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May 2022 Acute Hepatitis Outbreak, is There a Role for COVID-19 and Other Viruses?

May 2022 Acute Hepatitis Outbreak

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Abstract

Background: There has been an increasing number of reported cases of acute hepatitis of unknown origin in previously healthy children since first reported on Mar 31, 2022. This clinical syndrome is identified by jaundice and markedly elevated liver enzymes with increased aspartate transaminase (AST) and/or alanine aminotransaminase (ALT) by more than 500 IU/L. **Methods:** We conducted an inclusive literature review by searching different electronic databases; related to acute hepatitis outbreaks in children using the terms acute hepatitis, outbreak, children, SARS-CoV-2, COVID-19, and Adenovirus. We included 52 out of 260 studies concerned with acute hepatitis of unknown cause in children. **Results:** According to the cumulative data we obtained from four main studies, the median age was four years with a male: female ratio of 1.3:1. Jaundice was the most common clinical manifestation (69%), followed by vomiting (63%), anorexia (52.9%), diarrhoea (47.2%), abdominal pain (39%), pyrexia (33.3%), pale stool (30%), and dark urine (30%). Coryza and lethargy were reported in 16.6%, while pruritus was reported in 2% of cases. Acute Live failure was observed in 25% of cases. The exact mechanism of this acute hepatitis outbreak is still not precisely clear. Adenoviruses and SARS-CoV-2 were detected in a significant portion of patients. Co-infection between Adenoviruses and SARS-CoV-2 could be a possible underlying mechanism. However, other possible infections and mechanisms are to be considered. **Conclusion**: Acute hepatitis of unknown origin is a serious problem in childhood during the COVID-19 pandemic but has not yet been precisely addressed. Many questions about the possible underlying mechanisms arise and need much effort and extensive research.

Key Words: Acute hepatitis of unknown origin; Children; Adenovirus; SARS-CoV-2; COVID-19; Hepatic Failure

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Core Tip: There has been an increasing number of acute hepatitis of unknown origin in children since first reported on Mar 31, 2022. The exact mechanism of this acute hepatitis outbreak is still unclear, but the increased detection rate of Adenoviruses and SARS-CoV-2 may imply their role in its pathogenesis. Coinfection between Adenoviruses and SARS-CoV-2 could be an underlying mechanism. However, we still need comprehensive research to reach the exact cause and mechanism. Till that, we should exert every effort to prevent the development of this syndrome in children using the proper hygienic conditions.

INTRODUCTION

Since it was first reported on Mar 31, 2022, in Scotland, and with the recent increase in the reported cases since Apr 15, 2022, in the United Kingdom (UK), the reason for the acute hepatitis of unknown origin in previously healthy children is not well defined, as it is either a real increase in the case numbers or related to the increased awareness and reporting levels. By the last week of April 2022, there had been 169 cases of acute hepatitis of unknown origin in children aged one month to 16 years, reported from 11 countries, including the UK, Spain, Israel, the United States of America (USA), Denmark, Ireland, the Netherlands, Italy, Norway, France, Romania, and Belgium [1]. By the End of May 2022, the number of reported cases increased to 746 from 36 countries distributed in four continents, mainly Europe and America (Figure 1: A and B) [2].

This clinical syndrome is identified by Jaundice and markedly elevated liver enzymes with increased aspartate transaminase (AST) and/or alanine aminotransaminase (ALT) by more than 500 IU/L. It could be preceded by gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhoea. Fever was reported in a few cases, as most affected children were afebrile. On the other side, many cases suffered further, more

severe complications, such as liver failure [3]. Most hepatotropic viruses that cause acute hepatitis, such as A, B, C, D, and E, were not detected. About 10% of the reported cases required liver transplantation, with one reported mortality case. Despite most cases being reported from Europe, Israel, and the USA, there is no link between travelling to specific countries and developing the syndrome [4].

The exact mechanism of this type of acute hepatitis outbreak is still not precise. However, Adenovirus was detected in 74 patients, and SARS-CoV-2 was detected in 20 patients. Co-infection of Adenovirus and SARS-Cov-2 was detected in 19 cases. Meanwhile, the UK and the Netherlands reported a concurrent increase in adenovirus infection in the community [5]. Although there is some evidence for the potential role of Adenovirus alone or with SARS-CoV-2 in the aetiology of this syndrome, other factors, such as immunopathogenesis and non-infectious factors, could play a role. The aim of this review is to shed some light on understanding this syndrome [6].

