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The origin of severe hepatitis of unknown aetiology in children: SARS-CoV-2 or adenovirus?

To the Editor:

Since April 5, 2022, a mysterious severe acute hepatitis of unknown aetiology was reported in previously healthy children in multiple countries, starting in the UK, and spreading across the European area.[1] With great interest, we read an article introducing the recent hepatitis outbreak by Mücke *et al.* published in the *Journal* in May 2022 and were inspired by their hypotheses.[2]

Up to July 28, 2022, a total of 508 cases of acute hepatitis of unknown aetiology in children have been reported in the European region (geographic distribution shown in Fig. 1A).[3] These 508 cases were identified as probable cases, which was defined as a child aged 16 years and younger, presenting with an acute hepatitis (not caused by hepatitis A–E viruses) with serum transaminase >500 IU/L.[4] The outbreak of hepatitis has raised alert around the world including in China, the National Health Commission of which released nationwide guidelines on acute severe hepatitis of unknown aetiology in children on June 16, 2022.[5] Urgent identification of the cause and underlying mechanisms of the disease is crucial in order to enable appropriate clinical management.

To investigate the potential link between infection with COVID-19 (Omicron variant) and severe hepatitis of unknown aetiology among children, Nishiura H and his colleagues[6] compared the absolute number of Omicron cumulative cases between the hepatitis-detected countries and hepatitis-undetected ones and they drew a conclusion that prior exposure to the Omicron variant (B.1.1.529) might be associated with an increased risk of severe hepatitis among children. However, the absolute number of cumulative Omicron cases is not a favourable indicator compared with cumulative incidence and more notably, the whole population cannot represent children, which biased their result. We collected the child-specific population data from the ECDC and performed an analysis of Omicron infection in children and its association with the emergence of severe hepatitis of unknown aetiology.

In our analysis, there was no significant difference (Fig. 1B, $p = 0.32$) in the cumulative incidence of Omicron cases among children between hepatitis-detected countries and hepatitis-undetected ones. Then, we further analysed the association of cumulative Omicron cases among children and hepatitis cases reported in hepatitis-detected countries by

