Immune pathology in paediatric acute hepatitis of unknown origin — uncovering the link to COVID-19

Isabella Lurje, Frank Tacke

Starting in late 2021, cases of paediatric acute hepatitis of unknown origin (AHUO) surged in frequency, coinciding with a reduction in pandemic lockdown measures. Patients tested negative for hepatotropic viruses A-E and lacked other common causes of acute hepatitis.[1] The highest incidence was reported in the UK, Europe and the USA, particularly among children under the age of 6 years.[1] A subset of patients developed acute liver failure, with around 6% of children requiring transplantation.[2]

The search for a causative agent sparked controversy, as multiple viral candidates were identified alongside potential triggers and co-infections. Early reports of paediatric AHUO highlighted a high prevalence of human adenovirus 41 F (HAdV-F41) infection.[1] Subsequent studies discovered high hepatic and systemic levels of the dependoparvovirus adeno-associated virus 2 (AAV2), which requires co-infection with a helper virus for replication.[3–6] Co-infection with a variety of respiratory and enteric viruses, including enterovirus, cytomegalovirus, Epstein-Barr virus and human herpesvirus (HHV)-6 was commonly observed.[6] IgG antibodies against SARS-CoV2 were detected in approximately half of the AAV2-associated AHUO cases.[5] A recent meta-analysis found that the prevalence of acute SARS-CoV2-positivity ranged from 8% to 15% and was associated with more severe clinical AHUO outcomes.[7]

Human adenovirus, AAV2 and SARS-Cov2 are hepatotropic viruses but only rarely cause severe hepatic inflammation or liver failure.[6] It is hypothesised that the rise in AHUO cases may be linked to aberrant immune responses triggered by a period of reduced pathogen exposure during the pandemic lockdown.[7] Notably, over 90% of children with AAV2-positive AHUO (compared with approximately 16% in controls) carried the HLA-DRB1*0401 allele,[4 5] which is associated with increased susceptibility to autoimmune responses. Acute AAV2 infection has previously been associated with increased CD8$^+$ T-cell infiltration with an activated phenotype, as well as inflammatory and T-cell response-associated cytokine profiles.[4] While proteomic analyses found increased HLAII profiles in liver tissue of AAV2-associated AHUO (consistent with antigen-presenting cell infiltration or antigen presentation), cellular interactions remained to be determined for AHUO.[4]

In *Gut*, Rötterle *et al*[8] undertook a rigorous examination of hepatic and systemic immunology of AHUO, investigating it as a post-acute sequela of COVID-19. The authors analysed a multicentric, international, adenovirus-negative cohort. Most children had a history of SARS-CoV-2 infection, but no acute viral infections were detected, and no viral replication in the liver was found.[8]

Multiplexed imaging of liver biopsies showed that higher immune cell infiltration, particularly CD8$^+$ T cell, neutrophil and myeloid cell infiltration, was associated with the severity of hepatitis and liver damage. A highly activated, exhausted CD8$^+$ T-cell phenotype was found in the liver and blood. Parenchymal cells adjacent to damaged regions demonstrated regenerative changes, with upregulated hepatocyte proliferation and increased markers of liver sinusoidal endothelial cell (LSEC) capillarisation. A higher LSEC density was associated with lower AST, bilirubin and histological liver injury.[8]

Immune-infiltrated areas were close to loci with high SARS-CoV-2 spike antigen positivity. Myeloid cells and LSECs expressed angiotensin-converting enzyme 2 (ACE2),[8] an enzyme and cell surface receptor through which the SARS-CoV-2 virus gains cellular entry.[9] Close cellular interactions were found between CD8$^+$ T cells, SARS-CoV-2 spike+myeloid cells and SARS-CoV-2 spike+LSECs (figure 1). These CD163$^+$ CD204$^+$ Tim-3+ myeloid cells were less frequent compared with hepatic macrophages in classical autoimmune hepatitis[8], suggesting a rather regulatory immune phenotype after infection or phagocytosis of SARS-CoV-2.

