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LETTER THE EDITOR

Severe Acute Hepatitis of Unknown Origin in the COVID-19 Era

Hepatitis aguda grave de origen desconocido en la era de la COVID-19

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Sir. Director:

At present, globally the pandemic of COVID-19 continues; cases associated with new variants of coronavirus have increased exponentially, changing between strains the contagiousness or virulence capacity. This scenario favors, from the perspective and experience of researchers, the emergence of future pandemics, which is inevitable.

On April 5, 2022, the UK National Focal Point (NFP) for the International Health Regulations (IHR) notified the WHO of ten cases of severe acute hepatitis of unknown etiology in previously healthy young children aged 11 months to 5 years in central Scotland.(1) As of July 29, 2022, more than 1000 probable cases of acute hepatitis of unknown cause had been reported worldwide,(2) with cases occurring on three different continents (Europe, North America and Asia).

The data reveal a high concentration of cases in Europe, the United Kingdom (273 cases) and the United States (109). Although in smaller numbers, other countries report the presence of these cases: Argentina (8), Brazil (16), Canada (7), Costa Rica (2), Indonesia (15), Israel (12), Japan (7), while Panama, Palestine, Serbia, Singapore and South Korea each report one case.(1)

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Hepatitis is an inflammation of the liver caused by a variety of viruses and non-infectious agents that cause various health problems, some fatal. There are five main strains of hepatitis virus, referred to as types A, B, C, D and E. While all cause liver disease, they differ in modes of transmission, severity of disease, geographic distribution and prevention. In particular, types B and C cause chronic disease in hundreds of millions of people and together are the most common cause of liver cirrhosis, liver cancer, and viral hepatitis-related deaths.[3]

The etiology and pathogenic mechanisms of the disease are still under investigation.[4,5] The UK incident team's initial hypotheses for the etiology of the cases focused on an infectious agent or possible toxic exposure. No link to the COVID-19 vaccine was identified, and detailed information collected through a case questionnaire on food, drink, and personal habits did not identify any common exposures. Toxicological investigations are ongoing, but an infectious etiology is considered more likely given the epidemiological picture and clinical features of the cases.[6]

Adenovirus subtype 41 (41F), seems to be the most likely explanation, about 70 % of the cases (according to a WHO press conference on May 10) were positive.[4] Several hypotheses have been proposed, changing the pathogenesis of adenoviruses to cause hepatitis in healthy children:[5]

- An immune deficit due to lack of exposure to pathogens during the COVID-19 pandemic could have made children more susceptible to adenovirus infection and rare outcomes of infection.
- As with other respiratory viruses, the "relaxation of pandemic restrictions" could have led to a massive wave of adenovirus infections, triggering rarer outcomes of infection.
- A previous infection or co-infection (with SARS-CoV-2 or an alternative pathogen), or exposure to a toxin, drug, or environmental factor, has altered the host response to adenovirus infection.

The clinical manifestations of the identified cases correspond to acute hepatitis with elevated transaminases, most cases presented with gastrointestinal symptoms, including jaundice (71 %), vomiting (63 %), pale stools (50 %), and diarrhea (45 %). Fever (31 %) and respiratory symptoms (19 %) were less frequent.[7] More than 20 children have required liver transplantation and eleven deaths were reported, including five in Indonesia, one in Palestine and five in the United States.[2]

At present, there is still insufficient evidence on severe acute hepatitis of unknown origin in children. Possible causes continue to be examined; more research is needed to make a strong case. Today, as never before, we need to apply the concepts of precision medicine, early case identification and appropriate therapeutic decisions.

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