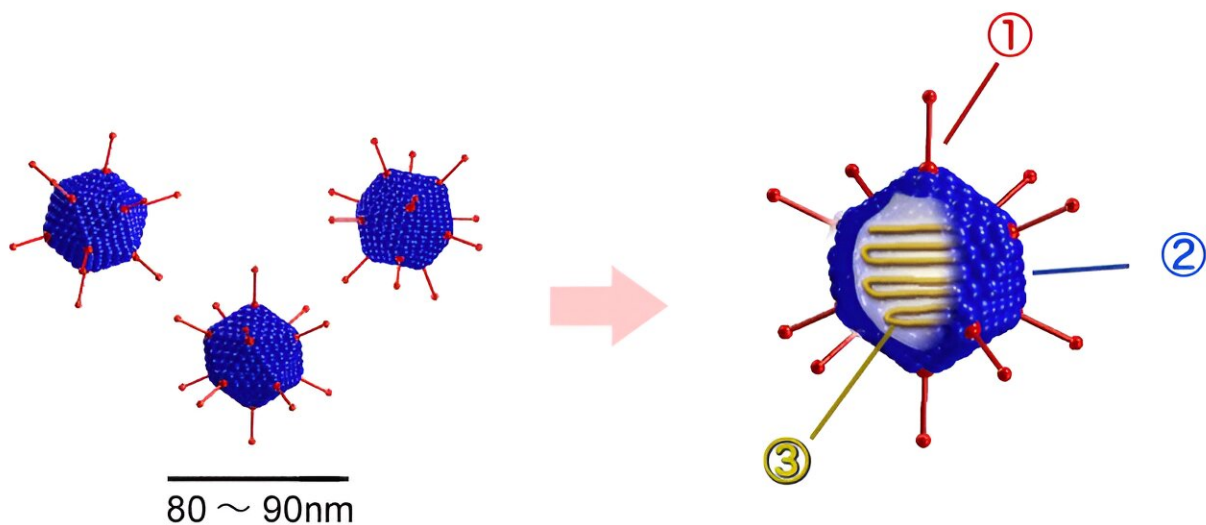


Investigating acute hepatitis of unknown origin in children

July 28 2023



Adenovirus structure. 1) penton capsomeres 2) hexon capsomeres 3) linear double-stranded DNA. Credit: American Society for Microbiology

Since Fall 2021, an increasing number of unexplained cases of severe acute hepatitis have been reported in children. Epidemiologic investigation is ongoing, and, to date, a cause of these outbreaks has not been identified. Because adenovirus infection has been detected in some (but not all) cases, it is being investigated as one of many potential causes of the hepatitis. What are the primary known causes of hepatitis?

How was adenovirus identified as a possible contributor? What else has the epidemiologic investigation revealed about these outbreaks, and what has yet to be determined?

What causes hepatitis?

Hepatitis means inflammation of the liver. The inflammation can impair functions of the liver and lead to release of enzymes normally found inside hepatocytes into the blood. Generally, hepatitis is acute if the liver inflammation lasts for less than 6 months. Many infectious and noninfectious conditions can cause hepatitis.

Viral causes of acute hepatitis include the hepatitis viruses (A-E), which together are the most common cause; Epstein Barr [virus](#) (EBV); cytomegalovirus (CMV); [herpes simplex virus](#) (HSV); coxsackievirus; [dengue virus](#); adenovirus and SARS-CoV-2. Approximately 1.4 million deaths are caused by viral hepatitis globally each year, 90% of which are attributed to the hepatitis B and C viruses.

Adenovirus infection in children

Human adenovirus was first discovered in 1953, when Dr. Wallace Rowe and his team isolated the virus from human adenoids, lymphatic tissues found in the back of the throat. Since this discovery, the human adenoviruses have been grouped into 7 species, and over 100 types have been characterized.

The adenoviruses are double-stranded, linear DNA viruses that cause various diseases and symptoms. Typically, individual adenovirus species are associated with specific infections. Examples of this include gastroenteritis (species F and G), pneumonia (species B, C, E), hepatitis (species C), meningoencephalitis (species A, B, D) and conjunctivitis

(species B and D).

Human adenovirus types F40 and F41 are significant causes of gastroenteritis in children worldwide. Unlike other types, adenovirus F41 possesses numerous characteristics that allow it to evade stomach pH and infect gastrointestinal tissue.

In addition, adenovirus infections can be severe in patients with underlying immune compromise and have been known to cause hepatitis in these patients. Finally, although adenovirus may play a role in liver injury in ordinarily healthy children, this has not been well-documented in the literature and is an area in need of further investigation.

The hepatitis outbreak

In October 2021, pediatricians at Children's Hospital of Alabama noticed a disturbing trend. Children began presenting with acute hepatitis and a variety of symptoms, including vomiting, diarrhea, abdominal pain and jaundice. Although they tested negative for hepatitis viruses, adenovirus was detected in their blood.

The presentation of 5 such patients resulted in a statewide alert across Alabama, and subsequent retrospective investigation revealed an additional 4 patients admitted for hepatitis of unknown etiology and concomitant [adenovirus infection](#). All 9 patients were previously healthy, with no significant known comorbidities, and adenovirus was detected in the blood of all patients using polymerase chain reaction (PCR) testing.

Sequencing of a region of the adenoviral hexon gene was performed on the samples from 5 patients, and adenovirus 41 was detected. Of the 9 patients with hepatitis, 7 had viral coinfection with adenovirus and at least one other virus confirmed by PCR. Co-infecting viruses included EBV (from blood) and several viruses from respiratory samples,

including enterovirus or rhinovirus, metapneumovirus, respiratory syncytial virus and human coronavirus OC43.

