MINI-NARRATIVE REVIEW

Severe acute hepatitis of unknown etiology in children in 2022: A Narrative Review

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Abstract

Severe cases of acute hepatitis have been reported all around the world since 5 April 2022. Common viral hepatitis agents (HAV, HBV, HCV, HDV, and HEV) were ruled out by laboratory investigations, impelling the term "acute non-A-E hepatitis". Common manifestations consist of abdominal pain, jaundice, and vomiting. A highly elevated level of liver enzymes was a remarkable laboratory finding among the patients. Currently, there is no clear etiology and thus treatment for the condition. Adenovirus serotype 41 (ad-41) was detected in most of the patients even though there is no elucidated link between Adenovirus and acute hepatitis. Other viral agents such as SARS-CoV-2 tested positive in a few cases. Treatment strategies depend on the severity, complications, and sequela of acute hepatitis and can vary widely from supportive therapy to liver transplantation. As of 8 July 2022, 1010 probable cases were reported from 35 countries. More than half were from the European region and were mostly children under the age of 6 years. Among different hypotheses about the etiology of severe acute non-A-E hepatitis, adenovirus-41 is of great importance but further assessments are needed to prove any definite link between ad-41 and severe acute hepatitis.

Keywords: Acute hepatitis, Children, Diagnosis, Epidemiology, Etiology, Pediatrics, Treatment, Unknown hepatitis
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1. Introduction

On April 5th, 2022, 10 cases of severe acute hepatitis of unknown cause between the age of 11 months to 5 years were reported by the United Kingdom (UK) to the World Health Organization's International Health Regulations (IHR) notification system. Further investigations excluded Viral hepatitis types A, B, C, D, and E, as well as other known causes of acute hepatitis [1,2].

Until 8 April 2022, the number of cases has risen by 74, mainly in previously healthy children and the common presentations were jaundice, vomiting, and pale stool. Six cases have undergone liver transplantation and no deaths were reported at that time [1,3].

The lack of a link between this condition commonly referred to as "acute non-A-E hepatitis," and the currently recognized viral hepatitis agents (HAV, HBV, HCV, HDV, and HEV), made the researchers eager to further investigate the etiology, pathophysiology, and outcome of this emerging illness [4] [1,3,5].

As of 8 July 2022, 1010 cases in five World Health Organization (WHO) regions have been reported, 46 (5%) children have required transplants, and 22 (2%) deaths have been reported to WHO which is an appalling feature of the condition [1,3,6–8].

In this review, we aim to summarize the currently available information about acute hepatitis of unknown etiology.

2. Methods

Search Strategy: We searched PubMed/Medline and Embase for all case reports or case series of ReA following COVID-19

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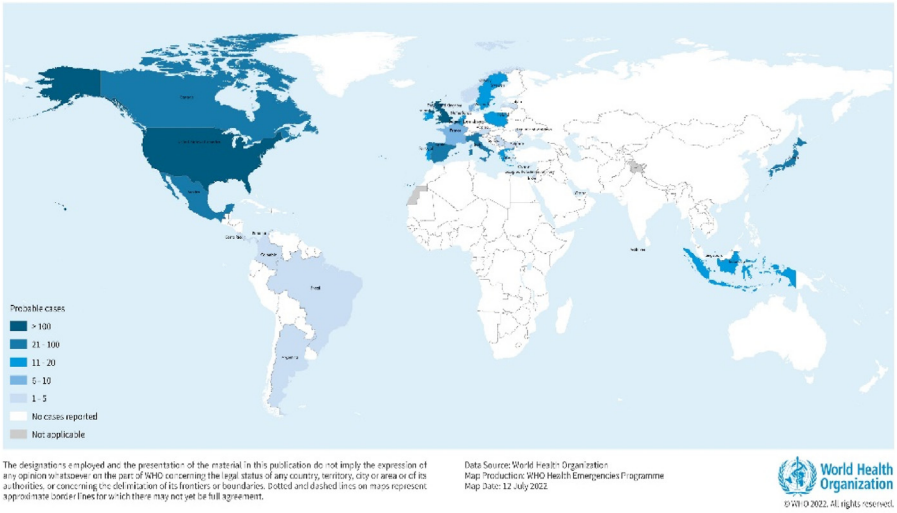

FIG. 1. Distribution of probable cases of severe acute hepatitis of unknown aetiology in children by country, as of 8 July 2022 (n = 1010), 5 PM CEST [8].

published up to 12th January 2023. The following terms were used for the search strategy: ["unknown hepatitis" OR "hepatitis of unknown origin" OR "hepatitis of unknown etiology" OR "non-A-E hepatitis" OR "novel hepatitis"].

2.1. Working case definition for acute Non-A-E hepatitis

Currently the probable, epidemiologically linked, pending, and discarded cases of acute non-A-E hepatitis are defined by WHO. Due to the lack of precise etiology, the definition of a confirmed case has not been provided.

