



REVIEW ARTICLE

Current knowledge about the outbreak of acute severe hepatitis of unknown origin among children

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Abstract

Background and Aim: A recent outbreak of acute severe hepatitis of unknown etiology (ASHeP-UA) among children 16 years old and younger has aroused global concern. Initially reported in central Scotland, the disease has been notified in 35 countries and linked to 22 deaths as of 25 September 2022. This review aimed to provide current knowledge about the outbreak of ASHeP-UA.

Methods and Results: The websites of the World Health Organization, the UK Health Security Agency, the European Center for Disease Prevention and Control, the Centers for Disease Control and Prevention, and the PubMed database were searched, based on the search term “acute severe hepatitis of unknown etiology.” The corresponding reports or literature previously released by the mentioned websites and database were integrated to obtain current information about ASHeP-UA.

Conclusion: Even though the potential relevance between ASHeP-UA and adenovirus, adeno-associated virus 2, and human herpes viruses was revealed, the etiology of ASHeP-UA is still unknown. More effort should be made to explore whether ASHeP-UA is caused by a novel virus or other environmental factors, to generate appropriate treatment strategies.

Relevance to Patients: ASHeP-UA has aroused global concern recently, which may lead to adverse outcomes such as liver transplants and death. The present review shares current development and information about the outbreak of acute severe hepatitis of unknown origin among children.

1. Introduction

On April 5, 2022, ten cases of acute severe hepatitis of unknown etiology (ASHeP-UA) were reported in children from 11 months to 5 years old in central Scotland. Symptoms included abdominal pain, diarrhea, jaundice, and vomiting, independently of the time of onset [1]. As of September 25, 2022, 1063 probable cases around the world have been notified, and the rapid increase has caught the attention of the World Health Organization (WHO), the European Center for Disease Prevention and Control and the United Kingdom Health Security Agency [2-4]. To help identify the causes of the disease, these organizations have called on health authorities to report cases and provide as detailed clinical and laboratory data as possible.

2. Methods

The related reports or literature were searched on the websites of the WHO (<https://www.who.int/>), the UK Health Security Agency (<https://www.gov.uk/government/organisations/>

uk-health-security-agency), the European Center for Disease Prevention and Control (<https://www.ecdc.europa.eu/en>), the Centers for Disease Control and Prevention (<https://www.cdc.gov/>), and the PubMed database (<https://pubmed.ncbi.nlm.nih.gov/advanced/>), based on the search terms “acute severe hepatitis of unknown etiology”. Due to the limited number of corresponding reports and literature, we integrated the information without setting any exclusion criteria.

3. Results

3.1. Geographic distribution of cases and deaths

As of September 25, 2022, 1063 probable cases of ASHep-UA have been notified in 35 countries [2-4]: Argentina (three cases), Austria (6), Belgium (14), Brazil (2), Bulgaria (1), Canada (21), Colombia (2), Costa Rica (3), Cyprus (2), Denmark (8), France (9), Greece (12), Ireland (26), Israel (5), Italy (36), Indonesia (18), Japan (67), Latvia (1), Luxembourg (1), Netherlands (15), Norway (6), Mexico (69), Maldives occupied (1), Republic of Moldova (1), Poland (18), Portugal (20), Panama (1), Palestinian territories (1), Qatar (1), Serbia (1), Spain (46), Sweden (12), Singapore (3), the United Kingdom (UK) (273), and the United States of America (358) (Figure 1). At least, 46 cases require liver transplants. Twenty-two deaths have been attributed to ASHep-UA: Americas (13 deaths), Eastern Mediterranean (1), Europe (2), and Southeast-Asia (6). The numbers of new cases and deaths are expected to increase.

3.2. Definition of ASHep-UA

The European Center for Disease Prevention and Control has released a reporting protocol for surveillance of ASHep-UA [5]. The UK and Scotland have harmonized their definition of ASHep-UA to facilitate clinical reporting [6] (Table 1).

3.3. Clinical presentation of ASHep-UA

Among the 195 confirmed and possible cases of ASHep-UA in England as of July 4, 2022, all were previously healthy children who presented most often with jaundice (69.2%), vomiting (57.9%), lethargy (47.7%), pale stool (40.5%), diarrhea (41.5%), abdominal pain (38.5%), and nausea (26.2%). Less frequent symptoms were fever (23.1%) and respiratory symptoms (17.9%) [6].

