

## Severe acute hepatitis in children: investigate SARS-CoV-2 superantigens

Recently, there have been reports of children with a severe acute form of hepatitis in the UK, Europe, the USA, Israel, and Japan.<sup>1</sup> Most patients present with gastrointestinal symptoms and then progress to jaundice and, in some cases, acute liver failure. So far, no common environmental exposures have been found, and an infectious agent remains the most plausible cause. Hepatitis viruses A, B, C, D, and E have not been found in these patients, but 72% of children with severe acute hepatitis in the UK who were tested for an adenovirus had an adenovirus detected, and out of 18 subtyped cases in the UK, all were identified as adenovirus 41F.<sup>1,2</sup> This is not an uncommon subtype, and it predominantly affects young children and immunocompromised patients. However, to our knowledge, adenovirus 41F has not previously been reported to cause severe acute hepatitis.

SARS-CoV-2 has been identified in 18% of reported cases in the UK and 11 (11%) of 97 cases in England with available data tested SARS-CoV-2 positive on admission; a further three cases had tested positive within the 8 weeks prior to admission.<sup>2</sup> Ongoing serological testing is likely to yield greater numbers of children with severe acute hepatitis and previous or current SARS-CoV-2 infection. Eleven of 12 of the Israeli patients were reported to have had COVID-19 in recent months,<sup>3</sup> and most reported cases of hepatitis were in patients too young to be eligible for COVID-19

vaccinations. SARS-CoV-2 infection can result in viral reservoir formation.<sup>4</sup> SARS-CoV-2 viral persistence in the gastrointestinal tract can lead to repeated release of viral proteins across the intestinal epithelium, giving rise to immune activation.<sup>5</sup> Such repeated immune activation might be mediated by a superantigen motif within the SARS-CoV-2 spike protein that bears resemblance to Staphylococcal enterotoxin B,<sup>6</sup> triggering broad and non-specific T-cell activation. This superantigen-mediated immune-cell activation has been proposed as a causal mechanism of multisystem inflammatory syndrome in children.<sup>4,7</sup>

Acute hepatitis has been reported in children with multisystem inflammatory syndrome, but co-infection of other viruses was not investigated.<sup>8</sup> We hypothesise that the recently reported cases of severe acute hepatitis in children could be a consequence of adenovirus infection with intestinal tropism in children previously infected by SARS-CoV-2 and carrying viral reservoirs (appendix). In mice, adenovirus infection sensitises to subsequent Staphylococcal enterotoxin-B-mediated toxic shock, leading to liver failure and death.<sup>9</sup> This outcome was explained by adenovirus-induced type-1 immune skewing, which, upon subsequent Staphylococcal enterotoxin B administration, led to excessive IFN- $\gamma$  production and IFN- $\gamma$ -mediated apoptosis of hepatocytes.<sup>9</sup> Translated to the current situation, we suggest that children with acute hepatitis be investigated for SARS-CoV-2 persistence in stool, T-cell receptor skewing, and IFN- $\gamma$  upregulation, because this could provide evidence of a SARS-CoV-2 superantigen mechanism in an adenovirus-41F-sensitised

host. If evidence of superantigen-mediated immune activation is found, immunomodulatory therapies should be considered in children with severe acute hepatitis.

We declare no competing interests.

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See Online for appendix