A probable case is defined as an individual who presents with acute hepatitis (non-hepatitis viruses A-E) with Alanine transaminase (ALT) or aspartate transaminase (AST) over 500 U/L with the age of 16 years or younger, since 1 October 2021.

An epi-linked case is an individual who presents with acute hepatitis of any age who was in close contact with a probable case since 1 October 2021.

If the serological tests for hepatitis A to E are waited for but other criteria are met, the patient is classified as a pending case. The discarded case is a formerly classified case that did not meet the case definition criteria with further investigations [9].

2.2. Common symptoms and associated lab data

The majority of symptoms described in the weeks leading up to hospital admissions were abdominal pain, vomiting, and diarrhea [3]. Together with jaundice, very high levels of liver enzymes (ALT and AST) were discovered [3,4]. Severely high levels of serum aminotransferases, which exceed 500 IU/L, are a remarkable feature. As Julia M. Baker et al. have figured out, severely high levels of serum aminotransferases, which exceed 500 IU/L were reported in nine affected children in Alabama with the ALT level ranging from 603 to 4696 IU/L, whereas the AST levels ranged from 447 to 4000 IU/L [10].

The WHO and the European Centre for Disease Prevention and Control (ECDC) both stated that fever was absent in the majority of patients [1,3]. The same pattern was followed in cases from Scotland, where no fever was noted in the weeks leading up to admission to the hospital [4]. The report on Alabama cases, on the other hand, revealed that fever was present in 5/9 (55.6 percent) of the cases [10]. Upper respiratory tract symptoms were noted in one-third of the children in Alabama cases before admission [10]. More than two-thirds of the cases in both Alabama and Scotland experienced vomiting and diarrhea [4,10].

Seven patients in Alabama presented with hepatomegaly; one had encephalopathy upon admission, with seven recovering without liver transplantation and two recovering after transplantation demonstrating the severity of acute non-A-E hepatitis [10].

2.3. Geographic distribution of reported cases

From 1 October 2021 to July 8th,2022, 1010 probable cases from 35 countries in five WHO Regions were reported. Approximately, half of the probable cases (484 cases) were from the WHO European Region, including 272 cases (27% of global cases) from the United Kingdom. The region of the Americas reported the second-highest number of probable cases (n = 435, including 334 cases from the United States of America). Western Pacific Region (n = 70), the South-East Asia Region (n = 19), and Eastern Mediterranean Region (n = 2) come next [8].

2.4. Demographic data

As of June 22nd, among 422 cases with available information on age and gender, 48% of cases are male (n = 202), and most of the cases (78%, n = 327) are under 6 years of age [6].(Fig. 1)

3. The hypothesis of probable etiologies

The exact underlying cause of acute non-A-E hepatitis is still unknown. All of the hypothesized etiologies in the literature are mentioned as the following.(Fig. 2)

3.1. Adenovirus infection

The role of adenovirus infection in cases of acute non-A-E hepatitis in children is now the most probable theory [1,3,5]. PCR detected adenovirus in 52% of cases (193/368) with available results [8]. The working hypothesis by the UK Health Security Agency is that a normal adenovirus infection in children can be worsened by a cofactor that causes the infection to become severe or immunopathologic [5]. During the COVID-19 pandemic, due to the lockdown restrictions, children did not encounter common infections, therefore they did not become immune to the common pathogens that they normally would be infected with. Thereafter, when the restrictions were lifted, exposure to these viruses without prior immunity resulted in severe manifestations such as acute liver failure (ALF) [11]. Former or concurrent infection with other viruses, such as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or exposure to toxins or other environmental chemicals are also probable cofactors [1,5].

Another possible explanation is a novel variant of adenovirus which may cause acute non-A-E, with or without the mentioned cofactors [1,5]. The discovery that more than three-quarters of the reported cases were positive for adenoviruses supports the theory that adenoviruses have a role in acute non-A-E hepatitis [1,3,5]. Scientists and clinicians should study whether the virus's genome has changed in a way that allows for hepatotropism, which can cause severe liver inflammation.

The reporting of acute non-A-E hepatitis during the COVID-19 pandemic is a vital point to be considered. This pandemic coincided with increased global virus molecular testing capabilities; consequently, the discovery of previously unknown instances of hepatitis linked to Adenovirus−41 exacerbated by delayed exposure to this prevalent infection could be a reasonable hypothesis that requires additional proof [12].

3.2. COVID-19

A new variant of SARS-CoV-2 was considered to be a probable cause of non-A-E hepatitis, however, given the vast numbers of cases that tested negative for SARS-CoV-2, this hypothesis is not shown to be highly considered as in the European region, polymerase chain reaction (PCR) testing detected SARS-CoV-2 in 15% of cases (47/307) with available results. 10% of cases (8/83) with available results tested positive for COVID-19 in the United States [6] Moreover, acute hepatitis is not a prevalent sequela of COVID-19 in children despite reports of its incidence [13].

