, 2022, so we excluded them. In addition, 4 patients were excluded due to lack of liver biopsy. Finally, 3 suspected cases were included.

2.2. Data and clinical specimen collection

Demographic, clinical, laboratory, and imaging data of 20 cases were extracted from electronic medical records. Clinical specimens, including serum samples and liver biopsy specimens, were obtained in accordance with the National Health Commission of China guidelines.

2.3. VNT for SARS-CoV-2 Omicron variants BA.1, BA.2 and BA.5

According to the Reed&Muench method, we performed the VNT assays to determine the neutralizing antibodies titre of SARS-CoV-2 Omicron variants BA.1, BA.2 and BA.5 by the Sinovac laboratory, China. The experimental procedure was divided into four parts: epithelial cell line VERO E6 culture; SARS-CoV-2 virus titration; viral growth in cell culture and micro-neutralization assay with subsequent cytopathic effect (CPE)-read out. The end-point titers were calculated according to the Reed & Muench method. Titer is considered effective greater than 1:48.

2.4. Diagnostic of hepatitis A-E viruses, CMV, EBV

The diagnostic of hepatitis A-E viruses and CMV, EBV was determined for patients at admission by clinical laboratory. We extracted relevant records.

2.5. Histological observation and IHC for non-hepatotropic virus

The liver biopsy specimens of patients were fixed with 4% neutral formaldehyde, embedded in paraffin, cut into 4 μm sections, dewaxed, and rehydrated by standard procedures. The slides were stained with H&E. IHC for CMV, HAdV, AAV2, HHV-6 were performed using automatic immunohistochemical staining instrument (UltraPATH ZSGB-BIO). The first antibodies were anti-Cytomegalovirus antibody [DDG9 & CCH2], prediluted (ab17073), anti-Adenovirus antibody [B025/AD51] (ab7428), at 1:500 dilution, anti-AAV VP1/VP2/VP3 rabbit polyclonal, OriGene, BP5024, 1:100, and mouse monoclonal [C3108-103] to HHV-6 respectively. The secondary antibodies (ZSGB-BIO, KIT-5030) were incubated for 15 min at room temperature. Then, wash the section with diaminobenzidine (DAB) (ZSGB-BIO, ZLI-9018), and then re-stain with hematoxylin. Finally, the pathologist read the results.

2.6. FISH for EBV detection

EBV was tested using EBER testing kit (ZSGB-BIO, ISH-7001). After the paraffin section was treated with gastric enzyme, 5 μL digoxin-labeled EBER probe was added and incubated overnight at 37 °C. Then added 30 μL of HRP-labeled anti-digoxin antibody and incubated at 37 °C for 30 min. Then, wash the section with DAB and re-stain with hematoxylin. Finally, the pathologist read the results.

3. Results

3.1. Case description

The twenty individuals were from different areas, and they were independent to one another. None of them shared exposures and connections with any ASHep-UA patients. The age ranges from 10 months old to 14 years old. The admission time of 13 patients was before January 1, 2022, and 4 patients did not undergo liver biopsy, so we excluded them. Finally, 3 suspected cases were included. Case 2 and 3 had a history of COVID-19. None of them had vaccination for SARS-CoV-2. The detailed information of the other 17 patients is shown in Table 2.

3.1.1. Case 1

Case 1 was a 11-year-old boy who was admitted due to abnormal liver function, presenting weakness and yellow urine. Transaminase elevated significantly (ALT peak level, 1100 IU/liter; AST peak level, 985 IU/liter). The levels of ALP and GGT were also abnormal, rising to 375 U/L and 68 U/L, respectively. The patient underwent infectious pathogen screening. There was no evidence of hepatitis A-E viruses by serology. He was positive for IgG of EBV, IgG and IgM of CMV by serology. In IHC, EBV, CMV, HAdV, AAV2, HHV-6 were all negative. Abdominal ultrasound indicates splenomegaly. He had a history of exposure to radioactive minerals, denied taking any medications. His admission date was January 8th, 2022, and eventually got better.

Liver biopsy showed moderate lobular inflammation with atypical fusion necrosis. A large number of apoptotic bodies formed. Moderate inflammation in the portal tracts with lymphocytic, plasma cells, neutrophils and eosinophils infiltrate were noted. There was also interface hepatitis and mixed inflammatory cell infiltration in hepatic sinuses. No virus inclusion body found (Fig. 1a).

3.1.2. Case 2

Case 2 was a 5-year-old boy who was hospitalized on March 2, 2022 due to jaundice. The biochemical tests showed exceptionally high levels

Table 2
Demographic and Clinical Characteristics of 17 cases.