METHODS:

We conducted an inclusive literature review by searching different electronic databases, including PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Cochrane Library, Scopus, Library and Information Science Abstracts (LISA), google search, and the National Library of Medicine (NLM) catalog up until Aug 31, 2022, related to Acute Hepatitis Outbreak in children using the terms acute hepatitis, outbreak, children, SARS-CoV-2, COVID-19, Adenovirus. Reference lists were inspected, and citation searches were done on the included studies. We included papers written in English and with open access. Figure 2 shows the flow chart of the reviewed articles. We reviewed 260 articles concerned with acute hepatitis of unknown aetiology outbreaks in children; 52 were included in the study.

CLINICAL SPECTRUM OF ACUTE HEPATITIS OF UNKNOWN CAUSE IN CHILDREN:

The World Health Organization (WHO) defined cases with the current outbreak of severe acute hepatitis of unknown origin as confirmed, probable, and Epi-linked. Confirmed cases did not have well-defined diagnostic criteria till now. Therefore, the probable case definition is the most used one. The probable cases are those who present with manifestations of acute non-HepA-E hepatitis with elevated serum aminotransferases of more than 500 IU/L. Their ages are 16 years or less since Oct 1, 2021. On the other hand, an Epi-linked case is a person presenting with acute (non-HepA-E) hepatitis of any age who has had a history of close contact with a probable case since Oct 1, 2021 [7]. The age range of the reported cases was between 1 mo to 16 years, according to the data obtained from WHO. However, three-quarters of the reported cases in European countries are below five years of age, as they were focused on children younger than ten [8]. According to the cumulative data we obtained from four main studies (two from the UK and two from the USA), the median age was four years with a male: female ratio of 1.3:1. Jaundice was the most common clinical manifestation (69%), followed by vomiting (63%), anorexia (52.9%), diarrhoea (47.2%), abdominal pain (39%), pyrexia (33.3%), pale stool (30%), and dark urine (30%). Coryza and lethargy were reported in 16.6%, while pruritus was reported in 2% of cases. Acute Live failure was observed in 25% of cases. Table 1 shows the percentage of clinical data from different studies [9, 10,11,12].

Kelgeri *et al*, who studied 44 cases, found that hepatitis resolved in most cases; however, it progressed into fulminant liver failure that requires liver transplantation in 14% of cases. This finding indicates the severity of the condition that should be handled seriously. The biochemical tests in the affected children during the prodromal phase indicate acute hepatitis. Meanwhile, the abdominal ultrasound markers of gall bladder wall thickening with pericholecystic fluid and enlarged mesenteric lymph nodes with mild hepatosplenomegaly are reliable with a potential viral aetiology, necessitating extensive viral work-up, especially for adenoviruses [9]. The laboratory work-up needed for diagnosing Acute Hepatitis of unknown aetiology is summarised in table 2.

GUT-LIVER AXIS AND HEPATIC DISEASES:

Gut microbiota affects essential body functions, including immunological, structural, metabolic, and neurological functions. It considerably impacts physical and mental human health. The gut is colonised by over 1000 microbial species, which start in utero and continue after birth in an ongoing, complex, dynamic process to help gut maturation and development [13]. Despite the number of microbial species of the gut microbiota in children and adolescents being like adult microbiota, they differ in the relative abundance of certain species with more abundances of *Faecalibacterium* spp., *Bifidobacterium* spp., and subspecies of the *Lachnospiraceae* [14]. In addition, fungi and viruses have essential shares in the gut microbiota. Gut virobiota includes bacteriophage viruses that can infect prokaryotic cells, viruses that can infect eukaryotic-host cells, and virus-derived genetic particles embedded in host chromosomes. The whole set of genes of virobiota constitutes what is known as 'virome' and is formed of all the virus-derived genetic elements found in the human genome [15].

In the oro-nasopharyngeal area; bacteriophages, Coronaviruses, Herpes viruses, Adenoviruses, Respiratory Syncytial Viruses, Picornaviruses, Influenza A viruses, and other uncharacterised eukaryotic viruses. The common viruses in the gastrointestinal tract include bacteriophages, Adenoviruses, Caliciviruses, Parvoviruses, Picornaviruses, Papillomaviruses, Astroviruses, plant viruses, and other uncharacterised eukaryotic viruses [16]. Some Eukaryotic DNA viruses, such as Anelloviruses, Herpesviruses, Human bocavirus, and Adenoviruses, and some RNA viruses, such as Picobirnaviruses and Parechoviruses can continue shedding for months and form a significant fraction of the typical human virome due to the high ability to set up a persistent infection [17]. Unfortunately, persistent gut infection with human Adenoviruses can be reactivated and cause serious morbidity and mortality, especially in immune-suppressed patients such as children with haematopoietic stem cell [18transplants].