3.3. COVID-19 vaccines

Given that the majority of acute hepatitis of unknown etiology occurred in children who had not received the COVID-19

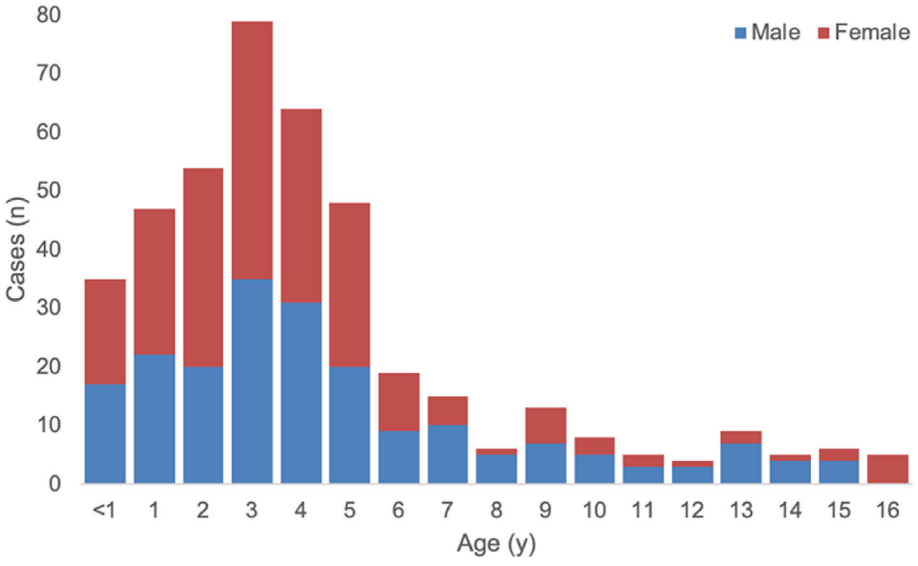

FIG. 2. Gender and age distribution of 422 probable cases of severe acute hepatitis with the unknown etiology with available data (n = 422) [6].

vaccine, a link between acute non-A-E hepatitis cases and COVID-19 vaccination seems unreasonable [3]. Furthermore, of the 99 cases reported by ECDC with available data on COVID-19 vaccination, 85 (85.9%) were unvaccinated [14].

3.4. Superantigen-mediated immune cell activation and immunopathology (immunogenicity)

The persistence of SARS-CoV-2 in the gastrointestinal tract can result in repeated viral protein releases across the intestinal epithelium, causing immunological activation [15]. A superantigen pattern of the SARS-CoV-2 spike protein that resembles Staphylococcal enterotoxin B6 may cause broad and non-specific T-cell activation, resulting in recurrent immunological activation. Superantigen-mediated immune-cell activation may be the probable cause of multisystem inflammatory syndrome [16,17]. Children with multisystem inflammatory syndrome have been diagnosed with acute hepatitis, but no other concurrent viral infections have been identified [18].

Adenovirus infection can make mice more susceptible to Staphylococcal enterotoxin-B-mediated toxic shock, which results in liver failure and death [19]. This result was explained by adenovirus-induced type-1 immunological skewing, which led to increased IFN-γ production and IFN-γ mediated hepatocyte death after Staphylococcal enterotoxin B administration [19]. One hypothesis is that the recent cases of severe acute hepatitis in children could be due to adenovirus infection with intestinal tropism in children who had been previously infected with SARS-CoV-2 and were carrying viral reservoirs. Given the recent scenario, testing for SARS-CoV-2 persistence in stool, T-cell receptor skewing, and IFN-upregulation are recommended since these observations potentially reveal a SARS-CoV-2 superantigen mechanism in a host sensitized to adenovirus type 41F.Immunomodulatory therapy should be evaluated in children with severe acute hepatitis if evidence of superantigen-mediated immune activation is detected [20].

3.5. Other viral agents

Other viral agents scarcely detected in UK patients include the Epstein-Barr virus, enterovirus, cytomegalovirus, respiratory syncytial virus, and human herpes viruses 6 and 7 [14].

3.6. Toxins/environmental agents

The possibility of a toxin originating from food or the environment is not excluded. The United Kingdom Health Security Agency (UKHSA) is undertaking epidemiological studies in which the children's environment, demographics, and food intake are assessed retrospectively. Some food has likely been contaminated with something, but there's no proof of that so far [21].

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has recently published research mentioning foodborne toxins as a probable underlying cause of the disease [22]. Given that food manufacturing can be a centralized process with distribution from a single producer to several locations around the world, this hypothesis should be tested. Due to the probable correlation of severe hepatic damage of the exposed individuals, aflatoxins appear as the leading candidate in this case scenario [22,23].

