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Perspective

Severe acute hepatitis in children with unknown aetiology, etiology analysis and the next action

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On April 5, 2022, United Kingdom (UK) reported 10 cases of severe acute hepatitis with unknown cause among children under 10 years old. The initial symptoms of these cases could date back to March 2022. A rapidly increasing number of cases lasted for a month and the growth seems to be slightly slowing down in May. As of May 27, 2022, the total number of children with acute hepatitis in UK reached to 222 (UKHSA, 2022a). European Union and European Economic Area reported 305 cases across 17 countries and none as epidemiologically linked as of May 31, 2022 (ECDC-WHO, 2022). The report from World Health Organization (WHO) noted that a total number of 650 cases worldwide including 38 (6%) cases required transplants and 9 (1%) deaths (Fig. 1) (WHO, 2022). The Center for Disease Control and Prevention (CDC) of United States, European Center for Disease Prevention and Control (ECDC) and WHO had issued a case-based surveillance system with a common case definition and reporting protocol. The extensive investigation for detailed clinical, laboratory, epidemiological, metabolic hereditary and environmental information is under way. However, the exact cause has not been identified at press time.

The affected children aged 16 years old or younger, predominantly (75.4%) under 5 years old. Mostly are not vaccinated with SARS-CoV-2 vaccine. Nearly all the children guardians reported previously-healthy status among cases before liver injury onset, no prior immunosuppression. The children were characterized with an acute hepatitis evidenced by aspartate transaminase (AST) or alanine transaminase (ALT) over 500 IU/L (most over 2000 IU/L) but had been ruled out hepatitis viruses A, B, C, D and E infection. According to the UK Health Security Agency (UKHSA) technical briefing (version 3, 19 May), for those who were defined as possible cases in England, the typical clinical features include jaundice (99 out of 144; 68.8%), abdominal pain (36.1%), diarrhoea (43.1%) and nausea (36.1%), yet fever (28.5%) and respiratory symptoms (18.1%) were less common. According to the report released by UKHSA, only two pairs of cases showed epidemiological link, which eliminated the worry of pandemic evolves.

1. Aetiology analysis

Among the 123 cases with available test data in UK, only 13 (10.6%) were tested positive for SARS-CoV-2 RNA. In contrast, adenovirus was detected in 79.4% (77/97) of blood or serum samples from cases who underwent PCR test for adenovirus. Noticeably, 35 of the 77 samples had been successfully subtyped, of which 27 (77%) are type 41F (UKHSA, 2022c).

Since the first discovery of human adenovirus (HAdVs) in the 1950s, more than 100 genotypes and 52 serotypes have been identified and classified into seven species (A to G) with different tissue tropism (Human Adenovirus Working Group, 2022). HAdVs can cause a spectrum of disease from typical mild infections involving the upper or lower respiratory tract, gastrointestinal tract, or conjunctiva, to rare manifestations include hemorrhagic cystitis, hepatitis, hemorrhagic colitis, pancreatitis, nephritis, or meningoencephalitis (Lynch and Kajon, 2021). As a kind of common viral pathogens in human society, HAdVs infections are more common in young children, due to lack of humoral immunity. The infections of HAdVs are usually self-limited in immunocompetent population, whereas in immunocompromised individuals, it can cause severe infections with multiple organs/tissue disseminations, including HAdVs induced hepatitis (Ronan et al., 2014).

The prevalence of HAdVs infection in the affected children would easily prompt calling up an association between recent hepatitis and HAdVs, especially after UKHSA technical briefing (version 2, 12 May) noted a significant increase in number of adenovirus-positive specimen among children aged 1–4 years (UKHSA, 2022b). But quite a lot of clinicians and investigators doubted that adenovirus infection as the direct cause of current hepatitis in children with unknown aetiology, largely because the absence of inclusion body in the liver tissues specimen derived from liver biopsy, as well as the extremely low abundance of adenovirus in circulating of patients. On 10 May, the technical note issued by the Pan American Health Organization/World Health

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Fig. 1. Map displaying the distribution of cases according to case definition used by the United Kingdom (UK) across the affected countries as of May 30, 2022 for Europe, May 30, 2022 for the UK, and May 27, 2022 for the rest of the world. (Data extract from "Joint ECDC-WHO/Europe: Hepatitis of unknown origin in children surveillance bulletin" issued May 31, 2022, and "Acute hepatitis of unknown aetiology in children-Multi-country" issued by WHO May 27, 2022, accessed May 31, 2022).