Cases in Scotland have not presented with fever, but have otherwise been similar to the cases in England, including signs of severe acute hepatitis, including jaundice and serum levels of aspartate transaminase or alanine transaminase > 500 IU/L [6,7].

A certain number of cases with elevated ammonia, lactate, and international normalized ratio were admitted to pediatric intensive care unit due to hepatic encephalopathy. All cases survived after receiving proper neuroprotected treatment and/or liver transplantation [8].

3.4. Microbiological analyses of ASHep-UA

Blood, throat swabs, stool, rectal swabs, and urine have been tested for adenovirus (AdV), cytomegalovirus, Epstein–Barr virus,

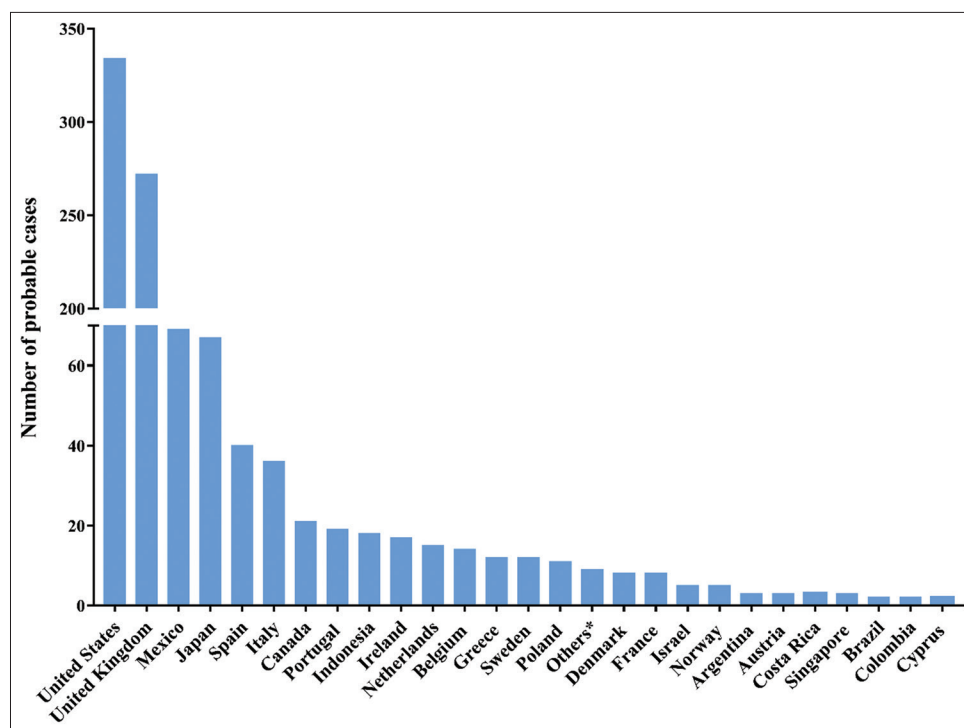


Figure 1. Number of identified cases of acute severe hepatitis of unknown etiology by country as of 25 September 2022. Data taken from [2-4].

*Nine countries with only one probable case including: Bulgaria, Latvia, Luxembourg, Maldives, Republic of Moldova, Occupied Palestinian Territories, Panama, Qatar and Serbia.

Table 1. Definitions of acute severe hepatitis of unknown etiology (ASHeP-UA) agreed by the European Center for Disease Prevention and Control, or by the health authorities of England, Wales, Northern Ireland and Scotland.

European Center for Disease Prevention and Control (as of May 6, 2022)	
Classification	Description
Confirmed	Not applicable
Probable	Individual 16 years old or younger who presents with acute hepatitis (non-hepatitis A-E) and serum transaminase (AST or ALT) > 500 IU/L after 1 October 2021
Epi-linked	Individual of any age who had close contact with a confirmed case and who presents with acute hepatitis (non-hepatitis A-E) after 1 October 2021
Health authorities of England, Wales, and Northern Ireland (as of May 19, 2022)	
Confirmed	Individual 10 years old and younger who presents with acute hepatitis (non-hepatitis A-E) and serum transaminase (AST or ALT) > 500 IU/L after January 1, 2022
Possible	Individual 11 – 15 years old who presents with acute hepatitis (non-hepatitis A-E) and serum transaminase (AST or ALT) > 500 IU/L after January 1, 2022
Epi-linked	Individual of any age who had close contact with a confirmed case and who presents with acute hepatitis (non-hepatitis A-E) after January 1, 2022
Health authority of Scotland (as of May 19, 2022)	
Confirmed	Individual who is 10 years old and younger or who had close contact to a confirmed case and who presents with serum transaminase (AST or ALT) > 500 IU/L in the absence of infection with hepatitis viruses A-E, cytomegalovirus or Epstein-Barr virus after January 1, 2022