The liver-gut-microbiota axis, including virobiota, is a bidirectional pathway between the gut and the liver where the portal veins transport the gut-derived products directly from the gut to the liver and the liver-manufactured bile and antibodies are transported

back to the gut (Figure 3). The gut microbiota products preserve the immune homeostasis of both intestine and the liver. Conversely, some microbial-derived metabolites, such as ethanol, trimethylamine, short-chain fatty acids (SCFAs), and secondary bile acids, may play a role in liver disease development. Meanwhile, liver diseases such as liver cirrhosis can induce significant gut microbiota changes with impaired vascular, epithelial, and immune barriers of the intestine [19]. Therefore, gut dysbiosis can induce abnormal mucosal immune response initiating homeostasis imbalance. The resulting imbalance causes microbial transport and immune cells to migrate to the liver, provoking inflammation-mediated hepatic injury and may cause tumour progression [20, 21].

ADENOVIRUS HEPATOTROPIC EFFECTS:

Adenoviruses are medium-sized, nonenveloped, double-stranded DNA viruses. They are named Adenovirus due to their isolation from the adenoid for the first time in 1953. Adenoviruses are widespread viruses that classically trigger mild cold- or flu-like disease, pneumonia, conjunctivitis, and acute gastroenteritis in all age groups throughout the year [22]. Adenoviruses are not hepatotropic viruses, especially in immune-competent children. However, they can cause hepatitis in children with liver stem cell transplantation, immune-suppressed children such as those with severe combined immune deficiency, and children receiving chemotherapy due to solid malignant neoplasms. The adenoviruses species C are the most involved, particularly type 5 [23]. At the same time, human species F adenoviruses, types 40 and 41, are well-known causes of paediatric gastroenteritis. Chhabra *et al* showed that F Adenovirus type 41 is more widespread than type 40 as a cause of viral gastroenteritis in children younger than five years of age [24]. Despite mainly causing respiratory infections, Adenoviruses can produce transient nonspecific "reactive hepatitis" in children during infection, with AST levels and ALT levels as good indicators of hepatitis severity [25]. Adenovirus infection can be diagnosed by direct antigen detection (blood, stool, and respiratory samples), polymerase chain reaction (PCR) amplification, virus culture and

isolation, and serology. Specimens are ideal to be collected within one week from the onset of the symptoms. A positive serology is expected in most children by the age of four years. However, a four-fold increase in the acute titre of adenovirus-specific antibodies indicates a recent infection. Adenovirus typing can be performed by molecular testing and is essential from the epidemiological point of view [26]. When doing Adenovirus molecular testing in suspected cases of acute hepatitis of unknown cause, we should consider using whole blood instead of serum or plasma specimens, as using whole blood has a higher yield for Adenovirus detection [12].

Out of 74 cases of acute hepatitis of unknown aetiology with detected Adenovirus, 18 patients were identified by molecular testing to be serotype F-type 41, and a few patients with F-type 40 [27], which may indicate the role of enteric adenoviral infection as a potential pathogenic hepatic infection through the "gut-liver" axis, which warrants further research [28]. However, the very low viral load in the clinical samples made the PCR genetic amplification of a part of the hexon gene and Sanger sequencing the available option to detect Adenoviruses in these samples. These also may alarm us to consider the low viral load when searching for Adenovirus in such cases. It also should be mentioned that children presented with acute hepatic failure had a high viral load. We also should consider the significant intratypic genetic variations for Adenoviruses serotype F-type 41 [29]. The Alabama Hospital's study in August 2022 showed three different strains of type F41 observed in five patients with acute hepatitis of unknown aetiology, indicating a decreased possibility of an outbreak with a specific Adenovirus serotype [30].

