Annals of Hepatology 27 (2022) 100731

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Editorial

Clues to decipher the origin of severe acute hepatitis in children: a new enigma during the COVID-19 pandemic

ARTICLE INFO

Key Words:
viral hepatitis
liver disease and children
Hepatitis E Virus

Recently, reports of pediatric patients with severe acute hepatitis have emerged worldwide. The etiology of the disease remains unknown. Whether Adenovirus, SARS-CoV-2 or other viral etiologies, including Hepatitis E Virus, are related to the disease is debated. On April 5, 2022, when the progressive return to normality post COVID-19 pandemic seemed to be a reality worldwide, the United Kingdom (UK) became a hotspot with the notification of acute severe hepatitis without a specific etiology in children [1]. After ten days of the first UK notification, the World Health Organization (WHO) published an alert on severe acute hepatitis cases of unknown origin in children. Since then, as of May 2022, over 400 cases have been reported from 21 countries [2,3].

Globally, the reported cases refer to previously healthy children aged one month to 16 years suffering from signs and symptoms of acute hepatitis, including vomiting, jaundice, abdominal pain and nausea. Several patients progressed to acute liver failure; at least one death has been reported and liver transplantation was required in 17 cases [4]. Hepatitis A, B, C, D and E viruses, typical infectious causes of liver disease, were not identified in any of the cases. Surprisingly, as many as half of the children tested for Adenovirus were positive, and out of 18 subtyped cases in the UK, all were identified as having Adenovirus 41 subtype F [5,6].

Adenovirus is a common virus transmitted by respiratory droplets and from direct contact with infected people or contaminated surfaces. It can cause diarrhea, conjunctivitis, vomiting, and cold symptoms, but rarely hepatitis; it predominantly affects immunocompromised individuals and young children [7]. In parallel, SARS-CoV-2 has been identified in 18% of the reported cases of severe acute hepatitis in the UK. Moreover, 11% of 97 cases of severe acute hepatitis in England tested positive for SARS-CoV-2 on admission and three additional cases prior to admission [5,6]. Ongoing serological testing will likely yield greater numbers of children with previous or current SARS-CoV-2 infection. Based on current information, most children with severe hepatitis had not received a COVID-19 vaccine, ruling out a link between these cases and vaccination. Although studies of hepatic involvement in COVID-19 in the pediatric population are limited, and most cases reported showed a mild elevation of ALST and AST [8], severe SARS-CoV-2 infection resulting in multiorgan failure and multisystem inflammatory syndrome in children (MIS-C) has been associated with clinically significant hepatitis in children [9]. Indeed, preliminary data suggest that in the absence of severe respiratory or other symptoms, SARS-CoV-2 infection may be associated with MIS-C as a result of complementary hyperactivation [10].

Currently, the leading hypotheses explaining severe acute hepatitis cases center around Adenovirus, either a new variant with a distinct clinical presentation or a routinely circulating variant that more severely impacts younger children who are immunologically naïve. However, when liver biopsies were conducted Adenovirus was not found in liver tissue. This finding is not consistent with the predominant role proposed for this virus in the severe acute hepatitis cases reported worldwide [11].

An additional hypothesis suggests that severe acute hepatitis might be a consequence of Adenovirus infection with intestinal trophism in children previously infected by SARS-CoV-2. The SARS-CoV-2 detected in feces of patients, even after their nasopharyngeal specimens were found to be negative, suggests that SARS-CoV-2 infection can result in the formation of viral reservoirs in the gut [8,12]. Therefore, viral persistence in the gastrointestinal tract can lead to repeated release of viral proteins across the intestinal epithelium, giving rise to immune activation. Such repeated immune activation might be mediated by a superantigen motif within the SARS-CoV-2 spike protein [13], triggering broad and non-specific T-cell activation. This superantigen-mediated immune cell activation has been proposed as a causal mechanism of MIS-C [14,15].

Finally, other etiologies cannot be discarded. Acute hepatitis has been reported in children with MIS, but coinfection with other viruses has not been investigated [2,4]. The possibility of typical viral hepatitis as etiologies causing severe acute hepatitis was discarded through conventional molecular methods that detect specific regions in viral genomes; therefore, it is also plausible that new variants are circulating without being detected. In this regard, HEV may be of special interest because of its broad distribution worldwide, which contrasts with the distribution of HAV, HBV and HCV, in which the infections are restricted to specific geographic regions. Moreover, the burden of liver disease caused by HEV infection is unknown [16]. Hence, HEV surveillance is required. This will allow anticipating the potential role of this virus in emergency situations as the result of the COVID-19 pandemic.

In summary, isolation of very young children during the pandemic lockdown may have left them immunologically vulnerable because

https://doi.org/10.1016/j.aohep.2022.100731
1665-2681/© 2022 Published by Elsevier España, S.L.U. on behalf of Fundación Clínica Médica Sur, A.C. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

they were not exposed to the multiplicity of common circulating viruses. Therefore, severe acute hepatitis cases might not have a single cause. Because current treatments seek to alleviate symptoms as well as to manage and stabilize the severe cases, parents and clinicians are expected to remain vigilant to symptoms such as vomiting or diarrhea and signs of jaundice. The WHO recommends that countries stay informed through technical support provided by official agencies and, monitor cases. Whether emerging or re-emerging viruses will affect liver function in the near future is unknown. Data are needed to characterize the enigmatic cause of severe acute hepatitis in children, with the ultimate goal of developing new diagnostics as well as preventive and therapeutic methods for treating the disease.

