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The recent outbreak of acute severe hepatitis in children of unknown origin – what is known so far

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Summary

At the beginning of April 2022, 10 cases of severe acute hepatitis of unknown origin in children <10 years of age were reported across central Scotland. Since then, case numbers have increased rapidly, with 191 probable cases identified across Europe, the United States of America, Israel and Japan. Until now, 17 children required liver transplantation and 1 died. Accordingly, the Centers for Disease Control and Prevention and the European Centre for Diseases Prevention and Control have both issued a warning on a hepatitis of unknown origin in children. This review focuses on the available information concerning this recent outbreak and introduces some of the potential explanations for its development.

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Introduction

On 5 April 2022, 10 cases of severe acute hepatitis of unknown origin in children <10 years of age were reported by the International Health Regulations (IHR) National Focal Point (NFP) for the United Kingdom across central Scotland.[1] Rapidly, numbers increased in the United Kingdom and cases have now been reported in 15 countries around the world. The majority of children were hospitalized. By now, the number of children admitted for acute hepatitis of unknown cause in 2022 is equal to or higher than the total number of annual admissions in England in previous years.[2,3] Recently, the Centers for Disease Control and Prevention (CDC) and the European Centre for Diseases Prevention and Control (ECDC) have issued a warning on a hepatitis of unknown origin in children.[4,5] To date, 17 children have required liver transplantation and 1 death has been reported.[6]

What is known?

Until 27 April 2022, reports of children with acute hepatitis have been continuing. At that time, approximately 191 probable cases of acute hepatitis of unknown aetiology from 15 countries have been identified, according to the definition used by the United Kingdom, with symptom onset since 1 January 2022. The majority of cases have been identified in Europe (the United Kingdom [111], Italy [17] Spain [12], Denmark [6], Ireland [<5], the Netherlands [4], Norway [2], France [2], Austria [2], Belgium [2], Germany [1], Poland [1] and Romania [1]). Additionally, 12 cases were reported in Israel and the United States of America and 1 case in Japan. A map displaying the distribution of cases across the affected countries is shown in Fig. 1. Seventeen children (~9%) have already required liver transplantation and 1 death has been reported.

The World Health Organization (WHO), the ECDC and the United Kingdom Security Agency posted reports on the recent outbreak with respect to all reported cases, cases from Europe and cases from the United Kingdom, respectively.[2,3,6] Affected children are mostly younger, aged from 1 month to 16 years old. As per case definition, severe acute hepatitis is present with high levels of aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] >500 IU/L). Thus, it is likely that there have been patients with milder cases of hepatitis which have not been reported.

For cases in England, the technical briefing reports 81 cases with a median age of 3 (IQR 3 to 4.5). 54.3% of children were female, the majority of white ethnicity (87.5%).[3] Patients presented predominantly with jaundice (74.1%) and vomiting (72.8%). Pale stools (58.0%), gastrointestinal symptoms (*i.e.* diarrhoea [49.4%] and nausea [39.5%]) and lethargy (55.6%) were frequently observed. Yet, fever (29.6%) and respiratory symptoms (19.8%) were less common.[3]

Typical viruses that are known to cause acute viral hepatitis (*i.e.* hepatitis A, B, C, D or E virus) have not been detected in the patients affected in any of the 15 countries. Interestingly, in England and Scotland, 75.5% and 50% of cases have tested positive for human adenoviruses (HAdVs). In some cases, molecular subtyping was performed; 18 children tested positive for adenovirus F type 41. However, other HAdV types have been detected in blood and non-blood samples, and the low levels of adenovirus present in blood samples make it difficult to recover high quality genomes.[3] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in 20 children, 19 of whom had HAdV and SARS-CoV-2 coinfection.[6] Data on