Variable	All Children (N = 17)	Normal Range
Median age (range) -yr	4.96 (0.83–14)	
Sex-no. (%)		
Female	6	
Male	11	
Fever	7	
Weakness	4	
Abdominal pain	3	
Diarrhea	1	
Vomit	2	
Jaundice	9	
Poor appetite	5	
Pale stools	2	
Hepatomegaly	4	
splenomegaly	3	
Median ALT level (range)-U/L		
Initial value	853 (100–3545.3)	0–40
Peak	1377 (533.7–4392)	0–40
Median AST level (range)-U/L		
Initial value	1137.2 (63–2196.8)	10–40
Peak	1438.5 (463–4365)	10–40
Median TBIL level (range)-μmol/L	123.5 (3.11–269)	5.1–19
Median DBIL level (range)-μmol/L	38.8 (1.4–352.7)	0–5.1
INR	1.13 (0.94–2.13)	1.0 ± 0.1
Median ALP level (range)-U/L	307 (155–550)	40–150
Median GGT level (range)-U/L	87 (14–302)	0–40
Median ALB level (range)-g/L	42 (31–61.6)	35–51
Median PT (range)-sec	12.6 (10.8–24)	12–16
Median PTA level (range)-%	72.3 (56.9–104.8)	75–100
Median blood ammonia level (range)-μmol/L	16.6 (13.4–19.8)	22–45
Median NEUT level (range)- %	56.5 (7.5–83.5)	50–70
Median Eosinophil level (range)- %	1.9 (0.1–6.8)	0.5–5
Median Lymph level (range)- %	29.9 (5.7–72.1)	20–40

ALT: alanine aminotransferase, AST: aspartate aminotransferase, TBIL: total bilirubin, DBIL: direct bilirubin, ALP: alkaline phosphatase, GGT: γ-glutamyl transpeptidase, ALB: albumin; PT: prothrombin time; PTA: prothrombin activity, NEUT: neutrophil, Eosinophil, acidophilicgranulocyte, Lymph: lymphocyte.

of transaminase (ALT level, 1400 IU/liter, AST level, 500 IU/liter), and total bilirubin (TB 296.1 μmol/L]. ALP and GGT levels increased to 314 U/L and 73 U/L. Children's Gan Mao Qing Re Granule, children's paracetamol sulfonamide, belladonna tablets, and micronomicin were used 7 days before onset. Clinical symptoms including weakness and pale stools were found. Hepatitis A-E virus, EBV and CMV were all negative by serology. But he was positive for IgG of chlamydia pneumoniae. VNT test results showed that the neutralizing antibody titer of case 2 was 1:96. EBV, CMV, HAdV, AAV2, HHV-6 were all negative by IHC. He met criteria for pediatric acute liver failure and got better at discharge.

Liver biopsy showed severe lobular inflammation with fusion necrosis. The hepatocytes showed balloon-like changes and apoptotic bodies formed. Other pathological manifestations include severe portal area inflammation and mixed inflammatory cell infiltration, mainly including lymphocytic, plasma cells, macrophage, neutrophils, and eosinophils. There was also interface hepatitis, cholestasis and mixed inflammatory cell infiltration in hepatic sinuses. No virus inclusion body found (Fig. 1b).

3.1.3. Case 3

Case 3 was a 5-year-old boy presenting with jaundice. Transaminase elevated significantly (ALT level, 590 IU/liter; AST level, 410 IU/liter). The levels of ALP and GGT were also abnormal, rising to 344 U/L and 44 U/L. Hepatitis A-E virus were negative by serology. He was positive for IgG of EBV, CMV by serology. IgG of herpes simplex virus was also positive. VNT test results showed that the neutralizing antibody titer was 1:48. EBV, CMV, HAdV, AAV2, HHV-6 were all negative by IHC. His was admission on September 4th, 2022, and got better at discharge.

Liver biopsy showed mild lobular and portal tracts inflammation. Apoptotic bodies were formed. There was no cholestasis, centrilobular necrosis, or interface hepatitis (Fig. 1c).

In summary, histological features of highly active lobular and portal/paraportal necroinflammation and vasculitis strongly suggested that ASHep-UA was an unknown pathogen mediated immunopathological liver injury. None had viral inclusions and immunohistochemical testing for CMV, EBV, HAdV, AAV2 and HHV-6 was negative in all patients.

