Hypothesis that acute hepatitis of unknown origin in children is caused by adeno-associated virus 2

Daisuke Miyazawa[1]

[1]Affiliation not available

May 9, 2022

Acute hepatitis of unknown origin in children is currently being reported around the world, especially in Europe and the United States.

Of the 163 cases in the UK outbreak, 126 were tested for adenovirus, 91 were detected, and 18 of the 33 cases with adenovirus in the blood were successfully subtyped, all of which were type 41, a well-known cause of acute gastroenteritis in children[1].

In the United Kingdom, positive adenovirus test reports in children aged 1-4 years decreased in the year beginning April 2020 compared to the previous 5 years, but have increased significantly since November 2021 compared to the previous 5 years[1]. The timing of this increase coincides with the occurrence of acute hepatitis of unknown origin. An increase in adenovirus circulation in the community has also been reported in the Netherlands recently [2]. Gastrointestinal symptoms such as diarrhea and nausea were commonly reported prior to admission, which is consistent with the typical clinical presentation of type 41 infection, an intestinal adenovirus [1,3].

Adenovirus DNA levels in blood and serum have been noted to be approximately 12 times higher in liver transplant recipients than in non-transplant recipients[4].

Normally, however, adenoviruses do not cause hepatitis in children with healthy immunity[1]. In immunodeficiency, some serotypes of adenovirus have been reported to cause hepatitis, but even then, serotype 41 is not common[5].

In the case of adenovirus, there is a "threshold effect" that prevents the virus from reaching the hepatocyte unless adenovirus capture by liver Kupffer cells is saturated[6]. Therefore, a small amount of adenovirus in the blood does not readily infect hepatocytes, and if it does, there should be at least a finding that the Kupffer cells are saturated with adenovirus. However, liver biopsies from six U.S. patients showed no immunohistochemical evidence of adenovirus and no electron microscopic evidence of viral particles[3]. Therefore, it is unlikely that the adenovirus is infecting the hepatocytes and causing hepatitis.

On the other hand, metagenomic analyses of blood and liver tissue have detected large amounts of adeno-associated virus type 2 (AAV-2) [1].

Adeno-associated virus (AAV) is used as a vector for gene therapy targeting hepatocytes and has the property of reaching hepatocytes efficiently. AAVs are generally considered non-pathogenic, but in a high-dose gene therapy trial with the AAV type 8 vector, two patients died due to progressive liver dysfunction[7].

Temporary liver inflammation and transient elevation of liver enzymes following intravenous administration of AAV-2 are reported[8].

Possible mechanisms of hepatotoxicity following high-dose intravenous administration of AAV may point to complement activation[9].

It is possible that inadequate immunity to AAV-2 or large amounts of AAV-2 can cause liver dysfunction. Since AAV is a virus that can multiply only in the presence of helper viruses such as adenovirus, it is reasonable to assume that AAV-2, detected in large quantities in blood and liver, multiplied as a result of adenovirus type 41 infection.

Adenovirus type 41 is transmitted through the fecal-oral route.

Countries where hepatitis of unknown origin in children is seen tend to be those with good sanitary conditions, such as Europe, the United States, and Japan. Prevalence of serum neutralizing antibodies to adenovirus type 41 in Chinese children is associated with age and sanitary conditions[10]. The younger the age and the better the sanitary conditions, the lower the prevalence.

The difference in adenovirus 41 neutralizing antibody titers diminished in children over 3 years of age[10]. These results indicate that childhood sanitary conditions is an important factor affecting adenovirus 41 neutralizing antibody titers. Neutralizing antibodies Prevalence of AAV-2 in adults is also low in the United States (30%) and Europe (about 35%), where sanitary conditions are considered good, and as high as 70% in Africa [11]. Positive rates of neutralizing antibodies to AAV-2 have also been reported to increase with age[12,13].

A possible link between waned immunity to respiratory syncytial virus in the COVID-19 pandemic and the interseasonal re-emergence of RSV cases seen worldwide has been raised. [14].

In countries with good sanitation, the proportion of children with low immunity to adenovirus and AAV-2 was originally high and may have been further exacerbated by the measures taken against COVID-19. If an outbreak of adenovirus 41 and AAV-2 were to occur among such children, it is possible that some children would develop hepatitis.

