



Acute Serious Hepatitis of Unknown Cause in Children

Çocuklarda Görülen Nedeni Bilinmeyen Akut Ciddi Hepatit

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ABSTRACT

On April 5, 2022, an increase in cases of acute hepatitis of unknown etiology was reported in previously healthy children under the age of 10 in the United Kingdom. Since there is no link between these patients, called acute non-HepA-E hepatitis, and viral hepatitis agents (hepatitis A, B, C, D, and E), the possible etiology, and pathogenesis of this emergency is being investigated. One of the alarming features of this epidemic is the high requirement for liver transplantation in a fraction of the cases. In cases other than hepatitis A, B, C, D, and E, a case definition is made by looking at a series of clinical pictures, including serum transaminase levels and age. As of August 26, 2022, 513 cases of acute hepatitis have been reported in Europe and 1,010 globally. Adenovirus was detected in 75% of cases tested in the UK, but data for other countries are still lacking. The role of other etiologic agents is still under investigation. The exact disease pathogenesis has not yet clear. Evidence of human-to-human transmission of the disease remains unclear. Epidemiological studies are critical in clarifying the uncertainties regarding the existence of links between the cases reported to date. Continuing the national and international surveillance activities of the countries in an organized manner is the most basic issue required for the elimination of the epidemic.

Keywords: Acute non-HepA-E hepatitis, children, unknown hepatitis, hepatitis epidemic

ÖZ

Birleşik Krallık tarafından 5 Nisan 2022'de önceden sağlıklı olan 10 yaşın altındaki çocuklarda etiyolojisi bilinmeyen akut hepatit olgularında artış bildirilmiştir. Akut HepA-E dışı hepatit olarak adlandırılan bu hastalık ile viral hepatit ajanları (hepatit A, B, C, D ve E) arasında bir bağlantı bulunmadığından, bu acil durumun olası etiyolojisi ve patogenezi araştırılmaktadır. Bu salgının endişe verici özelliklerinden biri, olguların bir kısmının karaciğer nakline ihtiyaç duymasıdır. Hepatit A, B, C, D ve E dışındaki olgularda serum transaminaz düzeyleri ve yaş gibi bir dizi klinik tabloya bakılarak olgu tanımı yapılmaktadır. Avrupa'da 513 ve dünya çapında 1.010 akut hepatit olgusu 26 Ağustos 2022 itibarıyla rapor edilmiştir. Birleşik Krallık'ta test edilen olguların %75'inde adenovirüs tespit edilmiş olup, diğer ülkelere ilişkin veriler eksiktir. Diğer etiyolojik ajanların rolü halen araştırılmaktadır. Hastalık patogenezi henüz net değildir. Hastalığın insandan insana bulaştığına dair kanıtlar belirsizliğini korumaktadır. Epidemiyolojik çalışmalar, bugüne kadar bildirilen olgular arasındaki bağlantıların aydınlatılması açısından oldukça önemlidir. Ülkelerin ulusal ve uluslararası gözetim faaliyetlerinin organize bir şekilde devam ettirilmesi salgının ortadan kaldırılması için gerekli olan en temel husustur.

Anahtar Kelimeler: Akut HepA-E dışı hepatit, çocuklar, bilinmeyen hepatit, hepatit salgını

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Introduction

As of January 2022, more than normal cases of hepatitis in children have started to occur in the world (1,2). As of the end of April 2022, although the number of cases is higher in Europe, cases have also been reported in North America and Asia (3,4,5,6). On July 8, 2022, it was reported that the number of cases was over 1,010 in 35 countries (Austria, Belgium, Bulgaria, Cyprus, Denmark,

France, Greece, Ireland, Israel, Italy, Latvia, Luxembourg, Republic of Moldova, Netherlands, Norway, Poland, Portugal, Serbia, Spain, Sweden, United Kingdom, Argentina, Brazil, Canada, Colombia, Costa Rica, Mexico, Panama, United States of America, Japan, Singapore, Indonesia, Maldives, occupied Palestinian territories and Qatar). These reports indicate that the disease affects children aged 16 years and younger and is more common in those aged

1-5 years (4,5,6,7). The possible etiology and pathogenesis of this emergency is being investigated, since there is no link between these patients, called acute non-HepA-E hepatitis, and viral hepatitis viruses (hepatitis A, B, C, D, and E) (4,5,6,8).