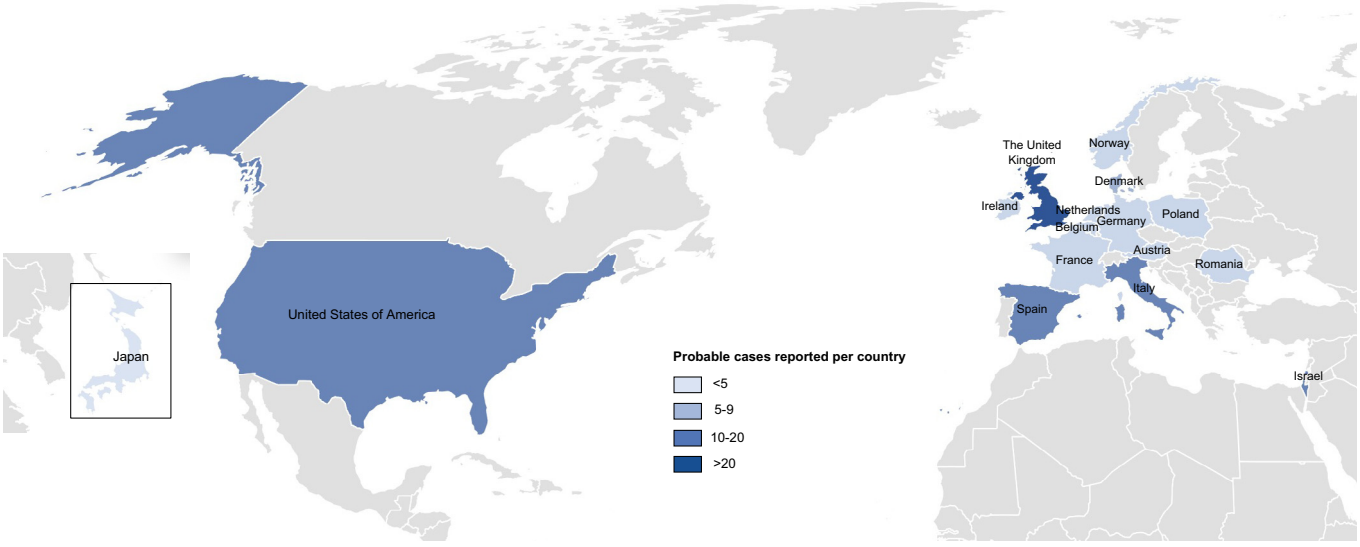

Fig. 1. Map displaying the distribution of cases according to case definition used by the UK across the affected countries as of 27 April 2022 for Europe, 25 April 2022 for the United States of America and Japan, 20 April 2022 for the United Kingdom and 19 April 2022 for Israel.

SARS-CoV-2 variants involved are limited at this time.[3]

Although initially epidemiological links were observed in Scotland (2 pairs of cases), no other clusters have been reported so far.[2] Trawling questionnaires have not revealed any notable exposures with regard to travel, family structure, parental occupation, diet, water source, exposure to animals or toxicants. No paracetamol overdoses, as an important hepatotoxic agent, have been recorded.[3] Reliable data from toxicology investigations are still pending.

Human adenovirus (HAdV) infection

HAdVs are non-enveloped doubled-stranded DNA viruses which are common pathogens with a worldwide distribution; they usually cause self-limited infections in the healthy population. However, severe or disseminated HAdV infections may occur in some individuals,[7] more commonly in immunocompromised patients.[8,9] More than 5-10% of all febrile illnesses in infants and young children are caused by HAdVs and nearly all adults have serologic evidence of past infection with one or more HAdVs.[10]

Infections present throughout the year without particular seasonality.[11] Epidemics occur globally, *e.g.* in closed or crowded settings or communities.[12,13] Typical transmissions are inhalation of aerosolized droplets, faecal-oral spread or conjunctival inoculation. As the virus can survive for long periods on environmental surfaces, acquisition from exogenous sources (*e.g.* pillows, linens) has been described.[14] Additionally, HAdV reactivation may occur in immunocompromised patients.[11] Polymerase chain reaction from respiratory material, stool, blood or urine samples is the most common method to establish the diagnosis.[15]

Following an incubation period of 2 to 14 days, typical serotype-specific clinical manifestations are observed, partially determined by differences in cell tropism.[11,15] Symptoms often reported include, but are not limited to, respiratory tract infections (*e.g.* pharyngitis, coryza or pneumonia, especially serotype 1-5, 7, 14 and 21), keratoconjunctivitis (particularly serotypes 8, 19 and 37), gastrointestinal symptoms (*e.g.* diarrhoea, abdominal pain, vomiting, notably serotype 40 and 41, but possible as concomitant symptoms for all serotypes, particularly in young children) or genitourinary tract infections (especially serotypes 11, 34 and 35).[15] Hepatitis is observed in immunocompromised patients including neonates, notably with serotypes 1,3,5 and 7.[8,15,16] Disseminated infection causing hepatitis has been reported in paediatric liver transplant recipients, with deaths being observed in this scenario.[8,17] So far, only a few cases of severe acute hepatitis or even liver failure have been described in immunocompetent children due to HAdV infection.[18,19]

HAdV F serotype 41, which has been identified in 18 children in the recent outbreak, belongs to a group of serotypes which are most commonly associated with human disease and is one of the most prevalent HAdVs in the United Kingdom.[15,20] Typical symptoms of HAdV serotype 41 infections include diarrhoea, vomiting and fever, often accompanied by respiratory infections. So far, this

serotype has not been associated with hepatitis or liver failure in immunocompetent children.[15,21]

Treatment options for HAdV infections are limited and are mainly supportive. There is no evidence supporting antiviral therapy, though there are reports of immunocompromised patients being successfully treated with cidofovir, which is used for severe or disseminated HAdV infections in transplant settings. Additional intravenous immunoglobulin may be beneficial in some patients, especially those with severe hypogammaglobulinemia.[22,23]

Perspective

To date, the aetiology of this outbreak of severe hepatitis in children remains unknown.