Organization (PAHO/WHO) articulated that adenovirus could be a coincidental rather than a causal factor (PAHO/WHO, 2022). However, for the limited available information and the high prevalence of adenovirus detection in affected children, it should not immediately rule out the potential connection between them. First, certain genotypes of HAdVs are known to cause liver inflammation in immunocompromised children, yet such hepatitis in healthy children is rare; second, though the adenovirus positivity by respiratory specimen remains stable across the recent two years, noted increase of adenovirus positivity by feces specimen could probably implicate a changed pattern of adenoviruses prevalence, according to the UKHSA report (UKHSA, 2022b). Additionally, the clinical feature of the children severe acute hepatitis was far from the previous typical adenovirus hepatitis, as compared in the following Table 1. It would be interesting to figure out whether the differences are caused by novel mutation or recombination between different subtypes of adenovirus.

Table 1
Clinical features of typical adenovirus hepatitis and recent severe acute hepatitis with unknown aetiology.

	Adenovirus hepatitis	Severe acute hepatitis with unknown aetiology
Immune status	Immunocompromised (Ronan et al., 2014)	Immunocompetent
Age (<17yr)	64% (Ronan et al., 2014)	100%
Underlying condition	Solid organ transplant, hematological malignancy or immune deficiency (Ronan et al., 2014)	Previously-healthy condition
Body temperature	All present fever (Schaberg et al., 2017)	Fever less commonly
Histopathology	All cases with intranuclear inclusions within hepatocytes (Schaberg et al., 2017)	No viral inclusion non-specific and there is no clear identifiable
Viremia viral load	High	Low

Antibiotics, supplementary nutrients and herbals are also well-known drugs can lead to children liver injury (Hoofnagle and Björnsson, 2019), but the information gathered does not support these suspicions. Three-quarters of respondents in UK mentioned paracetamol use, whereas the drug concentration in plasma and urine samples collected in the early phase of diseases was lower than expected (UKHSA, 2022c). It is unlikely to ascribe the hepatitis to paracetamol. Toxicological substance or drug-related causes cannot be identified by the data so far, it should continuously collect relative information until the final cause have been confirmed. In addition, from ECDC and WHO surveillance bulletin, Epstein-Barr virus (18.3%, 23/126), cytomegalovirus (10.4%, 14/135), human herpesvirus 6 (31%, 20/64), human herpesvirus 7 (45%, 18/40) and other pathogens were also detected in these cases. Auto-antibody (ANA or SMA) were also detected in 44% cases from Alabama, but none met probable or definite criteria for diagnosis of autoimmune hepatitis (Baker et al., 2022). Distinguishing hepatitis with known aetiology from unknown aetiology in possible cases probably helps us find real aetiology.

2. The hypothesis of superantigen-mediated hepatocellular injury

On 13 May, Dr. Brodin and Arditi (2022) issued a hypothesis to explain the suspected cause(s) of reported severe acute hepatitis with unknown cause in children. They hypothesized that superantigen-mediated immune-cell activation might be a causal mechanism underlying severe acute hepatitis of unknown aetiology in young children. Like in multisystem inflammatory syndrome in children (MIS-C), they proposed that SARS-CoV-2 could reside in gastrointestinal tract, and repeatedly release spike protein bearing a superantigen motif across the intestinal

epithelium, then a later adenovirus infection would elicit spike protein-mediated hyperinflammatory response and result in severe liver injury. The hypothesis by Brodin and Arditi provisionally connected the severe acute hepatitis in children with the recent prevalence of the omicron variant. It had been reported that by February 2022, most children of 1–4 years old had been infected during the wave of omicron in United States (Mallapaty, 2022). Later on, severe acute hepatitis was reported in March and April 2022, with a lag similar to the interval between waves of MIS-C and the corresponding peaks of COVID-19 cases (Fig. 2) (Miller et al., 2021), where the latter is thought to be another superantigen-mediated disease in children during the pandemic (Kouo and Chaisawangwong, 2021). Moreover, the hypothesis could also partially explain why neither MIS-C nor severe acute hepatitis case has been reported in China, which accounts for a fifth of the world population but without extensive spreading of SARS-CoV-2 yet.