Meanwhile, serotyping data obtained from four patients of the European cohort with positive testing for Adenovirus showed that two patients had type F41 in, one patient had type F40, and one patient had a type "other," which could indicate the potential Adenovirus pathogenicity towards liver reaching it through the "gut-liver" axis. This pathogenic effect of Adenovirus on the liver could be due to the development of new genomic mutation resulting in tropism towards the liver cells. This hypothesis needs to be confirmed by whole genome sequencing to detect this possible mutation [28]. Despite

being isolated from a significant number of children with acute hepatitis of unknown origin, the exact role of Adenoviruses in the pathogenicity of this condition still needs to be confirmed. Infection with adenoviruses is usually mild and resolves spontaneously. However, it could be associated with high morbidity and mortality in immunocompromised children, particularly those with allogeneic stem cell transplants. Though Adenoviruses have been known for a long time, currently, there is no FDA-approved antiviral to treat human Adenovirus infection. Currently, Cidofovir, Brincidofovir, and ribavirin are the only antiviral drugs used as first-line therapy to treat adenoviral infections. Brincidofovir has no nephrotoxicity and better bioavailability than Cidofovir; however, it is not produced anymore [31,32].

CORONAVIRUSES HEPATOTROPIC EFFECTS:

Despite the lungs being the primary target and the pulmonary symptoms being the dominant clinical presentation of COVID-19, SARS-CoV-2 may also affect other organs and systems, producing a variety of organ dysfunctions, including the liver [33]. The liver is affected by about 14–53% of infections caused by SARS-CoV-2 in the presence or absence of pre-existing liver disease, especially in males and in more severe infections [34]. SARS-CoV-2 gets access to the liver through the ACE-2 receptors deliberately expressed on cholangiocytes in the ductal organoids, with minimal expression on hepatocytes and complete absence on Kupffer cells [35]. The COVID-19-associated liver injury (Figure 4) could be related to immune-mediated damage with a severe inflammatory response to SARS-CoV-2 infection, direct cytotoxicity due to active viral replication inside the liver cells, COVID-19-associated anoxic liver damage, drug-associated liver injury, and reactivation of pre-existing liver infections such as Hepatitis B infection [30]. SARS-CoV-2 infection can also activate autoimmune hepatitis during systemic immune hyperstimulation, through molecular mimicry, or both.

Meanwhile, few autoimmune hepatitis cases were reported after SARS-CoV-2 vaccination; all showed complete remission with steroid therapy [36]. Crisan *et al* showed that patients who presented with elevated liver enzymes and abnormal chemistry on

arrival were more susceptible to a worse disease and poor outcome. The presence of fibrosis in hospitalized patients with COVID-19 is associated with increased mortality [37]. Therefore, regular monitoring of liver functions should be done for all patients with COVID-19 disease with serological testing of specific hepatotropic viruses (e.g., Hepatitis B or C according to the local epidemiological status) and other specific investigations to detect pre-existing hepatic disease [38].

Figure 4 shows the effects of COVID-19 infection of the liver as indicated by increased liver enzymes. The virus reaches the liver from the gut-liver-lung axis, which may be re-shed back to the gut through the bile. These effects are mediated through the impact of hypoxia, systemic venous congestion, immune-mediated hepatic damage by inflammatory mediators induced by SARS-CoV-2 infection, the direct hepatic cytopathic effect of SARS-CoV-2, and the hepatotoxic effects of some medications used to treat SARS-CoV-2 infection such as Azithromycin, Chloroquine, Lopinavir, Ritonavir, and Tocilizumab. The hepatic damage could also result from SARS-CoV-2 reactivation of pre-existing liver diseases such as hepatitis B or C [39, 40].

SYNERGISM BETWEEN SARS-COV-2 AND ADENOVIRUS

Many studies showed an increased incidence of Adenovirus among children infected with SARS-CoV-2. Coinfection with SARS-CoV-2 and Adenovirus may also occur. Mohammadi *et al* showed that the rate of SARS-CoV-2 and Adenovirus coinfection is 1.1%, and all had mild respiratory disease [41]. Another study from Chicago, Illinois., The USA showed a 0.4% rate of SARS-CoV-2 and Adenovirus coinfection to come as the third common coinfection after Rhinovirus/Enterovirus and Influenza A viruses [42]. Another study from the UK showed a rate of 2% of coinfection of SARS-CoV-2 and Adenovirus, which increased the odds of death by 1.22 [43]. Another study from China found a slightly higher rate of 2.8% associated with a worse diagnosis than bacterial coinfection [44].