The WHO has created a current working case definition which both the WHO and the ECDC recommend using to identify and classify future cases for the time being (Table 1). Earlier, slightly differing case definitions were used in the United Kingdom, which the ECDC asked countries to use early in the outbreak; case numbers presented in current reports from the UK and ECDC and in this review are based on this older definition (Table 1).

Further results on epidemiological investigations, clinical and exposure history, virological/microbiological and toxicological testing are pending. The WHO and the ECDC are supporting these investigations and for Europe, a joint WHO/ECDC data collection initiative has been established, using the European Surveillance System (TESSy). Cases fulfilling the case definition (see also Table 1) should be reported to TESSy.[2,6] The reporting protocol can be downloaded elsewhere.[24]

In the meantime, the ECDC recommends reinforcing general hygienic practices (*e.g.* hand hygiene, disinfection of surfaces etc.) in settings attended by young children.[2] Table 2 depicts a testing approach for probable and epi-linked cases of severe acute hepatitis that was recently suggested by the ECDC.[2]

HAdVs were found in many children, and in all cases from England – where molecular subtyping was performed – the HAdV serotype F 41 was identified.[3] This serotype has been associated with gastrointestinal symptoms in the past, but hepatitis has not been reported in healthy individuals infected with this serotype until recently. Moreover, hepatitis resulting from HAdV infections is usually asymptomatic in immunocompetent children or the clinical manifestations are mild and self-limiting. In this outbreak many hepatic manifestations are severe and several liver failures necessitating liver transplantation have been reported. Thus, HAdV infections with an additional (not yet identified) cofactor rendering normal infections more severe or causing them to trigger immunopathology are the most likely assumption supported by the current data. Interestingly, laboratory data revealed a marked exceedance of HAdVs, driven by HAdVs in faecal samples (in comparison to respiratory samples).[3] As gut tropism of HAdVs F 41 is a well-known feature of this serotype this might already explain the observed phenomenon. However, it could also imply and even closer linkage of this HAdV (variant) to the gut and liver (i.e. the reported hepatotropic features).

During the COVID-19 pandemic, a lower level of circulation of several respiratory viruses has been observed, including HAdVs in adults and children.[25–27] Similar to the HAdV outbreak in the United Kingdom and the Netherlands, an increase of other viruses, *i.e.* respiratory syncytial virus

Table 1. Working case definition of the current outbreak of acute severe hepatitis of unknown origin by the WHO, England, Wales, Northern Ireland and Scotland as of 25 April 2022.[6]

Current WHO and ECDC case definition	
Case definition	**Description**
Confirmed	N/A at present
Probable	A person presenting with an acute hepatitis (non-HepA-E) with serum aminotransferases >500 IU/L (AST or ALT), who is 16 years and younger, since 1 October 2021
Epi-linked	A person presenting with an acute hepatitis (non-HepA-E) of any age who is a close contact of a probable case, since 1 October 2021
England, Wales, Norther Ireland case definition (previously used by ECDC)	
Case definition	Description
Confirmed	A person presenting with an acute hepatitis (non-hepA-E) with serum aminotransferases >500 IU/L (AST or ALT), who is 10 years old and under, since 1 January 2022
Probable	A person presenting with an acute hepatitis (non-hepA-E) with serum aminotransferases >500 IU/L (AST or ALT), who is 11 to 16 years old, since 1 January 2022
Epi-linked	A person presenting with an acute hepatitis (non-hepA-E*) of any age who is a close contact of a confirmed case, since 1 January 2022
Scotland case definition (used in Scotland for initial cases)	
Case definition	Description
Confirmed	A person presenting with serum aminotransferases >500 IU/L (AST or ALT) without any known cause, who is 10 years and under or a contact of any age of a possible or confirmed case, since 1 January 2022
Probable	A person presenting with jaundice without any known cause, who is 10 years and under or a contact of any age of a possible or confirmed case, since 1 January 2022

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 2. ECDC's recommended testing approach for probable and epi-linked cases of severe acute hepatitis of unknown origin - adopted from the rapid risk assessment report.[2]