Coronavirus OC43 is different from SARS-CoV-2, the coronavirus that causes COVID-19. Hepatitis A, B and C viruses were not detected in any of the children.

On April 5, 2022, the World Health Organization (WHO) was notified of severe acute hepatitis of unknown cause in 10 children across Scotland. All patients were noted to be previously healthy, and their ages ranged from 11 months to 5 years. Most patients developed symptoms a month earlier, which included jaundice, diarrhea, vomiting and abdominal pain.

This cluster of cases led to further retrospective investigation across the United Kingdom, where a total of 74 cases were identified. Importantly, the hepatitis viruses (A, B, C, E and D where applicable) were ruled out in all cases.

As of April 21, WHO reported at least 169 cases of acute hepatitis of unknown cause(s) in patients aged 1 month to 16 years across the world. Early in the outbreak, detailed questionnaires were used in the U.K. to determine patient's eating, drinking and personal habits, which failed to identify a common exposure between cases. In the absence of data supporting a toxicologic or environmental cause, health agencies suspect that an infectious agent is the most likely cause of the current acute hepatitis outbreak.

According to WHO and the European Center for Disease Prevention and Control (ECDC), viruses have been detected in samples from some of the hepatitis patients and these include:

- Adenovirus has been detected in at least 74 out of 169 cases.

- In England and Scotland, 75.5% and 50% of cases were positive for adenovirus, respectively.
- Subtyping of 11 cases from the U.K. confirmed the presence of adenovirus F41.
- SARS-CoV-2 was detected in 20 cases.
- Adenovirus and SARS-CoV-2 coinfection was detected in 19 cases.

Although the investigation into infectious and environmental causes of acute hepatitis in children is underway, the COVID-19 vaccine is considered a very unlikely cause, since most of the affected children have not received the vaccine. Currently, the Centers for Disease Control (CDC) recommends that clinicians continue to evaluate and treat patients with hepatitis of unknown etiology as they normally would and also consider adenovirus testing, preferably by PCR of blood, in these patients.

Because this is an ongoing investigation, and etiologies other than adenovirus are also being explored, the CDC requests information about cases that meet the definition of acute hepatitis. Providers and laboratories should contact their public health department when a possible case is encountered. The CDC continues to work closely with providers and laboratories to determine best testing practices.

The outbreak investigation process

It is important to note that determining the cause of an outbreak is not as straightforward as simply counting cases and picking the most common exposure. After deciding a working case definition of a condition, epidemiologists collect data on cases and use an appropriate denominator (i.e., the number of people in a population) to calculate disease rates. These rates can then be compared over time to assess trends in the prevalence of disease.

Context is also key to understanding the association between exposures and disease. For example, understanding the current levels of viral infection in the community by different age groups can help investigators understand if infection rates, particularly with adenovirus, are above what would typically be expected. As of April 29, the ECDC reported that the number of positive adenovirus tests in young children (ages 1-4) is currently higher than in the previous 5 years.

Between November 2021 and March 2022, 200-300 cases were reported per week, whereas 50-150 were reported per week in the pre-pandemic period.

While various factors may contribute to the increased number of positive adenovirus tests, it is essential to consider changes in diagnostic testing approaches and the impact of improved detection methods that may have been implemented over the last several years.

The current working hypotheses

The outbreak data collected to date demonstrate that the current cause of acute hepatitis in children may be more complicated than just 1 [infectious agent](#). While the hypotheses of outbreak investigations are subject to change as new data are collected, forming a working hypothesis is critical to the investigation. The working hypotheses are as follows, in order of best fit with currently available data:

A cofactor is causing normally mild adenovirus infections to be more severe or is causing them to trigger a severe immune response in children. These cofactors (according to the ECDC) may include:

1. Patient susceptibility (for example, due to a lack of prior exposure to adenoviruses during the pandemic); a prior infection with SARS-CoV-2 or another infection; a coinfection with SARS-

CoV-2 or another infection; a toxin, drug or environmental exposure.

2. A novel variant adenovirus, with, or without, a contribution from a cofactor as listed above.
3. A drug, toxin or environmental exposure.
4. A novel pathogen, either acting alone, or as a coinfection.
5. A new variant of SARS-CoV-2.

The full rapid risk assessment from the ECDC can be found [here](#).

Investigation updates

As of July 5, 2023 the cause of the pediatric acute hepatitis outbreak was still unknown, with 395 patients under investigation. The CDC classifies a patient as being under investigation if they meet the following criteria, "Children 500 U/L) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) since October 1, 2021, who have an unknown etiology for their hepatitis (with or without any adenovirus testing results, irrespective of the results)." Adenovirus infection is still the leading working hypothesis. Of the 299 patients under investigation who received adenovirus testing, 45% were found to be positive.

In the U.K. cohort of children undergoing investigation, 66% of children who received adenovirus testing were positive for human adenovirus. Further sequencing investigation of these patients demonstrated that human adenovirus 41F was the predominant subtype in patients with acute liver failure. However, adenovirus 41F is not known to infect liver cells, making its role in pediatric acute liver failure unclear.

Researchers in the U.K. and the U.S. have also found large amounts of adeno-associated virus type 2 (AAV-2) on analysis of blood and tissue from these same patients, a virus which cannot replicate without a helper virus like human adenovirus. It is possible that a combination of host

immunologic factors and the interplay between human [adenovirus](#) and AAV-2 may be responsible for the liver failure seen in pediatric [patients](#).

Although reports of acute [hepatitis](#) in children have seemed to wane in recent months, investigations into the cause are ongoing. Public health agencies continue to recommend good handwashing practices and staying home when sick to help prevent the spread of common childhood infectious diseases

Provided by American Society for Microbiology

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