Funding

This work was partially funded by Grant IA201422 awarded to N. A. F. by the Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica (PAPIIT), Dirección General de Asuntos del Personal Académico (DGAPA), Universidad Nacional Autónoma de México (UNAM).

Declarations of interest

None

References

[1] PAHO/WHO. Technical Note: Acute, severe hepatitis of unknown origin in children. 29 April 2022. (who.int) Health Emergencies (/en/health-emergencies) Epidemiological Alerts and Updates
[2] Multi-Country-Acute, severe hepatitis of unknown origin in children (who.int)
[3] Centers for Disease Contro and Prevention. Update on children with acute hepatitis of unknown cause. https://www.cdc.gov/media/releases/2022/s0518-acute-hepatitis.html
[4] European Centre for Disease Prevention and Control. Increase in severe acute hepatitis cases of unknown aetiology in children −28 April 2022. https://www.ecdc.europa.eu/en/publications-data/increase-severe-acute- hepatitis-cases-unknown-aetiology-children (accessed May 12, 2022).
[5] UK Health Security Agency. Acute hepatitis: technical briefing. https://www.gov.uk/government/publications/acute-hepatitis- technical-briefing (accessed May 12, 2022).
[6] Zheng N, wang Y, Rong H, Wang K, Huang X. Human Adenovirus associated hepatic injury. Front Public Health 2022;28(10):878161 doi: 10.3389/fpubh.2022.878161. eCollection 2022.
[7] Calitri C, Fumi I, Ignaccolo MG, Banino E, Benetti S, Lupica MM, Fantone F, et al. World J Gastroenterol 2021;27(23):3303–16. https://doi.org/10.3748/wjg.v27.i23.3303.
[8] Cantor A, Miller J, Zachariah P, DaSilva B, Margolis K, Martinez M. Acute Hepatitis Is a Prominent Presentation of the Multisystem Inflammatory Syndrome in Children: A Single-Center Report. Hepatology 2020;72(5):1522–7 Epub 2020 October 27. https://doi.org/10.1002/hep.31526.
[9] Swati A, Diamond T, Kociolek LK, Shah AA, Chapin CA. Severe hepatitis inpediatric coronoavirus disease 2019. J Pediatr Gastroenterol Nutr 2022;74(5):631–5. https://doi.org/10.1097/MPG.0000000000003404.
[10] Wadman M. Mysterious hepatitis outbreak sickens young children in Europe as CDC probes cases in Alabama. Scienceinsider Europe April 2022. https://www.science.org/content/article/mysterious-hepatitis-outbreak-sickens-young-children-europe-cdc-probes-cases-alabama
[11] Gu J, Han B, Wang J. COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology 2020;158(6):1518–9. https://doi.org/10.1053/j.gastro.2020.02.054.
[12] Cheng MH, Zhang S, Porritt RA, Noval Rivas M, Paschold L, Willscher E, Binder M. Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation. Proc Natl Acad Sci USA 2020;117(41):25254–62. https://doi.org/10.1073/pnas.2010722117.
[13] Brodin P. SARS-CoV-2 infections in children: understanding diverse outcomes. Immunity 2022;55(2):201–9. https://doi.org/10.1016/j.immuni.2022.01.014.
[14] Porritt RA, Paschold L, Rivas MN, McArdle Yonker LMAlter G, Chandnani HK. HLA class I-associated expansion of TRBV11-2 T cells in multisystem inflammatory syndrome in children. J Clin Invest 2021;131(20):e146614. https://doi.org/10.1172/JCI151520.
[15] Brodin P, Arditi M. Severe acute hepatitis in children: investigate SARS-CoV-2 superantigens. Lancet Gastroenterol Hepatol 2022 S2468-1253(22)00166-2. https://doi.org/10.1016/S2468-1253(22)00166-2.
[16] Kupke P, Werner JM. Hepatitis E virus infection -Immune responses to an understimated global threat. Cells 2021;10(9):2281. https://doi.org/10.3390/cells10092281.

Misael Uribe
Arturo Panduro
Gisela DuPont
Nora A. Fierro*
Obesity and Digestive Diseases Unit, Medica Sur Clinic & Foundation, Puente de Piedra 150, Toriello Guerra Tlalpan, Z.C. 14050 Mexico City, Mexico
Department of Genomic Medicine in Hepatology, Fray Antonio Alcalde, Health Sciences Center, University of Guadalajara, Hospital Civil de Guadalajara, Hospital278, Col. El Retiro Z.C. 44280 Guadalajara, Jalisco, Mexico
Department of Immunology, Biomedical Research Institute, National Autonomous University of Mexico, Ciudad Universitaria Z.C. 045210 Mexico City, Mexico

*Corresponding author.
E-mail address: noraalma@iibiomedicas.unam.mx (N.A. Fierro).