Sample type	Pathogen
Blood	
Serology	Hepatitis A, B, C, D*, E, cytomegalovirus, Epstein-Bar virus, varicella, HIV, SARS-CoV-2 anti-S and anti-N), adenovirus**
Serology	*Brucella* spp., *Bartonella henselae, Borrelia burgdorferi* (if epidemiologically appropriate)
Culture	Routine procedures for bacterial pathogens, if clinically applicable
Culture	Adenovirus, cytomegalovirus, Epstein-Bar virus, herpes simplex virus, influenza
PCR	Adenovirus**, enteroviruses, cytomegalovirus, Epstein-Bar virus, herpes simplex virus, HHV6 and 7, parechovirus, hepatitis A, C, E
Toxicological screening	
Throat swab	
PCR	Respiratory virus screening by multiplex assay (including influenza, adenovirus, parainfluenza, rhinovirus, respiratory syncytial virus, human bocavirus 1-3 etc), SARS-CoV-2, enteroviruses, human metapneumovirus
Culture	Streptococcus group A
Stool or rectal swab	
PCR	Enteric viruses screening by multiplex assay (including, norovirus, enteroviruses, rotavirus, astrovirus, sapovirus)
PCR	Enteric bacterial pathogens
Culture	*Campylobacter, Salmonella, Shigella, E. coli* 0157
Culture	Adenovirus, Enteroviruses, Rotavirus
Urine	
PCR	*Leptospira*
Culture	Routine procedures for bacterial pathogens, if clinically applicable
Toxicological screening	

*Testing for hepatitis D, only in cases positive for hepatitis B.
**In adenovirus testing, detection in whole blood is regarded as superior to testing in serum.

infections, as a part of a delayed epidemiological peak has recently been reported in children.[27] The severity of this outbreak could be the result of an increased susceptibility amongst young children that developed during the COVID-19 pandemic as a consequence of a lower level of HAdV circulation in the last 2 years.

Another cofactor influencing HAdV infections' severity might be a prior or coincidental SARS-CoV-2 infection. SARS-CoV-2 infection has been confirmed in 20 children so far. Yet, not all children were initially tested for SARS-CoV-2 as reported by local authorities and it is unknown how many children have already gone through (an unnoticed) infection earlier.[3,6] In fact, hepatic involvement has been described in children with COVID-19.[28] However, it typically presents with mild hepatitis and preserved liver function. There are rare cases of severe hepatitis described in the literature that may occur as part of COVID-19 or multisystem inflammatory syndrome in children.[28,29] The effect of consecutive or coincidental infections with HAdV and SARS-CoV-2 – which may involve only the Omicron or other SARS-CoV-2 variants – are not known. Other cofactors (*i.e.* toxins, drugs, environmental exposure or another infection) that might affect HAdV infection have not yet been unravelled.[3]

Apart from that, there is the possibility that the outbreak is caused by the emergence of a new HAdV with altered characteristics with or without a contribution of one of the cofactors mentioned above. Durable data to support this hypothesis are lacking, especially as results of whole genome sequencing from multiple cases are pending. However, the phenomenon that a novel human HAdV arises from naturally occurring genome recombination is a possible scenario.[30]

Though rather unlikely, the detection of HAdV infections may be merely coincidental. In fact, in the United Kingdom and also in the Netherlands a significant increase in HAdV infections (particularly in faecal samples in children) have been reported.[3,6] However, it is possible that the increment in diagnosed HAdV infections is the result of increased testing and current vigilance.[6] Similarly, as part of the ongoing pandemic, SARS-CoV-2 infections may just be coincidental. Then, another drug, toxin, a novel pathogen or environmental exposure would be the alternative explanation.

At present, COVID-19 vaccinations can be ruled out as a potential trigger as most children affected have not been vaccinated.[6] No links have been seen so far regarding (other) adenovirus-based vaccines. Beside others, HAdV serotype 5 has been widely used for the construction of adenoviral vectors.[31] As cultivation of HAdV F 41 remains difficult, using this serotype for studies involving the construction of vectors for vaccination or gene transfer has been an exception.[32,33] Yet, further data is needed to investigate possible similarities and resulting interactions between currently used vaccine vectors and this (new) HAdV variant.

Taken together, as information is limited, additional data is urgently needed to confirm or dismiss one of these hypotheses and explain the described outbreak of severe hepatitis. Original articles on

the pathogenesis, the clinical course and the respective treatment options would be welcomed by the *Journal of Hepatology*.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDC, Centers for Disease Control and Prevention; ECDC, European Centre for Diseases Prevention and Control; HAdV, human adenovirus; IHR, International Health Regulations; NFP, National Focal Point; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TESSy, European Surveillance System; WHO, Word Health Organization.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Authors' contributions

The authors contributed equally to the production of this manuscript.

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