One of the alarming features of this epidemic is the high requirement for liver transplantation in a proportion of cases (4,6). Fifteen of the 270 confirmed cases in the UK through 19 July 2022 required liver transplantation (4).

Further surveillance studies are ongoing in countries where cases are identified, examining patients' clinical and exposure histories, and where environmental and food toxicology and virological testing is performed. The World Health Organization (WHO) and the European Center for Disease Prevention and Control (ECDC) are supporting the countries with the epidemic and collecting data with ongoing research. All available data is collected more quickly and effectively by countries through institutions such as the Hepatitis Networks and European Association for Liver Research, the European Society for Clinical Microbiology and Infectious Diseases, and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (9).

In this review, it is aimed to examine the present status of hepatitis cases of uncertain etiology in children.

Case Description

Case definitions are made by WHO, ECDC and the UK Health Security Agency. Case description; based on the clinical presentation including age, time of presentation, liver enzyme levels in the absence of acute viral hepatitis markers except acute hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV) and hepatitis D virus (HDV) during chronic HBV disease (4,6,8).

Nowadays, WHO/ECDC/WHO has not been able to provide a description for approved cases of acute non-HepA-E hepatitis, owing to the lack of determination of the underlying etiology and the possibility of other microorganisms and agents other than infectious agents that may cause the disease (4,6). The ECDC and the UK Health Safety Agency have defined a approved case of acute non-HepA-E hepatitis by definition as a case of acute hepatitis with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels more than 500 (IU)/L in children under 11 years of age at any time from 1 January 2022. In addition, possible case definitions of the WHO are as follows:

Likely: Children aged 16 years and younger presenting with acute hepatitis (non-HepA-E) with serum transaminase >500 IU/L (AST or ALT) presenting after October 1, 2021.

Epi-linked: A person presenting with acute hepatitis (non-HepA-E*) of any age who is a close contact of a probable case occurring after 1 October 2021 (2).

Regional Distribution

As of 19 July 2022, the UK Health Safety Agency in the UK reported that it had detected a total of 270 children aged 9 and younger with acute hepatitis of unknown etiology. Fifteen of them are known to be liver transplant patients (4). On 26 August 2022,

the European Union and the European Economic Area, 27 countries, except the United Kingdom, declared more than 513 cases of non-HepA-E acute hepatitis [18]. Additionally, the total number of cases declared globally is 1010 (10). As of 26 August 2022, ECDC reported that 513 cases of acute hepatitis of unknown etiology had been reported in children aged 16 years and younger in Europe. He stated that 513 of the cases were classified as probable by 21 countries and none of them could be found to be epidemiologically related. Notifying countries; Austria [6], Belgium [14], Bulgaria [1], Cyprus [2], Denmark [8], France [9], Greece [12], Ireland [26], Israel [5], Italy [36], Latvia [1], Luxembourg [1], Netherlands [15], Norway [6], Poland [18], Portugal [20], Republic of Moldova [1], Serbia [1], Spain [46], Sweden [12] and United Kingdom [273] (11) (Table 1).

Clinic and Prognosis

So far, it is known that most children affected by acute non-HepA-E hepatitis are 10 years old or younger. Unlike the mean, 12 out of 13 cases declared in Scotland were five years old or younger (5). Six of nine patients identified in Alabama were reported to be less than five years old (7).

The predominant symptoms seen in patients are abdominal pain, vomiting, and diarrhea reported prior to hospital admission (6). In addition, ALT and AST enzymes were found to be elevated with icterus (5,6). Elevated serum aminotransferase levels exceeding 500 IU/L were also detected in patients. Baker et al. (7) They reported that nine affected children in Alabama had ALT levels between 603 and 4696 IU/L and AST between 447 and 4000 IU/L.

WHO and ECDC reported that majority cases were free of fever (4,6). Cases in Scotland also reported no fever in the few weeks prior to hospitalization (5). However, fever was demonstrated in five (55.6%) of nine cases in Alabama (7).