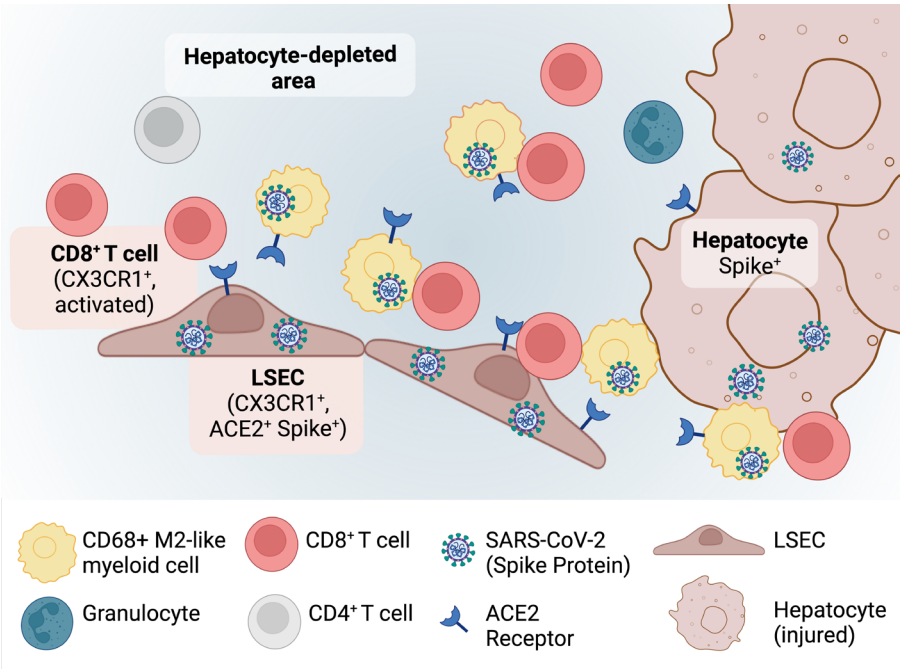

Figure 1 Spatial interaction of liver-resident cells and leucocytes in paediatric AHUO. Rötterle *et al*[8] analysed paediatric adenovirus-negative AHUO, finding that SARS-CoV-2 spike protein co-localised with LSECs, M2-like myeloid cells and hepatocytes and with the expression of the ACE2 receptor. Livers had a high number of infiltrating activated CX3CR1$^+$ CD8$^+$ T cells, which co-localised with the Spike-protein-positive cells and correlated to the degree of liver injury. Figure created with Biorender.com. ACE2, angiotensin-converting enzyme 2; AHUO, acute hepatitis of unknown origin; LSEC, liver sinusoidal endothelial cell.

Department of Gastroenterology and Hepatology, Campus Charité Mitte and Campus Virchow Klinikum, Charité - Universitätsmedizin Berlin, Berlin, Germany

Correspondence to Professor Frank Tacke; frank.tacke@charite.de

Previous studies in AHUO were able to confirm hepatotropism of the causative agent but no immunogenic persistence beyond acute stages: in acute AAV2-associated AHUO, active viral replication indicated by AAV2-RNA was sporadically observed in hepatocytes and in arterial endothelial cells[6] while liver RNA-Seq data indicated active replication in the liver[4]. At the same time, AAV2 or HAdV viral proteins were not detected using proteomics on explanted livers.[4] Therefore, Rötterle *et al* have made a unique observation regarding an immunogenic chronic SARS-CoV-2 protein persistence in the liver—one that has not previously been identified in other viral causes of AHUO.