Obviously, several challenges need to be addressed before the Brodin and Arditi hypothesis being commonly accepted. First of all, fundamental evidences support the persistent presence of residual SARS-CoV-2 in the intestinal epithelium of individuals who have already eliminated the virus from their upper respiratory tract and lung. Several recent studies provide some insightful information. Zollner et al. reported that SARS-CoV-2 RNA and antigen could persist in the gut mucosa for seven months after mild acute COVID-19 and instigate immune perturbation result in long-COVID sequelae (Zollner et al., 2022). Natarajan et al. found that 12.7% of participants continued to shed SARS-CoV-2 RNA in the feces at four months after diagnosis of COVID-19, and fecal viral RNA shedding was correlated with prolonged gastrointestinal symptoms (Natarajan et al., 2022). Moreover, according to the report about an autopsies study on 44 individuals who had recovered from COVID-19 but died from other incidences, SARS-CoV-2 RNAs were found in multiple anatomic sites including regions throughout the brain, for up to 230 days following symptom onset (Chertow et al., 2021). These studies suggest that SARS-CoV-2 RNA and/or proteins might persist in different organs or tissues even after respiratory symptoms resolved and long-term viral reservoirs may contribute to long COVID-19.

It has been reported that anti-SARS-CoV-2 S protein antibodies reacted to human tissue antigens, and as a result, anti-nuclear antibodies, anti-actin and anti-mitochondrial antibodies the immune-mediated markers were found significantly elevated (Vojdani and Kharrazian, 2020). More than that, a recent study indicated that monoclonal antibodies from S1 subunit immunized animals could recognize both S1 receptor-binding domain and angiotensin-converting enzyme 2 (ACE-2), which might be another potential explanation for multiorgan involvement secondary to SARS-CoV-2 infection (Lai et al., 2022). Most likely, the main pathogenesis of the severe acute hepatitis of unknown origin in children was mediated by host immune responses, but up to date the data regarding the mechanism behind hepatic injury is very limited. Then, it would be essential to explain theoretically that unlike the multisystem inflammatory damage seen in MIS-C, only liver was mainly injured in the Brodin and Arditi hypothesis. We had previously observed the direct cause of hepatic impairment in patients with COVID-19 (Wang et al., 2020), and proposed a mechanism of virus direct infection of neonatal hepatocytes via angiotensin converting enzyme (ACE) receptors, following liver damage and regeneration caused by cytokine storm during COVID-19 (Guan et al., 2020; Gao et al., 2020). It would be interesting to investigate the persistence of SARS-CoV-2 residuals in the liver tissue of children suffering sever acute hepatitis with unknown cause. A recent study addressed the indirect liver injury caused inflammatory activity in COVID-19, in which the authors demonstrated that the IL-6 signaling complex causes harmful changes to liver sinusoidal endothelial cells and consequently the blood clotting (Saviano and Baumert, 2021), and such endotheliopathy was suggested as a possible mechanism of coagulopathy-related liver injury seen in patients of COVID-19 (Mcconnell et al., 2021).

It has been acknowledged that disease tolerance is an immune defense strategy used when the immune response to a pathogen is more damaging than the pathogen itself (Moreews et al., 2021), and growing children are more likely to choose disease tolerance to avoid systemic inflammatory response whenever possible (Brodin, 2022). As a consequence, they were likely to present a mild or asymptomatic clinical