In cases in Alabama, 1/3 of children have reported upper respiratory symptoms prior to hospitalization (7). Vomiting and diarrhea were reported in more than 2/3 of cases in Alabama and Scotland (5,7). Seven of the Alabama cases had hepatomegaly and one patient had encephalopathy at the time of acceptance to the hospital. While seven patients recovered without liver transplantation, the violence of acute non-A-E hepatitis emerges when compared to the two cases who recovered after transplantation (7).

Possible Etiologies and Hypotheses

ECDC works in close cooperation with relevant countries, WHO and other relevant institutions to investigate the etiology of acute hepatitis syndrome of unknown origin in children. The current hypothesis put forward in the ECDC Rapid Risk Assessment; a co-factor that normally affects young children with mild adenovirus infection triggers a more serious infection or immune-mediated liver injury. These co-factors are;

- Increased susceptibility due to decreased exposure to microorganisms in the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic,
- History of SARS-CoV-2 infection or other infection,
- Co-infection with SARS-CoV-2 and/or a different agent,
- Toxins are in the form of drugs or environmental exposure (12).

Adenovirus was detected in 75% of cases tested in the UK and data for other countries are still lacking. Most of the cases reported so far have been confirmed as adenovirus type 41 (in 35/27 cases). Adenovirus-associated virus-2 has also been detected in a small number of cases in the UK using meta-genomics in liver and blood samples. However, in most other cases, appropriate samples were not obtained, emphasizing the importance of drawing whole blood to accurately characterize the type of Adenovirus detected. In addition, adenovirus type 41 infection has not previously been associated with such a clinical presentation in healthy children (13).

The role of other etiologic agents is still under investigation. The exact disease pathogenesis is not yet clear. Evidence for human-to-human transmission of the disease remains unclear. Cases in the EU/EEA have been reported to be almost entirely sporadic (11).

Laboratory Research

Serological testing for HAV-HEV is recommended in suspected cases (4,8). Epstein-Barr virus (EBV) was identified by molecular methods in six of nine cases in Alabama. However, the absence of immunoglobulin M antibody suggested that these patients had EBV reactivation, not acute infection (7).

Although SARS-CoV-2 presence has been detected in a small number of cases, molecular tests are recommended among suspected cases of acute non-HepA-E hepatitis (14). In the exhaustive report of Baker et al. (7), it was reported that the cells were free of viral inclusions and no adenovirus was detected by electron microscopy and immunohistochemical staining. Further testing of liver biopsies from severe cases may provide more in-depth information on the role and immunopathology of Adenoviruses in this disease (9).

The laboratory tests that should be performed in cases with suspected acute non-HepA-E hepatitis in the current guidelines are as follows:

- Polymerase chain reaction (PCR) test on blood/serum samples for adenovirus, enterovirus, HAV, HCV, HEV, human herpesviruses types 1, 2, 3, 4, 5, 6 and 7,
- Serological tests for SARS-CoV-2, HAV, HBV, HCV, HEV, EBV and cytomegalovirus,
- Blood culture if fever is present,
- Studying multiplex PCR respiratory viruses panel (adenovirus, enterovirus, influenza virus, human bocavirus and SARS-CoV-2) from nasopharyngeal swab as soon as possible,
- Study of multiplex PCR gastrointestinal system viruses panel (adenovirus, sapovirus, norovirus, enterovirus) in stool, and,
- *Salmonella* spp. etc. stool culture is required for bacterial enteric pathogens (4,14) (Figure 1).

Anti-streptolysin O serological tests, nasopharyngeal swab culture for group A β -hemolytic *Streptococci*, and serum/urine testing for leptospirosis should be considered if clinically indicated. Toxicological screening can also be done using blood and urine samples (14).

Detection of Adenovirus

It is recommended to collect the following samples for adenovirus testing.

- Whole blood or plasma taken into a purple capped EDTA tube,
- Nasopharyngeal swab, sputum or bronchioalveolar lavage [must be taken into Viral Transport Medium (VTM) or Universal Transport Medium (UTM)],
- Stool sample (or VTM/UTM rectal swab). A stool sample should be preferred over a rectal swab,
- If a liver biopsy has already been performed from a natural liver explant or autopsy as a clinical indication:
 - *Formalin-fixed, paraffin-embedded liver tissue,
 - *Fresh liver tissue should be frozen on dry ice or liquid nitrogen as soon as possible and stored at ≤ -70 °C.

