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## Correspondence



## Emerging cases of acute hepatitis of unknown origin in children amid the ongoing COVID-19 pandemic: Needs attention – Correspondence

Dear Editor,

The Coronavirus disease (COVID-19) after its emergence from Wuhan, China, in late December 2019, has rapidly spread across the globe and has become a devastating pandemic posing high public health concerns and adversely impacting many socio-economic and routine life activities [1]. The common clinical presentation of COVID-19 include respiratory symptoms consisting mainly of dry cough, fever, shortness of breath, fatigue, dyspnea, and associated interstitial pneumonia. The causative virus, severe acute respiratory syndrome coronavirus – 2 (SARS-CoV-2), can further affect the heart, kidneys, gastrointestinal, and the nervous system, and may lead to multiple organ dysfunction [2]. It can also cause severe complications in immunocompromised and elderly persons having diabetes, cardiovascular disorders and hypertension. The SARS-CoV-2 infection in the liver can directly contribute to hepatic impairment and acute liver injury in COVID-19 patients [3]. A recent study assessed that acute hepatic injuries, liver enzyme abnormalities, and hypoproteinaemia are frequent hepatic complications in the hospitalized COVID-19 patients [4]. Moreover, the COVID-19 patients with pre-existing hepatic diseases experience the worse outcome.

Recently on 5th April 2022, the WHO has identified 10 cases of severe acute hepatitis with unknown aetiology in previously healthy children (<10 years) in central Scotland [5]. Moreover, 74 more cases have also been identified in the United Kingdom by April 8, 2022. A few cases (children/adolescents) have also been reported in Denmark, the Netherlands, Ireland and Spain. Very recently, nine such mysterious cases of acute hepatitis have also been detected among children in the United States, suspected to have a connection to adenovirus [6]. As per recent reports, more than 169 such unusual cases of hepatitis have been identified from 11 countries [7]. The symptoms included vomiting, diarrhoea, jaundice, abdominal pain and malaise. The clinical syndrome was of acute hepatitis with markedly elevated liver enzymes (AST or ALT >500 IU/L). Some children were referred to specialist children's liver units and nearly 10% of children have undergone liver transplantation with one reported death.

Generally, hepatitis is associated to viral infections, and is posing emerging public health concerns requiring special attention as it could lead to life-threatening conditions such as liver cirrhosis and liver failure. Hepatitis A, B, C, D and E are the different forms of viral hepatitis (<https://www.hopkinsmedicine.org/health/conditions-and-diseases/hepatitis/hepatitis-in-children>). Surprisingly, none of the five hepatitis viruses (A-E) have been detected in any of the reported children patients with acute hepatitis. So, the common causes of hepatitis here were ruled out and the public health authorities are searching for new answers. Most of the children had tested positive for either adenovirus or SARS-CoV-2 or both. Adenoviruses may cause hepatitis, however it is extremely rare. In the UK, adenovirus is co-circulating with SARS-CoV-2.

However, the reason by which acute hepatitis develops in children is yet not clear. Adenoviruses are double-stranded DNA viruses and spread by respiratory droplets, close contact, and fomites. Adenovirus infection causes hepatitis in immunocompromised children but severe hepatitis in healthy children is unusual. So, any emergence of a novel adenovirus or its co-infection with SARS-CoV-2 in these children needs to be further investigated [8,9]. A new adenovirus variant may have emerged that can more easily cause hepatitis is a hypothesis [6]. Another possibility is both adenovirus and coronavirus infecting the same child may lead to a totally different virus that has not been detected yet (<https://theconversation.com/hepatitis-cases-are-increasing-among-children-in-the-uk-could-covid-have-a-role-to-play-181303>). A recent study from India suggested that either the Delta variant or its interaction with adenovirus or newer recombinants of Delta variant may possibly be associated with pediatric hepatitis which needs urgent and thorough investigations [10]. Another possible reason is autoimmune hepatitis (the body itself attacks the liver); however it is also a rare condition that is causing a cluster of cases in children. As per the FDA in conjunction with the CDC reports, the use of alkaline bottled water products may be a possible reason for hepatitis in children [11]. It is also highly recommended to investigate environmental toxins as a cause for hepatitis in children. Moreover, most of these children have not received COVID-19 vaccines, so any adverse effect of vaccine may not be responsible for this cluster of cases. International travel links in these cases have not been identified as a factor.

