Sudden onset hepatitis in children

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The recent increase in unexplained acute hepatitis in children in 2022 has focused attention on acute paediatric liver disease. We discuss emerging evidence and leading causal hypotheses in context with potential long-term effects of the COVID-19 pandemic for young children.

Sudden onset hepatitis of unknown cause (indeterminate or non-A-E hepatitis) accounts for ~30% of children who develop acute liver failure in the developing world[1]. In the UK, there are ~20 such cases per year, whereas, as of 23 June 2022, there were 258 cases, of whom 12 required liver transplantation and no deaths (UK Health Security Agency (UKHSA) report; Supplementary Box 1). Thankfully, most patients recovered with conservative medical management. Notably, liver sequelae are not often obvious in mild disease, so it is likely that milder, self-limiting cases were not recorded (FIG. 1).

As of 24 June 2022, up to 920 probable cases fitting the case definition have been reported to the World Health Organization (WHO) and the World Hepatitis Alliance from 34 countries (Supplementary Box 1; WHO and European Centre for Disease Prevention and Control (ECDC)). At least 45 children required liver transplantation and 18 children have died. Why this substantial increase in such a rare disease?

Several lines of investigation are currently co-ordinated by the UKHSA, including evaluation of genetic backgrounds of the children and their parents, their immune status and response to viruses (including severe acute respiratory syndrome coronavirus 2, SARS-CoV-2), metagenomics of the identified viruses and a case–control study of affected cases. Examination of tissue from explanted livers showed histology typical of non-A-E hepatitis, with no evidence of paracetamol toxicity or underlying chronic liver disease and no viral inclusions, so further investigations are required (Supplementary Box 1, ESPGHAN conference and ECDC reports; R. M. Brown, personal communication).

A new disease?

In the winters of 1921–1922, sporadic cases of hepatitis were recorded in children from various US states, with jaundice raising the alarm for liver disease[2]. Sanitary supervisor Huntington Williams described an increase in such cases in New York State in young children. Analysis of 700 cases highlighted features similar to the current outbreak: fever, with several days of anorexia, nausea, vomiting, abdominal pain, constipation, clay-coloured stools and bile-stained urine lasting 3 days to 1 week, followed by a decrease of abdominal symptoms and onset of jaundice that resolved over several weeks. Five cases led to liver failure, which was fatal in the pre-transplantation era.

At the time, it was hypothesized that these cases could be related to the influenza pandemic of 1918. The current paediatric hepatitis outbreak was also suggested to be related to the lifting of COVID-19 pandemic restrictions in the UK[3]. In view of the young age of these children, it is likely that they were not exposed to common viruses until the end of pandemic restrictions. Furthermore, this exposure might have coincided with a reduction of maternal immunity that wanes after 18 months, making the children additionally vulnerable.

Burden of (co-)infection

UKHSA data reveal a substantial reduction in most childhood infections during 2020 and 2021, with a dramatic increase in norovirus, rotavirus and adenovirus in 2022 in 1–4-year-olds (Supplementary Box 1). Most of the UK children with unexplained hepatitis were <5 years old (median 3 years) and therefore had not received the COVID-19 vaccine; 70% had adenovirus detected in blood or stool, whereas some were co-infected with adenovirus and a variety of other common viruses including cytomegalovirus, Epstein–Barr virus and enterovirus, among others (Supplementary Fig. 1 and Supplementary Box 1). Adenovirus does not usually cause severe hepatitis in immune-competent children; however, it is possible that coinfections could alter its pathogenesis. Only 18% of the UK cases were positive for SARS-CoV-2 on presentation, but this finding does not rule out a past recent infection, which could have sensitized the children to other viruses, in the same way as children in the first wave of the pandemic developed a multi-system inflammatory syndrome (MIS-C) many weeks after primary COVID-19 (REF.[4]).

In a retrospective study of 44 children with MIS-C in New York, USA, hepatitis was a common feature and associated with more severe disease and persistent elevation of liver function tests[5]. Up to 10% of children with COVID-19 could develop hepatitis symptoms according to preliminary reports (Supplementary Box 1). SARS-CoV-2 remnants in the gut have been detected in adults for up to 4 months after infection, and adults with 'long COVID' showed elevated levels of interferons for months after infection[6]. Brodin and Arditi suggest