ALT, alanine transaminase; AST, aspartate transaminase.

enterovirus, herpes simplex virus, hepatitis viruses A-E, human herpes viruses 6 and 7 (HHV-6,7), influenza virus, norovirus, sapovirus, SARS-CoV-2, and *Salmonella* [9]. Among 452 cases of ASHeP-UA tested for AdV, 209 were positive (by PCR), of which 31 are type 41F [2]. In the WHO European Region, AdV was detected more often in blood or serum than in stool or respiratory samples [3].

Seventy-eight of 612 cases were positive for SARS-CoV-2 (by PCR) [2]. The previous report showed that eight cases in England showed coinfection with SARS-CoV-2 and AdV [6]. Although a Japanese study suggested a link between the “Omicron” variant of SARS-CoV-2 and ASHeP-UA, United Kingdom Health Security Agency indicated that there was no statistical significance on previous positive rate for SARS-CoV-2 testing between cases and random age-weighted children [6,10].

Other reported pathogens in cases of ASHeP-UA include cytomegalovirus, Epstein-Barr virus, herpes simplex virus, respiratory syncytial virus, parvovirus, influenza virus, HHV-6, 7, mycoplasma, varicella, enterovirus, parainfluenza, and bocavirus [3].

3.5. Metagenomic sequencing of ASHeP-UA

Metagenomic sequencing allows for the identification of viruses that cannot be detected by traditional diagnostic techniques (culture, serology test, and PCR) [11]. An investigation

of University College London (UCL) and Great Ormond Street Hospital demonstrated that adeno-associated virus 2 (AAV2) was detected in liver and blood samples of five ASHeP-UA cases who underwent liver transplantation through metagenomics sequencing. Helper viruses of AAV2 and HHV-6 were detected in liver samples but at lower levels, while AdV was detected in only one blood sample [12]. The presence of AAV2 in serum, liver biopsies, fecal, rectal, and throat swab samples of ASHeP-UA cases detected by metagenomic sequencing was proved in the study of University of Glasgow Center for Virus Research [13]. Consistent with the results of UCL study, AdV and HHV-6 were detected at lower levels. High viral titers of AAV2 in liver or plasma samples of ASHeP-UA cases were confirmed by PCR. Moreover, comparisons between ASHeP-UA cases and control subjects showed that there were significantly higher AAV2 levels (detected by PCR) in cases. However, the cycle threshold values of AdV and HHV-6 were not significantly different between cases and controls [12,13].

3.6. Epidemiology of ASHeP-UA

Previously, healthy children were most under 6 years old, and females made up more than half of cases [2]. A detailed survey of the cases in England failed to identify common features, such as exposure to medicines or toxins, family structure, parental occupation, diet, or water source. Among 92 cases who received questionnaires, 64 (70%) reported contact with pet dogs; however, cases with or without dog contact did not differ in the patterns of illness or presence of viruses [14]. As of Scotland, there are two pairs of epidemiologically linked cases [7].

Analysis of the cases in England and Scotland failed to reveal an association between immune suppression and ASHeP-UA [7,9].

3.7. Toxicology of ASHeP-UA

No obvious pattern of toxin exposure has been linked to ASHeP-UA. Detailed toxicological investigations for organic compounds and metals are being conducted in the UK, but so far no clear associations with ASHeP-UA have emerged, including paracetamol, fluconazole or mycotoxins [14]. Even increased levels of metals were detected in blood and urine, they are not likely to be causative [6].