SARS-CoV-2 infection has been associated with multiple inflammatory syndrome (MIS) in the pediatric age group [12]. Some asymptomatic SARS-CoV-2 infection in children or adolescents (n = 33) developed into acute hepatitis with no history of pre-existing liver disease. The patients (n = 8) with MIS having a high level of inflammatory markers which required admission to critical care, and three patients had an adverse outcome [13]. Pessoa and his coworkers have reported the first case of hepatitis in a male child infected with SARS-CoV-2 that has the Toll-like receptor 7 (TLR-7) Gln11Leu single nucleotide polymorphism, which could impair an efficient initial immune response [14]. Furthermore, Antala and coworkers have reported severe hepatitis in four previously healthy children as the primary manifestation of SARS-CoV-2 infection without respiratory symptoms, out of which two patients had acute liver failure [15]. In pediatric patients, the liver function should be evaluated in children affected with severe COVID-19. WHO has recommended for testing of blood, serum, urine, stool, respiratory samples and liver biopsy samples with further virus sequencing [16]. It is also suggested that testing whole blood by PCR may be more sensitive than testing plasma [17].

A 24-year-old COVID-19 male patient with acute active hepatitis B virus infection was reported by Yigit and coworkers [18]. The patient

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had fever and cough for three days. The initial blood tests showed severely elevated urea, transaminases, creatinine, and ammonium in addition to severe liver failure. On the 10th day after admission, the patient developed cardiac arrest [18]. COVID-19 induced hepatitis is a novel clinical syndrome in this current pandemic. A 59-year-old woman with a chief concern of dark urine was admitted to hospital and tested COVID-19 positive with acute nonicteric hepatitis [19]. Moreover, Dehghani and Teimouri reported severe acute hepatitis in a 39-year-old man infected with SARS-CoV-2 [20]. The patient was also infected with hepatitis A and herpes simplex virus simultaneously. Abnormal liver enzymes are one of the reported presentations in hospitalized COVID-19 patients. In one study, 58–78% patients showed liver injury and damage [21]. Physicians should take all the possible causes of such patients with SARS-CoV-2 infection into consideration to reduce the risk of overlooking the underlying disease.

As the cases of acute hepatitis in children are sharply increasing, it is assumed that more such cases will be reported in the near future. Acute hepatitis in children or adolescents is very rare and its cause in many cases is yet to be understood properly, particularly for this highly unusual rise in cases at the present time. Therefore, the actual aetiology of the clusters of such recent acute hepatitis cases in children need to be further investigated in details, along with exploring any feasible direct or indirect role of SARS-CoV-2 or its emerging variants amid the ongoing COVID-19 pandemic. The ongoing COVID-19 vaccination drive needs to appropriately cover children also so as to render them adequate protection against SARS-CoV-2 and its emerging variants.