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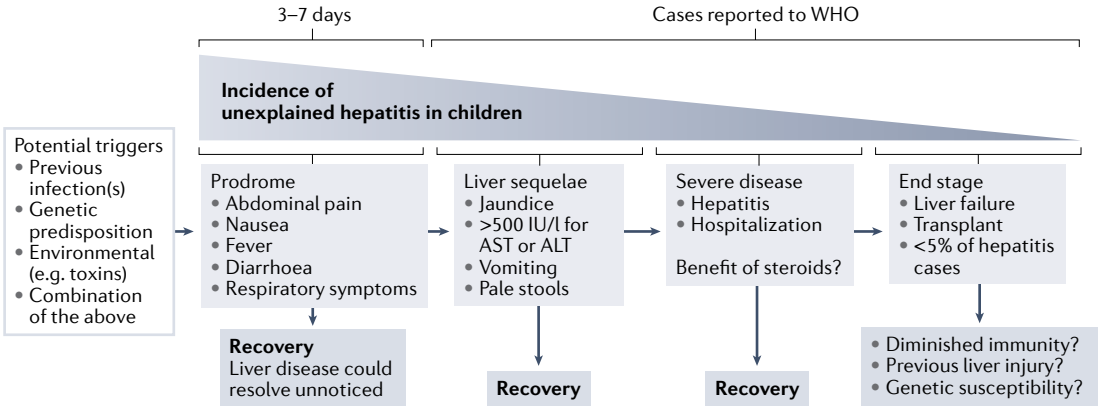

Fig. 1 | **Unexplained sudden onset hepatitis in children in the UK.** Disease progression and liver sequelae in acute hepatitis in children. ALT, alanine transaminase; AST, aspartate transaminase; WHO, World Health Organization.

measuring IFNγ levels and searching for SARS-CoV-2 antigen in children's stools to document potential liver sensitization by previous COVID-19 (REF.[7]). This suggestion is based on the hypothesis that persistent SARS-CoV-2 infection in the gut could result in the release of superantigens, leading to non-specific T cell activation and tissue injury. Biochemical investigations are not routinely requested in confirmed COVID-19 cases in children in the UK.

Harmful immune responses

Beyond IFNγ-induced hepatotoxicity[7], virus-specific $CD8^+$ T cells could cause or exacerbate collateral damage to the liver. $CD8^+$ T cell infiltrates were previously shown to be clonal, indicating an antigen-driven response in 37 children with hepatitis and indeterminate acute liver failure[8]. Infiltrates of cytotoxic T cells could signpost infection; however, hepatotoxicity in patients with checkpoint inhibitor hepatitis is also $CD8^+$ T cell-driven and it resembles acute liver failure rather than autoimmunity (Supplementary Box 1). In the current outbreak, it is unclear why most children recover and <5% develop liver failure; it is crucial to revisit these cases and perform detailed comparative analyses to pinpoint the origins of vulnerability.

Following the UK alert, 12 children with severe unexplained hepatitis were hospitalized in Israel, of whom 2 developed liver failure requiring transplantation (Supplementary Box 1). Consistent with 3 children from Denmark treated with prednisolone (M. Hørby Jørgensen, personal communication), 10 children in Israel were treated and improved after steroid treatment. Steroid administration is not indicated in sudden onset hepatitis as immune competence might be important to control putative infection; however, the RECOVERY group showed improved outcomes with dexamethasone for hospitalized adults with COVID-19 (REF.[9]). In the UK, steroids were used in transplanted cases (Supplementary Box 1, EASL studio webinar); however, it remains an evidence-free approach and a clinical trial is needed. Response to steroids highlights a benefit in controlling potentially harmful immune responses. It is important to establish effective treatments for these rare paediatric cases to prevent liver failure.

Almost a century after the unexplained hepatitis accounts from New York State, are we closer to determining the cause of such outbreaks? Apart from full microbiology analysis and genetic characterization, we now have access to sophisticated inflammatory biomarker and immune profiling technologies that can decipher immune cell specificities and point to likely disease triggers. UKHSA has triggered a special Comprehensive Clinical Characterisation Collaboration (ISARIC4C, Supplementary Box 1) in response to the outbreak of unexplained hepatitis in children. Given the rare and sporadic presentation of such cases, global collaboration is crucial to increase sample size and coordinate investigations. We have a golden opportunity to elucidate non-A-E hepatitis in children.

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Competing interests
D.A.K. is a member of the UK Health Security Agency (UKHSA) technical expert panel. Z.S. collaborates with AstraZeneca, UK, as principal investigator and lead supervisor for a Medical Research Council Industrial Cooperative Awards in Science & Technology (MRC iCASE) PhD studentship.

Supplementary information
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