For all these samples, nucleic acid amplification test (PCR etc.) should be preferred. Testing whole blood by PCR is more sensitive than testing plasma by PCR and is recommended (15).

Discussion

Cases of severe acute hepatitis of unknown source in children have currently been declared in 19 countries worldwide. The rapid increase in the disease is a cause for concern and requires careful surveillance and coordinated studies to determine its possible etiology and transmission routes.

Detection of newly emerging cases is critical. In addition to surveillance, surveillance studies should be conducted by investigating epidemiological links. Marsh et al. (5) in a study conducted in Scotland, they showed that two children had close contact with two other cases in one setting, although no epidemiological link has been identified so far in the Alabama cases (7).

Another aspect of the involvement of microorganisms in the etiology of acute non-HepA-E hepatitis is the need to explore the hypothesis established for the potential role of immunopathological mechanisms. In the liver biopsies examined in Alabama cases, adenoviruses were not detected as a result of electron microscopy and immunohistochemical examination methods. For this reason, research to detect other microorganisms is important (7).

If adenoviruses are indeed associated with the etiology of acute non-HepA-E hepatitis, non-molecular testing for adenoviruses in blood and stool samples may preclude detection of cases. Therefore, it is crucial to provide up-to-date guidelines for adenovirus detection and to report cases and establish basic but reliable methods for adenovirus identification, including lateral flow testing (9). Moreover, considering the higher efficiency of whole blood for detection of adenovirus compared to plasma, it is reported that molecular tests for adenoviruses in cases of suspected acute non-HepA-E give more accurate results using whole blood instead of serum/plasma samples (4,7).

If adenoviruses were to have a definitive role in the current cases, various infection control precautions would be essential,

including appropriate hand cleaning and surface disinfection practices (due to its long-term stability and being a non-enveloped virus) (16,17).

Considering the higher-than-normal prevalence of adenoviruses among non-HepA-E acute hepatitis cases, the possibility of being an etiologic agent seems more robust, but other possible hypotheses mentioned earlier should not be ignored and should be carefully examined. Since microorganisms cannot be detected in the etiology of acute non-HepA-E hepatitis, continued investigation of toxicological and potential environmental factors should be a priority (9). In addition, given the limited surveillance capacity in most regions, the number of cases may be underestimated.

Common transmission measures for non-HepA-E acute hepatitis cases; regular hand washing and respiratory hygiene should be practiced. Based on the available information, WHO has not yet proposed any restrictions on travel and/or trade with the UK or other countries where cases have been detected.

WHO recommendations for the surveillance of the disease are as follows;

- Member states should be encouraged to identify, investigate and report potential cases that fit the case definition.

- Epidemiological data and risk factors should be made available by member states to WHO and partner organizations through agreed reporting tools.

- These data must be recorded as any epidemiological link between cases may provide clues to trace the origin of the disease.

- The time of occurrence of the cases and close contacts with the geographical regions where they occur should be reviewed in terms of possible risk factors (6).

Conclusion

Epidemiological studies are very important to clarify the uncertainties about the existence of links between the cases reported to date. The fact that there are no cases in our country yet may be due to patients that do not show symptoms and experience mild illness. Continuing the national and international surveillance works of the countries in an organized manner is the most basic issue required to eliminate the epidemic.

Ethics

Peer-review: Externally peer-reviewed.

Table 1. Summary of cases of severe acute hepatitis of unknown etiology published by ECDC on 26 August 2022 (18)

| Country name | Number of cases | Hospitalised | Intensive care unit | Transplanted |
|-----------------------|-----------------|--------------|---------------------|--------------|
| Austria | 6 | 3 | 0 | 0 |
| Belgium | 14 | 0 | 1 | 0 |
| Bulgaria | 1 | 1 | 0 | 0 |
| Cyprus | 2 | 2 | 0 | 0 |
| Denmark | 8 | 0 | 0 | 0 |
| France | 9 | 0 | 0 | 0 |
| Greece | 12 | 10 | 1 | 0 |
| Ireland | 26 | 25 | 5 | 2 |
| Israel | 5 | 2 | 0 | 0 |
| Italy | 36 | 31 | 0 | 1 |
| Latvia | 1 | 1 | 0 | 0 |
| Luxembourg | 1 | 1 | 0 | 0 |
| Moldova | 1 | 1 | 1 | 0 |
| Netherlands | 15 | 13 | 1 | 4 |
| Norway | 6 | 6 | 1 | 0 |
| Poland | 18 | 18 | 1 | 0 |
| Portugal | 20 | 17 | 0 | 0 |
| Serbia | 1 | 1 | 0 | 0 |
| Spain | 46 | 27 | 6 | 1 |
| Sweden | 12 | 8 | 3 | 1 |
| United Kingdom | 273 | 191 | 69 | 13 |
| Total number of cases | 513 | 358 | 89 | 22 |
| Adenovirus positivity | 218/404 | - | - | - |
| SARS-CoV-2 positivity | 96/445 | - | - | - |
| HHV7 positivity | 34/109 | - | - | - |