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#### References

- [1] R.K. Mohapatra, S. Mishra, M. Azam, K. Dhama, COVID-19, WHO guidelines, pedagogy, and respite, *Open Med.* 16 (2021) 491–493.
- [2] W. Zhao, H. Li, J. Li, B. Xu, J. Xu, The mechanism of multiple organ dysfunction syndrome in patients with COVID-19, *J. Med. Virol.* 94 (5) (2022) 1886–1892, <https://doi.org/10.1002/jmv.27627>.
- [3] Y. Wang, S. Liu, H. Liu, W. Li, F. Lin, L. Jiang, et al., SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19, *J. Hepatol.* (2020), <https://doi.org/10.1016/j.jhep.2020.05.002>.
- [4] M. Bongiovanni, T. Zago, Acute hepatitis caused by asymptomatic COVID-19 Infection, *J. Infect.* 82 (2021) e25–e26.
- [5] WHO, Acute hepatitis of unknown aetiology – the United Kingdom of Great Britain and Northern Ireland, 15 April 2022. <https://www.who.int/emergencies/disease-outbreak-news/item/acute-hepatitis-of-unknown-aetiology—the-united-kingdom-of-great-britain-and-northern-ireland>, 2022.
- [6] CDC, CDC alerts providers to hepatitis cases of unknown origin, April 21, 2022, <https://www.cdc.gov/media/releases/2022/s0421-hepatitis-alert.html>, 2022. accessed on 24-04-22.
- [7] WHO, Multi-Country – acute, severe hepatitis of unknown origin in children 23 April 2022. <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON376>, 2022 accessed on 6-5-22.
- [8] W.H.O. Europe, Q&A on hepatitis in children, 04-05-2022. <https://www.euro.who.int/en/health-topics/communicable-diseases/hepatitis/news/news/2022/4/q-and-a-on-hepatitis-in-children>, 2022 accessed on 6-5-22.
- [9] B. Christie, *BMJ* (2022) 377, <https://doi.org/10.1136/bmj.o982> (Published 14 April 2022).
- [10] S.K. Rawat, A.A. Asati, A. Jain, N. Mishra, R.K. Ratho, COVID-19 Associated Hepatitis in Children (CAH-C) during the second wave of SARS-CoV-2 infections in Central India: is it a complication or transient phenomenon, *medRxiv* (2021). <https://www.medrxiv.org/content/10.1101/2021.07.23>.
- [11] A. Turney, FDA in Brief: viral hepatitis cases possibly linked to bottled alkaline water. FDA news- events. <https://www.fda.gov/news-events/fda-brief/fda-brief-fda-investigates-source-non-viral-hepatitis-cases-possibly-linked-bottled-alkaline-water>, 2021.
- [12] M. Striha, R. Edjoc, N. Bresee, N. Atchessi, L. Waddell, T.L. Bennett, E. Thompson, M. El Jaouhari, S. Bonti-Ankomah, Rapid review of multisystem inflammatory syndrome in paediatrics: what we know one year later, *Can. Comm. Dis. Rep.* 47 (11) (2021) 466–472, <https://doi.org/10.14745/ccdr.v47i11a04>.
- [13] S.K. Rawat, A.A. Asat, A. Jain, R.K. Ratho, Covid-19 Associated Hepatitis in Children (CACH) during the second wave of SARS-CoV-2 infections in Central India: is it a complication or transient phenomenon, *medRxiv* [preprint], doi, <https://doi.org/10.1101/2021.07.23.21260716>, 2021.
- [14] N.L. Pessoa, A.A. Bentes, A.L. de Carvalho, T.B. de Souza Silva, P.A. Alves, E.V. de Sousa Reis, T.A. Rodrigues, E.G. Kroon, M.A. Campos, Case report: hepatitis in a child infected with SARS-CoV-2 presenting toll-like receptor 7 Gln11Leu single nucleotide polymorphism, *Virol. J.* 180 (2021) 18, <https://doi.org/10.1186/s12985-021-01656-3>.
- [15] S. Antala, T. Diamond, L.K. Kocielek, A.A. Shah, C.A. Chapin, Severe hepatitis in pediatric COVID-19, *Journal of pediatric gastroenterology and Nutrition*, 2022, <https://doi.org/10.1097/MPG.0000000000003404>.
- [16] WHO, Multi-Country – acute, severe hepatitis of unknown origin in children 23 April 2022. <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON376>, 2022 accessed on 6-5-22.
- [17] CDC, Recommendations for adenovirus testing and reporting of children with acute hepatitis of unknown etiology, April 21, 2022, <https://emergency.cdc.gov/han/2022/han00462.asp>, 2022. accessed on 06-05-22.
- [18] Y. Yigit, M. Haddad, A. Elmoheen, M.R. Shogaa, R. Tawel, Y.K. Mohamed, W. Salem, M.F. Eltawagny, Can COVID-19 cause flare-ups of acute hepatitis B? An atypical presentation of COVID-19 with acute hepatitis B, case reports in infectious diseases, Article ID 8818678, <https://doi.org/10.1155/2021/8818678>, 2021.
- [19] P. Wander, M. Epstein, D. Bernstein, COVID-19 presenting as acute hepatitis, *Am. J. Gastroenterol.* (2020) 1–2, <https://doi.org/10.14309/ajg.0000000000000660>, 00.
- [20] S. Dehghani, A. Teimouri, Severe acute hepatitis in a COVID-19 patient: a case report., *Clin Case Rep.* 9 (2021) e04869.
- [21] L. Xu, J. Liu, M. Lu, D. Yang, X. Zheng, Liver injury during highly pathogenic human coronavirus infections, *Liver Int.* 40 (2020) 998–1004.

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