4. Discussion

Currently, the real cause and underlying mechanism of ASHep-UA are still undetermined. The most plausible hypotheses include: (1) Common adenovirus infection; (2) A new variant of adenovirus; (3) A syndrome after SARS-CoV-2 infection; (4) Exposure to specific drugs, poisons or environment; (5) New pathogens infection; (6) A new variant of SARS-CoV-2 [7–9].

ASHep-UA occurred during the prevalence of the Omicron variant during the COVID-19 epidemic. In our study, the neutralizing antibody for SARS-CoV-2 was detected in case 2 and case 3. The antibody titer is 1:96, 1:48, respectively. They have no history of vaccination. We suspected that acute hepatitis might follow with immune disorder and storm of inflammatory factors after SARS-CoV-2 infection. Brodin et al. [10] assumed that the occurrence of ASHep-UA may be related to the super antigenicity caused by COVID-19. Studies have proved that children with SARS-CoV-2 infection can lead to the persistent presence of COVID-19 in the gastrointestinal tract, inducing repeated release of viral proteins in intestinal epithelial cells, thus result in immune activation,

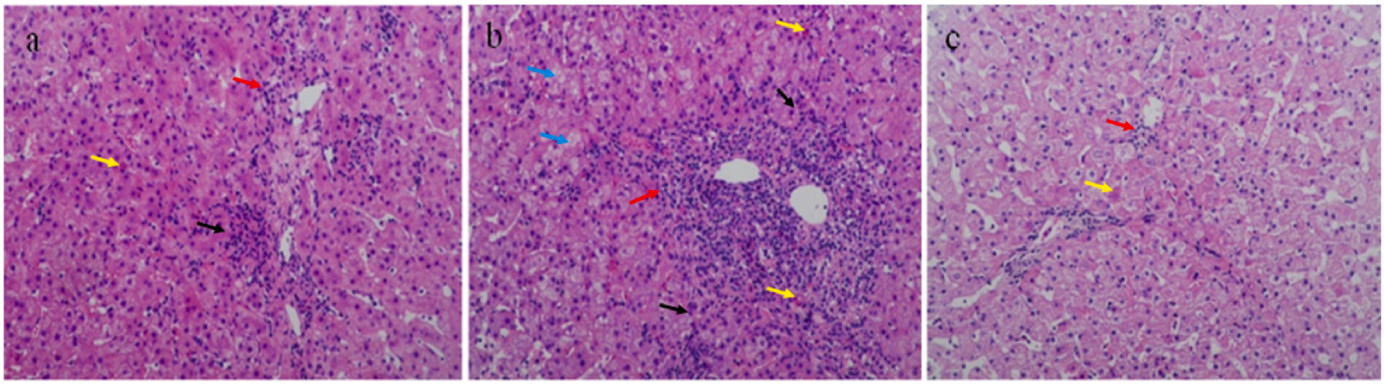

Fig. 1. a (case1), b (case2), c (case3): Histological characteristics of liver biopsy specimens 20x HE: Black Arrow: interface hepatitis, Blue Arrow: feathering (ballooning) change of hepatocytes, Yellow arrow: apoptotic hepatocytes, Red arrow: inflammatory cell infiltration. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

which may be mediated by the superantigen motif in the spike protein of COVID-19 [10–12]. ASHep-UA may be caused by the presence of a virus pool in the intestinal tract after infection with COVID-19. When infected with other virus, antibodies titres would rise. Among the three cases, two children had a history of COVID-19. They are probably caused by the existence of the virus pool after infection with SARS-CoV-2 and then infected with other virus. Unfortunately, we have no evidence of HAdV and other viruses in blood samples, nor did IHC. The laboratory test of autoimmune hepatitis-related antibodies such as ANA, SSA, AMA M2, and ss-DNA, were also negative. Another possible explanation is SARS-CoV-2 might be a co-factor contributing to abnormal susceptibility or host response, for instance, because of the lockdown restrictions during the COVID-19 pandemic, the children lack exposure to pathogens causing immunocompromised. Once they expose to the environment again and fall ill [13–15]. Overall, it remains controversial whether childhood hepatitis results from SARS-CoV-2.

IgG of EBV and CMV were positive for two cases in our analysis. EBV and CMV infections are common and associated with a variety of liver manifestations. Immunocompetent hosts commonly manifest as acute hepatitis, with severity varying from asymptomatic, self-limited icteric hepatitis to acute liver failure [16]. In accordance with our laboratory tests, both case 1 and case 3 has prior EBV and CMV infection, meanwhile case 1 is recently infected by CMV. However, it is negative in the liver biopsies, providing evidence against EBV or CMV-driven hepatitis. Histopathology from the 3 patients demonstrated various degrees of portal and lobular hepatitis characterized by mixed inflammation, consisting of lymphocytes, plasma cells, macrophage and neutrophils, with no viral inclusions, no immunohistochemical evidence for EBV and CMV. Therefore, whether there is any effect on ASHep-UA remains to need further investigations.