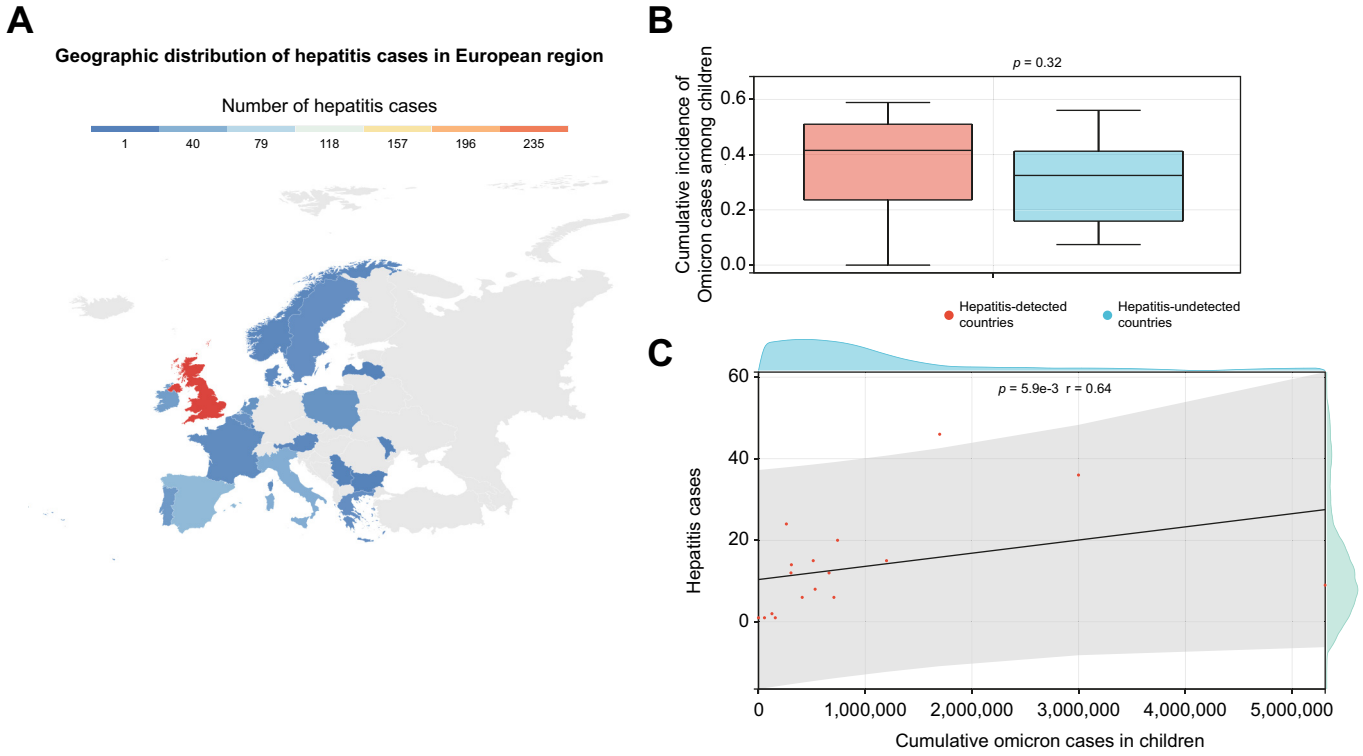

Fig. 1. Comparing the distribution of hepatitis cases and Omicron cases across Europe. (A) Geographic distribution of hepatitis cases in European region. (B) Cumulative incidence of Omicron cases among children (<15 years old) in relation to the detection of severe acute hepatitis of unknown aetiology among children. (Wilcoxon rank sum test, box plot measures the quartiles and median) (C) Correlation analysis of cumulative Omicron cases among children and hepatitis cases reported. (Spearman correlation analysis used. Each red dot represents one hepatitis-detected country).

conducting a Spearman correlation analysis. The results showed that there was a positive association between Omicron cases in children and hepatitis cases (Fig. 1C, r = 0.64, p = 5.9e-3). The results were consistent with an analysis two months ago[7] which proved that these results were time-independent and strengthened their validity.

Laboratory investigations conducted by the UK Health Security Agency (UKHSA) found that adenovirus 41F was positive in 72% of the cases; and out of the 398 cases in European countries tested for adenovirus, 217 (54.5%) tested positive, so current hypotheses continue to focus on adenovirus as a potential aetiology.[3,8] Moreover, though lacking positive liver histologic findings for adenoviral inclusion, a clinical study by Kelgeri *et al.* reported that biochemical tests and ultrasonographic results are consistent with a viral cause, and serum levels of adenovirus were significantly higher in the patients who progressed to liver failure than those who spontaneously recovered.[9,10] However, adenovirus alone is rarely associated with severe hepatitis, so other factors that lead to abnormal susceptibility or host response may contribute to the severity of the disease. Contributing factors include lack of previous exposure due to quarantine during the SARS-CoV-2 pandemic, abnormal susceptibility caused by previous infection or co-infection with SARS-CoV-2 or other pathogens.[8]

We speculated that the severe acute hepatitis was possibly induced by adenovirus, while SARS-CoV-2 acted as a cofactor and allowed adenovirus infection to progress more frequently to severe hepatitis. Our hypotheses are based on the following factors. Firstly, SARS-CoV-2 is probably not the main cause of hepatitis since there were no differences in incidence rates among children between the two country groups. Instead, SARS-CoV-2 might play a role in disease progression. Secondly, we believe the positive association between Omicron cases and hepatitis cases reported is possibly biased by the shared route of transmission of Omicron and adenovirus since these two types of viruses are mainly transmitted through the respiratory tract.[11] Thus, a potential positive relationship between adenovirus cases and Omicron cases exits in one country endowed with the similar public health and social measures. Thirdly, previous studies have reported a lower circulation of adenovirus due to the COVID-19 pandemic quarantine, and lack of exposure to adenovirus resulted in increased susceptibility among children, thus leading to the severity of this adenovirus outbreak.[2] In addition, the UKHSA suggested that prior infection or co-infection with SARS-CoV-2 may have led to abnormal host responses or susceptibility to adenovirus infection.[12,13]

The specific mechanism and the extent to which SARS-CoV-2 affects adenovirus infections resulting in severe acute hepatitis remains a mystery. In the future, much attention should be paid to this area to put an end to this severe hepatitis outbreak.

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Conflict of interest

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Authors' contributions

Hang Yi, Yiwen Lin and Bin Lu were involved in conceptualizing, literature review, drafting of the letter and Yousheng Mao revised the letter for final submission. All authors approved the final version for submission and publication of the content.