4. Treatment

Due to the emerging nature and lack of sufficient information on the cause of this disease, there is still no specific treatment strategy. However, symptomatic and supportive treatments are at the top of the current treatment strategies.

Adequate rest, avoidance of excessive protein consumption, and prevention of complications are the main supportive treatments [24].

The noteworthy points to which doctors must pay attention during the treatment period are the patient's consciousness, blood electrolytes, liver function, and coagulation function, as well as water, electrolyte, and acid-base balance.

As the next step, to prevent severe complications such as hepatic encephalopathy and hepatorenal syndrome, symptoms such as hypovolemia, hypoproteinemia, gastrointestinal bleeding, infection, and hypoglycemia must be taken seriously [25].

Another treatment strategy is against adenovirus infection. Adenoviruses have been detected in almost half of the known cases of this disease through PCR tests. For these cases, supportive treatment is still at the top of the order, although cidofovir has shown promise [25,26].

Acute liver failure (ALF) may result in coagulation abnormalities due to many reasons, including decreased coagulation factor synthesis, decreased hepatic thrombopoietin, and secondary bacterial infection [27]. In clinical practice, coagulation function can be evaluated using prothrombin activity (PTA) and INR. Newer techniques including thrombo-elastography (TEG) are also suggested [28]. There are no blood transfusion recommendations for kids with ALF at this moment. Plasma transfusion in large quantities can change the INR trend of ALF during therapy. Therefore, it is not advised to use fresh frozen plasma or platelets to treat coagulation problems on a preventative basis [29]. In case of vitamin K deficiency, it should be prescribed; the dosage of cryoprecipitate can be changed following the TEG value to keep fibrinogen within the normal range [25].

In the case of hepatic encephalopathy, treatment may be limited to general methods, serum ammonia-lowering therapy, treatment for intracranial hypertension, and artificial liver support. To prevent unnecessary interference, having a supine position with the head of the bed raised by 20 to 30 °C is recommended. Grading of hepatic encephalopathy needs to be assessed periodically. Endotracheal intubation is advised for children with grades III and IV hepatic encephalopathy to protect the airway and manage ventilation to maintain efficient ventilation and sufficient oxygenation [25,30].

To increase intestinal peristalsis and decrease the absorption of intestinally generated ammonia and toxins, lactulose and lactitol can be administrated orally. Ammonia-lowering medications like arginine can be taken if necessary, depending on the patient's internal environment, including electrolytes and acid-base imbalances [25,31,32].

Three main therapeutic medications to lower intracranial pressure consist of hypertonic saline, mannitol, and furosemide. Maintaining serum sodium at 145–150 mmol/L is advised when using hypertonic saline [25,31]. The drug mannitol is frequently used to reduce sudden increases in intracranial pressure. In case of renal failure, hypovolemia, serum osmolality greater than 320 mOsm/L [33], or prophylactic use, it is not recommended.

An important treatment for ALFis artificial liver support. Plasma exchange (PE), molecular adsorption recycling, and continuous blood purification are artificial liver support systems that are appropriate for children. The pathophysiological traits of the patient's illness, the idea behind the artificial liver model, and the intended effects of the therapy should all be taken into consideration while deciding when to start artificial liver therapy [34].

4.1. Liver transplant

About 6–10% of patients, particularly those with poor prognoses, require a liver transplant (LT) [35]. Children with ALF who don't improve or even progress gradually after receiving active, comprehensive medical care require urgent LT [36,37]. It's not generally accepted whether there is any indication of LT in ALF children. Nadalin S et al. established the pursuing standards: INR >2, or INR >1.5 and linked with HE, bilirubin >18 mg/dL, increased propensity to hypoglycemia, and decreased liver size evaluated by sonography are all signs of grade III HE [36,38].

4.2. Prevention

Since the etiology and specific treatments of severe acute hepatitis in children are still unknown, it is crucial to prevent the disease from spreading. Currently, routine preventative measurements against respiratory viruses and adenovirus, such as hand cleanliness and respiratory hygiene, are advised. Clinicians are recommended to identify and report any possible cases of children presenting with hepatitis symptoms and indications that may call for serum transaminase testing [24,25].

4.3. Conclusion

The global outbreak of severe acute non-A-E hepatitis is a matter of great concern. Further investigation is needed to point out any probable epidemiologic links. So far, the underlying cause of the disease is not determined. Adenovirus infection may be a probable cause, however, there is no proven link between adenovirus infection and acute hepatitis in children.

Author contribution

KN, ANG and SFA contributed equally to this paper. KN and ANG contributed to the investigation, supervision, validation, reviewing, and editing and revised it critically under supervision of SFA. All the authors approved the final version of the manuscript.

Transparency declaration

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