3.8. Guidance on diagnosing ASHeP-UA

On May 25, 2022, the European Center for Disease Prevention and Control published guidance on testing suspected cases of ASHeP-UA [15]. These guidelines call for detection and typing of both AdV and SARS-CoV-2, while recommending whole-genome sequencing of AdV (Table 2). The guidance also recommends investigating potential links between the disease and liver-damaging drugs such as acetaminophen, antimicrobials, non-steroidal anti-inflammatory drugs, and valproic acid. It recommends metagenomic analysis to detect known and novel pathogens.

Table 2. Approach for testing suspected cases of acute severe hepatitis of unknown etiology (ASHep-UA), as recommended by the European Center for Disease Prevention and Control (as of May 25, 2022).

Sample type	Test type	Pathogen
Blood (whole and plasma)	Serology	Hepatitis viruses A/B/C/D ¹ /E, CMV, EBV, Varicella, HIV, SARS-CoV-2 (if possible, IgG and IgM against S and N proteins)
	Serology	<i>Brucella spp</i> , <i>Bartonella henselae</i> , <i>Borrelia burgdorferi</i> (if epidemiologically appropriate), leptospira (if relevant clinical history)
	Culture	Routine procedures for bacteria/fungi (if clinically indicated, e.g., fever)
	Culture ²	Adenovirus, CMV, EBV, HSV, influenza virus
	PCR	Adenovirus ³ , enteroviruses, CMV, EBV, HSV, HHV 6/7, parechovirus, parvovirus B19, hepatitis viruses A/C/E, leptospira (if relevant clinical history)
Oro/Nasopharyngeal swab	PCR	Respiratory virus screening (including but not limited to influenza virus, adenovirus, parainfluenza virus, rhinovirus, respiratory syncytial virus, human bocavirus 1-3, SARS-CoV-2, enteroviruses, human metapneumovirus, parechovirus, human coronaviruses)
	Culture	<i>Streptococcus</i> group A
Stool or rectal swab	PCR	Enteric virus screening (including but not limited to adenovirus, norovirus, enteroviruses, rotavirus, astrovirus, sapovirus, SARS-CoV-2)
	PCR	Enteric bacterial pathogens (if a screening panel is used, <i>Salmonella</i> spp. should be included)
	Culture	<i>Campylobacter</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>E. coli</i> 0157
	Culture ²	Adenovirus, enteroviruses, rotavirus
Urine	PCR	Leptospira (if relevant clinical history), adenovirus
	Culture	Routine procedures for bacterial pathogens (if clinically indicated)

CMV: Cytomegalovirus, EBV: Epstein-barr virus, HHV: Human herpes virus, HIV: Human immunodeficiency virus, HSV: Herpes simplex virus.

¹Samples should be tested for hepatitis D virus only when HBV is present.

²Should be performed in laboratories experienced in cell culture.

³Whole blood is preferred to plasma. If quantitative assays for adenovirus are unavailable, quantification should be conducted using cycle threshold values as a proxy for viral load.

3.9. Possible causes of ASHep-UA

Several possible causes of ASHep-UA have been proposed [14]. One is weak immune response to AdV infection that allows the normally mild disease course to develop into severe ASHep-UA. Possible factors contributing to this weak response include reduced natural exposure as a result of lockdowns, coinfection with SARS-CoV-2 or other pathogens, or the contribution of toxins, drugs or other factors in the environment.

Other possible causes of ASHep-UA include a novel variant AdV or hepatitis virus other than A-E, a new variant of SARS-CoV-2, or a drug, toxin or factor in the environment acting independently/cooperatively.

3.10. Prospects for explaining the causes of ASHep-UA

Even a report from Alabama demonstrated that there is no immunohistochemical evidence of AdV, or no viral particles

identified by microscopy in six cases of ASHep-UA, AdV continues to be the most frequently detected pathogen, highlighting the need to investigate further possible links [2,16]. More than 100 subtypes of human AdV have been described, which target different tissues and trigger different clinical manifestations [17-19]. Known subtypes do not typically cause hepatic injury, and cases of AdV-associated liver injury usually involve immunoparesis caused by chemotherapy, infection with human immunodeficiency virus, or transplantation [20]. Therefore, whole-genome sequencing of AdV in individuals with ASHep-UA is important to detect potentially novel adenovirus subtypes. The study of UCL identified partial sequences as AdV-F41 (without whole genomes as a result of high CT values), and the study fails to find any new or specific amino acid substitutions related to the replication of AAV2 [12].