Data availability statement

The present study used publicly available data from the ECDC (https://www.ecdc.europa.eu/en).

Ethics approval statement

The publicly available data were anonymous and ethical approval and patient consent statement can be waived.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.08.032.

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Author names in bold designate shared co-first authorship

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The association between liver fibrosis and cognitive impairment in type 2 diabetes

To the Editor:

Kronsten and colleagues discuss the gut-brain-liver axis linking depression and chronic liver disease.[1] In their proposed model, gut dysbiosis and increased gut permeability lead to systemic inflammation, which drives liver disease and depression. As a further manifestation of gut-brain-liver axis dysfunction, the authors note that cognitive impairment is prevalent in chronic liver disease and that novel interventions, such as antibiotics and faecal transplantation, may improve cognitive function.

Whilst studies have found an association between cognitive impairment and chronic liver disease such as non-alcoholic fatty liver disease (NAFLD),[2] none has specifically in type 2 diabetes (T2D). This is important because T2D is associated with gut dysbiosis, increased intestinal permeability and chronic immune activation,[3] and further is a strong risk factor for NAFLD, cognitive impairment and depression.[4] For the first time in a T2D population, we tested whether patients with comorbid liver fibrosis have worse depression and poorer cognitive performance than those without fibrosis.

Our study was a follow-up sub-study of the South London Diabetes (SOUL-D) cohort. Originally recruited between 2008-2011, SOUL-D was an inner-London cohort study in individuals with newly diagnosed (<6 months) T2D.[5] In the present study, we consecutively invited patients (according to order recruited to the original study) for 10-year follow-up between April 2018 and October 2019. Ethical approval was granted (UK reference 17/EE/0272) and all participants gave informed consent.

Co-primary outcomes were current depressive symptoms using the Patient Health Questionnaire-9, previously validated in this cohort,[5] and cognitive function using the Rey-Osterrieth complex figure (ROCF) test (Fig. 1).[6] As secondary outcomes, we measured cognition using the telephone interview for cognitive status (TICS-M) (testing verbal memory); Stroop colour word test (testing attention and executive function); and verbal fluency (testing executive function by asking participants to name as many animals as they can in 1 min). These cognitive tests have been found to be discriminatory in T2D.[7,8]

The primary predictor was liver fibrosis, estimated using transient elastrography (Fibroscan) of the liver. All patients fasted ≥6 hours prior. We defined any liver fibrosis using the cut-off of liver stiffness measurement ≥7.0, validated for mild (F1) fibrosis in T2D.[9] As secondary predictors, we measured liver steatosis using controlled attenuation parameter ≥260 dB/m and serum liver biochemical enzymes (alanine

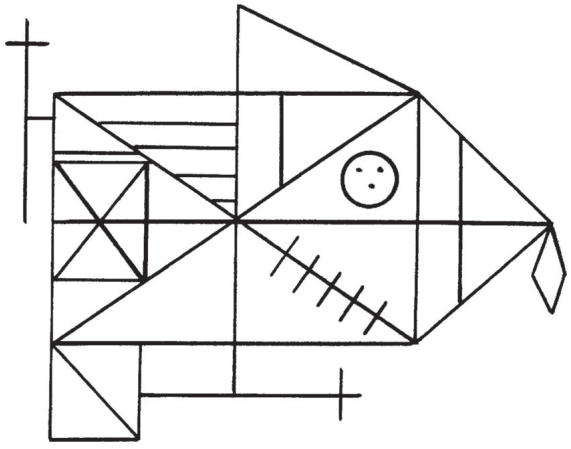

Fig. 1. The Rey-Osterrieth Complex Figure (ROCF) test. This is a neuropsychological assessment, in which participants reproduce a complicated line drawing under three conditions: 1) copying (testing attention and concentration, planning, organisation and visuospatial perception); 2) immediate recall without reference to the figure (testing immediate visuospatial memory); and 3) recall after a 30-minute delay (testing delayed visuospatial memory). Using the Osterrieth scoring system, the diagram is split into 18 units, each scored 2 if unit correct and placed properly; 1 if correct but placed poorly; 1 if distorted (but recognisable) and placed properly; ½ if distorted (but recognisable) and placed poorly; and 0 if absent or unrecognisable. The total on each condition is 36 and one assessor (CDM) scored all assessments to ensure consistency.