EPSTEIN-BARR VIRUS AS A POSSIBLE CAUSE:

Epstein-Barr virus (EBV) is a member of the Herpes virus family. It causes a heterogeneous group of infections in children and adults with a classic presentation, such as infectious mononucleosis and many other atypical presentations. Baker *et al* showed that EBV was identified in six out of nine children with acute hepatitis of unknown cause using molecular testing in Alabama, US. However, due to the absence of Ig M, it could be a reactivation of an old infection and not a primary one [12]. However, EBV was reported to cause acute hepatitis in adults as well. Garcia-Martinez *et al* reported coinfection of SARS-CoV-2 and EBV in 19 years old lady who presented with pyrexia, bilateral eyelid, and hemifacial swelling with splenomegaly, cervical lymphadenopathy and elevated AST and ALT [45]. In addition, Nadeen *et al* described the reactivation of EBV infection in a 62-year-old senior man due to coinfection with SARS-CoV-2. The patient presented with high AST and ALT [46]. However, the hepatitis-related causality of EBV cannot be proved, as many other factors were present in the reported cases.

QUESTIONS NEED TO BE ANSWERED:

Although both Adenoviruses and SARS-CoV-2 are not typically hepatotropic viruses and rarely cause acute hepatitis in immune-competent patients, coinfection with both viruses may produce significant effects on the liver and induce acute hepatitis-like syndrome. Many questions arise and need answers that could lead to uncovering the hidden possibilities for acute hepatitis of unknown origin. As there is an increased rate of autoimmune diseases after COVID-19 and its vaccines, could acute hepatitis of unknown cause be a type of COVID-19 -immune-triggered reaction? Could this syndrome be caused by new variants of either Adenovirus or SARS-CoV-2? Could Co-infections of SARS-CoV-2 and Adenoviruses trigger aggravated inflammatory responses affecting a sensitized liver and consequently induce acute hepatitis? Could acute hepatitis be a local form of the multisystem inflammatory syndrome as described by Cantor *et al* [47]? Could Adenoviruses serve as a vector for SARS-CoV-2 easing the access of SARS-CoV-2 inside the liver cells? Could this syndrome of acute hepatitis be

related to other non-discovered microbial or non-microbial agents? Other aetiologies cannot be ignored. Despite being isolated from cases with acute hepatitis of unknown cause, the role of adenoviruses in the pathogenesis of this syndrome is not yet proven. We need to have answers to these questions and a better-confirmed correlation between SARS-CoV-2 and Adenovirus infection and the development of this syndrome.

TREATMENT:

Treatment of acute hepatitis of unknown cause in children is mainly symptomatic, with supporting the liver function till recovery and treating of complications when present. Cidofovir can be tried when Adenovirus infection is suspected, particularly in children with organ transplants or severe viremia [48,49]. When multisystem inflammatory syndrome in children (MIS-C) is suspected as a cause of acute hepatitis, the treatment protocol is the same as the management of MIS-C [47]. Liver transplantation is indicated in children with acute fulminant hepatic failure not responding to aggressive supportive therapy or continuing to deteriorate despite active thorough medical treatment [50]. A summary of the treatment of acute hepatitis of unknown cause is illustrated in figure 5.

PREVENTION:

As SARS-CoV-2, Adenoviruses, EBV, and other viruses are highly suspected as a possible cause of acute hepatitis of unknown cause, appropriate hand hygiene and regular surface disinfection are highly required. Manoeuvres for hand and respiratory hygiene are essential for nonenveloped viruses such as Adenoviruses [49]. Healthcare professionals should be alert to the symptoms and signs of hepatitis in children. In suspected cases, clinicians should order serum ALT and AST transaminase testing to detect, diagnose, and suspect cases early.

CONCLUSION

There has been an increasing number of acute hepatitis of unknown origin in children since first reported on Mar 31, 2022. The exact aetiology of acute hepatitis of unknown cause in children that increased during the COVID-19 pandemic is still unclear. Despite Adenoviruses and SARS-CoV-2 being isolated from some patients with acute hepatitis of unknown cause, their role in the pathogenesis of this syndrome is not yet proven. Co-infection of SARS-CoV-2 with other viruses could be one of the possible mechanisms. However, many questions arise and need much effort and extensive and comprehensive research to reach the exact cause. Till that, we should exert every effort to prevent the development of this syndrome in children using the proper hygienic conditions. Prevention can be achieved through appropriate hand hygiene and regular surface disinfection. Treatment of acute hepatitis of unknown cause in children is mainly symptomatic, with liver support and treating complications when present.

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