A potential association between SARS-CoV-2 and ASHep-UA should continue to be explored. The spike protein of SARS-CoV-2 possesses a superantigen motif similar to that of *Staphylococcus* enterotoxin B, which activates T-cells strongly and non-specifically. Persistence of SARS-CoV-2 in the gastrointestinal tract may lead to immune activation that induces multisystem inflammatory syndrome in children [21]. AdV infection sensitizes *Staphylococcus* enterotoxin B-mediated toxic shock in mice, leading to liver failure and death [22]. Superantigen of SARS-CoV-2-mediated immune activation should be investigated in cases with coinfection (SARS-CoV-2 and AdV). Moreover, some adults developed autoimmune hepatitis after vaccination against SARS-CoV-2 [23]. Whether such sensitization also occurs in children is unclear.

AAV2 belongs to the Parvoviridae family, whose replication relies on the coinfection with AdV or herpesvirus [24]. Considering the high abundance of AAV2 (detected by metagenomic sequencing and PCR), hypotheses had been proposed, which suggested that AAV2 may be involved in the pathology of ASHep-UA, following transmission or reactivation through coinfection with AdV and/or HHV-6 [13]. However, AAV2 proteins were not detected by immunohistochemistry or proteomics, and viral particles were not identified on electron microscopy [12]. Even though the levels of AAV2 in the controls with AdV viremia and hepatitis are still lower than in ASHep-UA cases, the relatively higher levels when compared with other controls may highlight the specific role of AAV2 in AdV hepatitis [12]. The HLA-DRB1*04:01 allele was found to be presented in the ASHep-UA cases, making the possibility that AdV infection and/or coinfection or reactivation of AAV2 results in more severe clinical outcomes of susceptible children than expected [13]. Further studies are needed to clarify the association between AAV2 and ASHep-UA, and its potential values as the biomarker for ASHep-UA.

4. Conclusion

Due to the unknown etiology of ASHep-UA, the WHO only advises implementation of general infection prevention and control practices [2]. Some treatment strategies have been proposed by clinicians, but only emphasize on symptomatic and supportive therapy, including management of coagulation disorders and

hepatic encephalopathy, and liver transplantation [25]. Further studies should also explore whether ASHep-UA is caused by a novel hepatitis virus or other environmental factors. Identifying the causes of this disease may facilitate the choice of the most effective treatment.

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Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