The study's findings indicate that post-COVID-19 AHUO may involve autoimmune mechanisms. The present cohort had an excellent transplantation-free response to steroids, 25% tested positive for the autoantibodies anti-LKM1 or anti-SMA and had a trend towards female predominance (8/12 females). Both post-COVID-19 AHUO and classical autoimmune hepatitis exhibit liver inflammation with lobular infiltration and concurrent hepatocyte injury. However, an additional control group with autoimmune hepatitis in this study had a markedly different immune cell composition, with increased levels of inflammation and prominent plasma cell infiltration.[8]

The authors propose that paediatric AHUO may be a post-COVID-19 sequela, arguing that viral persistence likely triggers and sustains inflammation. Notably, most post-acute sequelae of COVID-19 are significantly more pronounced in adults requiring hospitalisation during the acute phase of infection. A recent analysis of US national healthcare data demonstrated that the risk of liver abnormalities was substantially higher in hospitalised individuals within the first 90 days post-infection (relative risk 6.27, compared with 1.55 when non-hospitalised, and 1.58 after more than 90 days).[10] Although the median time from COVID-19 history to AHUO onset was similar (2 months), children generally exhibit minimal symptoms, and no COVID-19 hospitalisations were reported in this study.[8]

The study by Rötterle *et al* suggests that hepatic persistence of SARS-CoV-2 may act as a triggering or sustaining factor in AHUO. A key finding is the spatial interaction between leucocytes, SARS-CoV-2 remnants and endothelial cells. This research lies at the intersection of autoimmunity, COVID-19-related pathologies and shared features with other viral AHUO causes. It raises important questions for future investigation: Which immunological aspects represent liver-specific immune responses, and which reflect broader mechanisms of host-SARS-CoV-2 interactions that could apply to other pathologies? In addition, the potential consequences for monitoring children post-COVID-19 as well as for optimised treatment strategies (eg, early steroid induction, antiviral therapy) remain to be clarified in future studies.

Contributors Both authors wrote the editorial. FT is the guarantor of the article.

Funding This study was funded by Deutsche Forschungsgemeinschaft (Ta434/8-1, CRC1382).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Lurje I, Tacke F. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2024-334453

Received 17 December 2024
Accepted 19 December 2024

► http://dx.doi.org/10.1136/gutjnl-2024-333880

Gut 2025;**0**:1–2.
doi:10.1136/gutjnl-2024-334453

ORCID iD
Frank Tacke http://orcid.org/0000-0001-6206-0226

REFERENCES

1 Kelgeri C, Couper M, Gupte GL, *et al*. Clinical Spectrum of Children with Acute Hepatitis of Unknown Cause. *N Engl J Med* 2022;387:611–9.
2 Cates J, Baker JM, Almendares O, *et al*. Paediatric acute hepatitis of unknown aetiology: a national surveillance investigation in the USA during 2021 and 2022. *Lancet Child Adolesc Health* 2023;7:773–85.
3 Tacke F. Severe hepatitis outbreak in children linked to AAV2 virus. *Nature New Biol* 2023;617:471–2.
4 Morfopoulou S, Buddle S, Torres Montaguth OE, *et al*. Genomic investigations of unexplained acute hepatitis in children. *Nature New Biol* 2023;617:564–73.
5 Ho A, Orton R, Tayler R, *et al*. Adeno-associated virus 2 infection in children with non-A-E hepatitis. *Nature New Biol* 2023;617:555–63.
6 Servellita V, Sotomayor Gonzalez A, Lamson DM, *et al*. Adeno-associated virus type 2 in US children with acute severe hepatitis. *Nature New Biol* 2023;617:574–80.
7 Phan J, Eslick GD, Elliott EJ. Demystifying the global outbreak of severe acute hepatitis of unknown aetiology in children: A systematic review and meta-analysis. *J Infect* 2024;88:2–14.
8 Rötterle F, Zollner A, Mogler C, *et al*. Characteristic immune cell interactions in livers of children with acute hepatitis revealed by spatial single-cell analysis identify a possible post-acute sequel of COVID-19. *Gut* 2025.
9 Hikmet F, Méar L, Edvinsson Å, *et al*. The protein expression profile of ACE2 in human tissues. *Mol Syst Biol* 2020;16:e9610.
10 Bowe B, Xie Y, Al-Aly Z. Postacute sequelae of COVID-19 at 2 years. *Nat Med* 2023;29:2347–57.