Additionally, HAdV infection is now the most likely potential cause in cases of ASHep-UA and the typing results are mostly HAdV-F41 [17]. Two independent studies [18,19] on ASHep-UA in the UK detected AAV2 in cases, which can only replicate in the presence of other viruses. These findings suggest that HAdV or HHV-6 might be a help factor of AAV2 leading to liver injury through an unknown immune mechanism. Adenovirus is a non-enveloped double stranded DNA virus with a diameter of 90 nm [20–22]. There are at least 100 types (serotype 1–52 and genotype 53–103), and divided into 7 subgroups (Ä G) [23]. Of which, HAdV-F41 commonly presents as diarrhea, vomiting and fever, whereas in some cases there is accompaniment by respiratory symptoms [24]. But fever symptoms were not common in children with ASHep-UA this time. The clinicopathological analysis of 12 cases of adenovirus hepatitis showed that the pathological features of the liver were punctate or massive coagulative necrosis of hepatocytes with characteristic inclusion bodies of hepatocytes, and most of them had no inflammation or only slight lymphocytic inflammatory infiltration [22]. However, we and other studies have not detected the virus through IHC and PCR or detected viral inclusion bodies under microscopy. AAVs are small, single-stranded DNA parvoviruses that are considered non-pathogenic in humans [25]. AAV2 is a common virus that infects almost everyone in early childhood [17,18]. Servellita V detected AAV2 sequences in 93% (13 of 14) cases, compared to 4 (3.5%) of 113 controls and to 0 of 30 patients with hepatitis of defined aetiology. HHV-6 were detected from blood in 7 (50%) of 14 cases and versus 1 (0.88%) of 113 controls [17]. To sum up, these findings suggest a significant association between co-infection of AAV2 with other pathogens such as HAdV, and the clinical manifestations of ASHep-UA, although a direct causal relationship has not been demonstrated.

Except for the above-mentioned virals infection, other infectious causes, such as bacterial and/or fungal infection, and non-infectious factors including unknown toxins, food, drugs, or environmental exposures cannot be ignored. In this study, Streptococcus A/Neisseria was detected in case 2, and case 1 has a history of exposure to radioactive minerals. This may be the cause of ASHep-UA, but there is no sufficient evidence, which is a limitation of this study, and more investigations need to be continued.

5. Conclusion

ASHep-UA is acute clinically, and a few cases can develop into acute liver failure. The main clinical manifestations are significant elevation of transaminase (ALT or AST>500U/L), often accompanied by jaundice, and liver enlargement. Pathogens including HAdV, HAdV-F41, AAV2 and HHV-6 were detected in liver histology and hematology of some cases, but the exact aetiology of ASHep-UA was unknown. Pathological assessment of 3 suspected ASHep-UA cases in our study showed necrosis of hepatocytes in different degrees, but it lacked characteristic pathological changes. In general, health administrative departments and medical institutions in all regions should carry out the monitoring of ASHep-UA, so as to timely grasp the epidemic development trend of ASHep-UA, identify pathogens, and timely develop corresponding detection technologies.

Funding

The work was supported by a grant from Beijing Natural Science Foundation-Haidian Primitive Innovation Joint Fund (No. L202025 to JM Zhao).

Authors' contributions

Substantial contributions to conception and design (Jingmin Zhao), acquisition of data (Min Zhang, Meiling Li), analysis and interpretation of data (Meiling Li, Lina Jiang, Shuhong Liu, Chaonan Guo, Li Zhu, Bokang Zhao, Yisi Liu);Drafting the article or revising it critically for important intellectual content (Meiling Li, Lina Jiang, Jingmin Zhao); Final approval of the version to be published (Jingmin Zhao). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethics approval

I promise that the study was performed according to the international, national and institutional rules considering clinical studies. This study was approved by Research Ethics Boards at the Fifth Medical Center of Chinese PLA General Hospital. Written informed consent was obtained.

Declaration of competing interest

The authors declare no conflicts of interest, financial or otherwise to this work.

Acknowledgments

The authors express their gratitude to the help of Sinovac laboratory and clinical laboratory of the Fifth Medical Center of Chinese PLA General Hospital.

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