ECDC: European Center for Disease Prevention and Control, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, HHV: Human herpesvirus

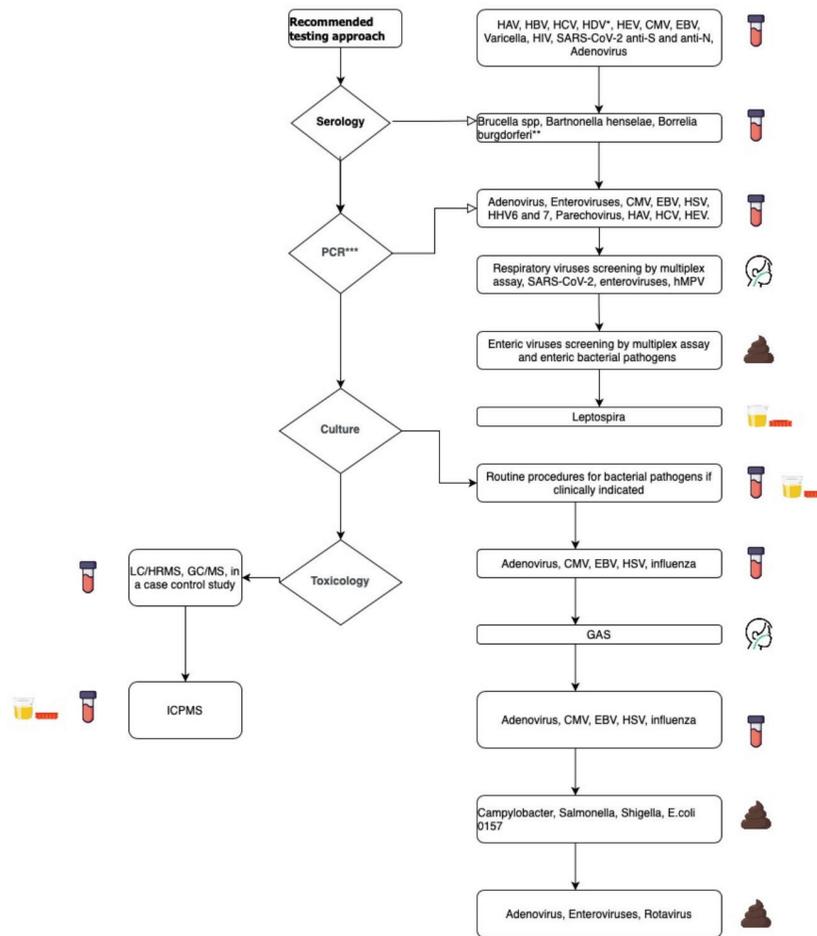


Figure 1. *Salmonella* spp. etc. stool culture is required for bacterial enteric pathogens (4,14)

HAV: Hepatitis A virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HDV: Hepatitis D virus, HEV: Hepatitis E virus, CMV: Citomegalovirus, EBV: Epstein-Barr virus, HIV: Human immunodeficiency virus, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, HSV: Herpesvirus, HHV: Human herpesvirus LC: Liquid chromatography, HRMS: High resolution mass spectrometry, GC: Gas chromatograph, MS: Mass spectrometry, GAS: Group A *Streptococcus*

Authorship Contributions

Surgical and Medical Practices: E.PK.K., M.A., Concept: E.PK.K., M.A., Design: M.A., Data Collection or Processing: E.PK.K., Analysis or Interpretation: E.PK.K., M.A., Literature Search: E.PK.K., Writing: E.PK.K., M.A.

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