References

- [1] World Health Organization. Acute Hepatitis of Unknown Aetiology-The United Kingdom of Great Britain and Northern Ireland. Geneva: World Health Organization; 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> [Last accessed on 2022 Jul 19].
- [2] World Health Organization. Disease Outbreak News; Acute Hepatitis of Unknown Aetiology in Children-Multi-Country. Available from: <https://www.who.int/emergencies/disease-outbreak-news/item/2022-Don400> [Last accessed on 2022 Sep 25].
- [3] European Centre for Disease Prevention and Control. Joint ECDC-Who Regional Office for Europe Hepatitis of Unknown Origin in Children Surveillance Bulletin, 26 August, 2022. Available from: <https://cdn.ecdc.europa.eu/novhep-surveillance> [Last accessed on 2022 Sep 25].
- [4] Centers for Disease Control. Technical Report: Acute Hepatitis of Unknown Cause. Available from: <https://www.cdc.gov/ncird/investigation/Hepatitis-Unknown-Cause/Technical-Report.html> [Last accessed on 2022 Sep 25].
- [5] European Centre for Disease Prevention and Control. Hepatitis of Unknown Origin Reporting Protocol 2022 Version 2.1. Stockholm: ECDC; 2022. Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/Hepatitis-of-Unknown-Origin-Reporting-Protocol-V2.1.pdf> [Last accessed on 2022 Jul 19].
- [6] UK Health Security Agency. Investigation into Acute Hepatitis of Unknown Aetiology in Children in England. London: UKHSA; 2022. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1094573/Acute-Hepatitis-Technical-Briefing-4.pdf [Last accessed on 2022 Sep 25].
- [7] 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.
- [8] Deep A, Grammatikopoulos T, Heaton N, Verma A, Dhawan A. Outbreak of Hepatitis in Children: Clinical Course of Children with Acute Liver Failure Admitted to the Intensive Care Unit. *Intensive Care Med* 2022;48:958-62.
- [9] UK Health Security Agency. Increase in Acute Hepatitis Cases of Unknown Aetiology in Children. London: UKHSA; 2022. Available from: <https://www.gov.uk/Government/Publications/Hepatitis-Increase-in-Acute-Cases-of-Unknown-Aetiology-in-Children/Increase-in-Acute-Hepatitis-Cases-of-Unknown-Aetiology-in-Children> [Last accessed on 2022 Jul 19].
- [10] Nishiura H, Jung SM, Hayashi K. High Population Burden of Omicron Variant (B.1.1.529) is Associated with the Emergence of Severe Hepatitis of Unknown Etiology in Children. *Int J Infect Dis* 2022;122:30-2.
- [11] Chiu CY, Miller SA. Clinical Metagenomics. *Nat Rev Genet* 2019;20:341-55.
- [12] Morfopoulou S, Buddle S, Montaguth OE, Atkinson L, Guerra-Assunção JA, Storey N, et al. Genomic Investigations of Acute Hepatitis of Unknown Aetiology in Children. *medRxiv* 2022;2022.2007.2028.22277963.
- [13] Ho A, Orton R, Tayler R, Asamaphan P, Tong L, Smollett K, et al. Adeno-Associated Virus 2 Infection in Children with Non-A-E Hepatitis. *medRxiv* 2022;2022.2007.2019.22277425.
- [14] UK Health Security Agency. Investigation into Acute Hepatitis of Unknown Aetiology in Children in England. London: UKHSA; 2022. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1077027/Acute-Hepatitis-Technical-Briefing_3.pdf [Last accessed on 2022 Jul 19].
- [15] Guidance for Diagnostic Testing of Cases with Severe Acute Hepatitis of Unknown Aetiology in Children. Stockholm: ECDC; 2022. Available from: https://www.ecdc.europa.eu/Sites/Default/Files/Documents/Guidance_Testing_Hepatitis_Final.pdf [Last accessed on 2022 Jul 19].
- [16] Baker JM, Buchfellner M, Britt W, Sanchez V, Potter JL, Ingram LA, et al. Acute Hepatitis and Adenovirus Infection among Children-Alabama, October 2021-February 2022. *Am J Transplant* 2022;22:1919-21.
- [17] Bányai K, Martella V, Meleg E, Kisfali P, Péterfi Z, Benkő M, et al. Searching for HADV-52, the Putative Gastroenteritis-Associated Human Adenovirus Serotype in Southern Hungary. *New Microbiol* 2009;32:185-8.
- [18] Yang C, Zhu C, Qian Y, Deng J, Zhang B, Zhu R, et al. Application of Human Adenovirus Genotyping by Phylogenetic Analysis in an Outbreak to Identify Nosocomial Infection. *Virol Sin* 2021;36:393-401.
- [19] Lynch JP 3rd, Kajon AE. Adenovirus: Epidemiology, Global Spread of Novel Serotypes, and Advances in Treatment

- and Prevention. *Semin Respir Crit Care Med* 2016;37:586-602.
- [20] Zheng N, Wang Y, Rong H, Wang K, Huang X. Human Adenovirus Associated Hepatic Injury. *Front Public Health* 2022;10:878161.
- [21] Yonker LM, Gilboa T, Ogata AF, Senussi Y, Lazarovits R, Boribong BP, *et al.* Multisystem Inflammatory Syndrome in Children is Driven by Zonulin-Dependent Loss of Gut Mucosal Barrier. *J Clin Invest* 2021;131:e149633.
- [22] Brodin P, Arditi M. Severe Acute Hepatitis in Children: Investigate Sars-Cov-2 Superantigens. *Lancet Gastroenterol Hepatol* 2022;7:594-5.
- [23] Avci E, Abasiyanik F. Autoimmune Hepatitis after Sars-Cov-2 Vaccine: New-onset or Flare-up? *J Autoimmun* 2021;125:102745.
- [24] Meier AF, Fraefel C, Seyffert M. The Interplay between Adeno-Associated Virus and Its Helper Viruses. *Viruses* 2020;12:662.
- [25] Chen YH, Lou JG, Yang ZH, Chen QJ, Hua CZ, Ye S, *et al.* Diagnosis, Treatment, and Prevention of Severe Acute Hepatitis of Unknown Etiology in Children. *World J Pediatr* 2022;18:538-44.