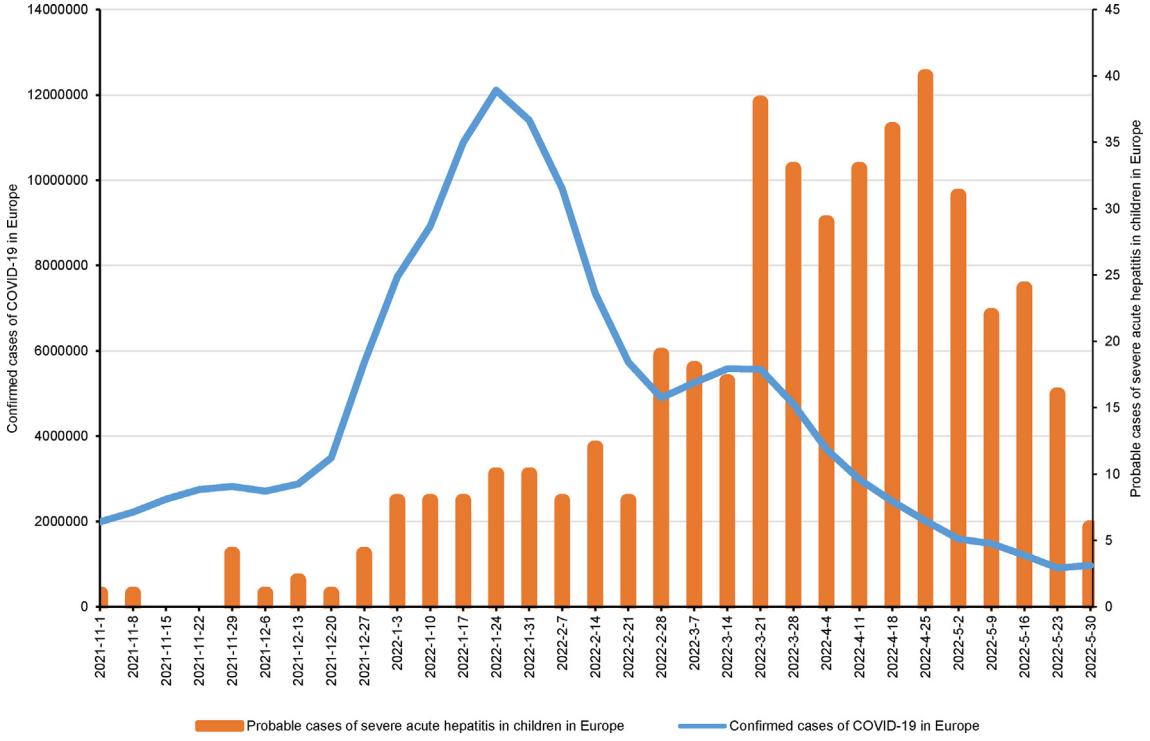

Fig. 2. Chart displaying the probable cases of severe acute hepatitis in children and confirmed cases of COVID-19 in Europe as of May 30, 2022 (Data is based on WHO COVID-19 Dashboard and Joint ECDC-WHO/Europe surveillance bulletin: Hepatitis of unknown origin in children issued May 31, 2022, accessed May 31, 2022).

course but lack of capability to eradicate the virus spontaneously (Brodin, 2022). Thus, it is reasonable to speculate that SARS-CoV-2 infection could form the viral reservoir in their gastrointestinal tracts.

To verify the above hypothesis, the core part of crucial evidences would be the prevalence rate of SARS-CoV-2 infection in the cases. Despite the low tested positive rate in the patients underwent SARS-CoV-2 RNA test, serological testing studies to investigate antibodies targeted the specific protein of SARS-CoV-2 virus might provide suggestive cues whether the hepatitis cases had been infected previously. Nevertheless, even though viral infections are considered to be one of the potential causes, the cases found so far are rather isolated. Therefore, the aetiology hypothesis raised recently needs more supportive evidences.

3. COVID-19 vaccine and unknown aetiology hepatitis

The pandemic is still raging, fortunately, COVID-19 vaccine had rescued millions of lives from SARS-CoV-2 infection. Besides directly induce acute respiratory distress syndrome by the virus, the viral proteins had been reported to be associated with immune abnormalities (Toscano et al., 2020; Zulfiqar et al., 2020). For vaccines contain the same viral protein or mRNA-based vaccine to the spike protein, it is plausible that vaccine would trigger the autoimmune diseases including autoimmune hepatitis (Bril et al., 2021). But for the rare incidence of such hepatitis, scholars did not acquire any solid evidence to prove the causality. Most of affected children did not vaccinate, thus it is very unlikely to attribute to COVID-19 vaccine. The other side of the coin, SARS-CoV-2 had been considered as a superantigen in MIS-C, probably act as the same role in unknown aetiology hepatitis. If the theory hold true, pre-existing immunity against SARS-CoV-2 would reduce viral shedding duration and restrict tissue dissemination (Ke et al., 2021), as did in other respiratory viruses (Gouma et al., 2016). A national population-based cohort study investigated patients aged 0–17 years hospitalized with MIS-C in Denmark, compared to those unimmunized children, vaccination brought an outstanding effectiveness of 94% against MIS-C after delta variant prevalence (Nygaard et al., 2022). It makes physicians intriguing to think whether vaccine could be a readily available means to prevent children from the severe acute hepatitis of unknown aetiology. Importantly, studies aimed to compare the incidence of unknown aetiology hepatitis regarding vaccination status from population-based cohort should start immediately and share data as early as possible.

Taken together, prolonged lockdown altered the host immune responses to infectious agents or environmental factors, the experience and evidence about interactions between immune system and the external stimuli were still lacking under such settings. During the pandemic, the wave of liver involvement among children in lower age remains difficult to confirm the real cause. Actively exploring but prudent decision-making would be a pragmatic way to face with unknown.

Footnotes

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