Adenovirus and AAV are non-enveloped viruses, and alcohol disinfection is less effective. Considering the above possibilities, it would be appropriate for facilities where children congregate to use disinfectants effective against non-enveloped viruses, such as hypochlorous acid, and to increase the frequency of hand washing under running water, as a precautionary principle. Also, as was the case with the re-emergence of RSV cases seen worldwide, if this hepatitis in children were caused by the above, the epidemic could form a peak and converge in 2-3 months. Closure of child care facilities for short periods of time during the most prevalent epidemics may also be a consideration. It may also be useful to investigate whether the child's attendance at day care centers or other facilities is a risk factor. During lockdown, it may be advisable to investigate the prevalence of adenovirus type 41 and AAV-2 antibodies in children, especially in countries with good original sanitary conditions.

1. UK Health Security Agency. Investigation into acute hepatitis of unknown aetiology in children in England Technical briefing 2. London, United Kingdom: Department of Health and Social Care, UK Health Security Agency; 2022.*https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1073704/acute-hepatitis-technical-briefing-2.pdf*

2. World Health Organization. Multi-Country – acute, severe hepatitis of unknown origin in children. Geneva, Switzerland: World Health Organization; 2022. Accessed April 23, 2022.*https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON376*

3. Baker JM, Buchfellner M, Britt W, et al. Acute Hepatitis and Adenovirus Infection Among Children - Alabama, October 2021-February 2022. MMWR Morb Mortal Wkly Rep. 2022 May 6;71(18):638-640. doi: 10.15585/mmwr.mm7118e1. PMID: 35511732.

https://www.cdc.gov/mmwr/volumes/71/wr/mm7118e1.htm

4. UK Health Security Agency. Investigation into acute hepatitis of unknown aetiology in children in England Technical briefing. London, United Kingdom: Department of Health and Social Care, UK Health Security Agency; 2022.

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_-data/file/1071198/acute-hepatitis-technical-briefing-1_4_.pdf

5. Hierholzer JC. Adenoviruses in the immunocompromised host. Clin Microbiol Rev 1992;5:262–74. *https://doi.org/10.1128/CMR.5.3.262external icon*

6. Tao N, Gao GP, Parr M, et al. Sequestration of adenoviral vector by Kupffer cells leads to a nonlinear dose response of transduction in liver. Mol Ther. 2001 Jan;3(1):28-35. doi: 10.1006/mthe.2000.0227. PMID: 11162308.

7. Morales L, Gambhir Y, Bennett J, Stedman HH. Broader Implications of Progressive Liver Dysfunction and Lethal Sepsis in Two Boys following Systemic High-Dose AAV. *Mol Ther* . 2020;28(8):1753-1755. doi:10.1016/j.ymthe.2020.07.009

8. Wang L, Wang H, Bell P, et al. Systematic evaluation of AAV vectors for liver directed gene transfer in murine models. *Mol Ther* . 2010;18(1):118-125. doi:10.1038/mt.2009.246

9. Flotte TR Editor-in-Chief. Revisiting the "New" Inflammatory Toxicities of Adeno-Associated Virus Vectors. Hum Gene Ther. 2020 Apr;31(7-8):398-399. doi: 10.1089/hum.2020.29117.trf. PMID: 32302233.

10. Yang WX, Zou XH, Jiang SY, et al. Prevalence of serum neutralizing antibodies to adenovirus type 5 (Ad5) and 41 (Ad41) in children is associated with age and sanitary conditions. Vaccine. 2016 Nov 4;34(46):5579-5586. doi: 10.1016/j.vaccine.2016.09.043. PMID: 27682509; PMCID: PMC7115419.

11. Roberto Calcedo, Luk H. Vandenberghe, Guangping Gao, et al. Worldwide Epidemiology of Neutralizing Antibodies to Adeno-Associated Viruses, *The Journal of Infectious Diseases* , Volume 199, Issue 3, 1 February 2009, Pages 381–390, *https://doi.org/10.1086/595830*

12. Calcedo R, Morizono H, Wang L, et al. Adeno-associated virus antibody profiles in newborns, children, and adolescents. *Clin Vaccine Immunol* . 2011;18(9):1586-1588. doi:10.1128/CVI.05107-11

13. Mimuro J, Mizukami H, Shima M, et al. The prevalence of neutralizing antibodies against adeno-associated virus capsids is reduced in young Japanese individuals. J Med Virol. 2014 Nov;86(11):1990-7. doi: 10.1002/jmv.23818. Epub 2013 Oct 17. PMID: 24136735.

14. Frederic Reicherz, Rui Yang Xu, Bahaa Abu-Raya, et al. Waning immunity against respiratory syncytial virus during the COVID-19 pandemic, *The Journal of Infectious Diseases* , 2022;, jiac192, *https://doi.org/10.1093/infdis/jiac192*