University of Tel Aviv study points to COVID as cause of recent unexplained acute liver failure among children

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On June 7, 2022, the World Health Organization (WHO) and the World Hepatitis Alliance, at their World Hepatitis Summit 2022, released a joint news statement in which they also briefly addressed the current cases of unexplained acute hepatitis (liver inflammation) among young children. There have been some 700 such cases in the last five months, spanning 34 countries, coinciding with the Omicron phase of the pandemic. The United Kingdom and the United States lead in the number of cases, each with more than 200.

The clinical signs of the disease come on suddenly, with a high proportion of children developing liver failure and around six percent needing a liver transplant. Nine have died. The most common symptoms are vomiting and jaundice, the yellowing of the skin and the sclera of the eyes.

Many in the scientific community speculated that the disease fell into the spectrum of the multisystem inflammatory syndrome-children (MIS-C) arising from a previous COVID infection, which can afflict a minority of children and adolescents after the acute phase of COVID has passed and their infections have already cleared, meaning that once acute hepatitis manifests, their COVID tests are negative. Many have also not had antibody tests conducted to confirm previous COVID infections.

Speaking with *New Scientist,* Dr. Deepti Gurdasani of Queen Mary University of London said, “I think we have seen hepatitis as part of MIS-C before, but not in the numbers that are being seen now.” She explained that the rise could be because Omicron has infected millions of children in a few short months.

Many public health officials, including the US Centers for Disease Control and Prevention (CDC) and the WHO, have placed undue emphasis on adenovirus infections, which commonly cause colds and flu-like symptoms in the population. However, they almost never cause liver failure among previously healthy children, or even the immuncocompromised, for that matter.

Despite experience with adenoviruses and ample expertise on viral infections and liver injury that have been amply documented in the literature, this didn’t stop the CDC from writing on May 6, 2022, “This cluster [in Kentucky], along with recently identified possible cases in Europe, suggest that adenovirus should be considered in the differential diagnosis of acute hepatitis of unknown etiology among children.”

But in their report they clearly stated that on liver biopsies no [adenovirus] viral infections were ever observed. Even with the use of the electron microscope, no viral particles were evident. In the very rare instances where adenoviruses have caused liver failure among immunocompromised children, in 100 percent of cases the adenovirus was detected in liver cells.

On May 22 the WHO provided a more nuanced perspective, writing, “While adenovirus is a plausible hypothesis as part of the pathogenesis mechanism [the manner of development of disease], further investigations are ongoing for the causative agent; adenovirus infection (which generally causes mild self-limiting gastrointestinal or respiratory infections in young children) does not fully explain the more severe clinical picture observed with these cases.”

Dr. Farid Jalali, a gastroenterologist, has emphatically denounced the claim that these recent unexplained pediatric acute liver failures are associated with the detection of adenovirus in the patients, especially in the

context of the COVID-19 pandemic and recent massive waves of Omicron infections. Adenoviruses are common and can colonize the areas of the respiratory and intestinal tracts. Finding them doesn't necessarily indicate they were the cause of the disease.

He emphasized that public health institutions are doing a disservice to the children and families of the afflicted by suggesting such an association and are only minimizing the dangers posed by the current policies that allow SARS-CoV-2 to persist in human communities.

The debate in the scientific community has been ongoing. However, a recent study from Tel Aviv University has provided new evidence that COVID is indeed responsible for these acute liver failure cases. Lead author Dr. Shiri Cooper and colleagues submitted a report last Friday to the *Journal of Pediatric Gastroenterology and Nutrition* on five pediatric cases that had recovered from asymptomatic or mild COVID and later suffered acute liver injury.

They distinguished two patterns of liver involvement after COVID-19: acute liver failure that required transplantation and acute hepatitis with injury to the bile system. Interestingly, the two patients with liver failure were aged only three and five months, and those older, aged eight to 13, developed a disease pattern similar to their adult counterparts.

In adults, post-COVID liver injury has been described in the medical literature but usually as a late complication of severe COVID and hospitalization that leads to progressive liver failure.

Cooper and colleagues in the current study from Tel Aviv University wrote, "The clinical manifestation of the pediatric patients suggests that the pathogenesis is not related to the severity of acute [COVID] disease" as it is in adults. The disease among children frequently presents several months after the diagnosis of COVID-19. In their study, the mean time from COVID to liver failure was 75 days, which explains why so many of these cases were missed as Long-COVID complications, because children are routinely missed in diagnosing the milder form of acute disease.

Many of the findings in the children with liver failure have also been seen in adults, such as the swelling and enlargement of the liver. The walls of the gallbladders were thickened, and the bile ducts were dilated. Biopsies of the liver showed extensive inflammation. In other words, the disease process that has been attributed to adults after their COVID infection has distinct parallels with these children and their acute liver inflammation.

Because of the claimed association with adenovirus, the authors of the Israeli study also attempted to investigate this hypothesis.

First, they commented on published results by the European CDC on 14 cases. None showed adenovirus in any residual liver cells, called hepatocytes: "One case underwent adenovirus PCR of liver tissue which was negative." In another case series of six patients, none of the liver biopsies showed the presence of any adenovirus particles. But as already noted, in rare cases of adenovirus-induced liver failure, liver biopsies in all the cases showed viral particles were present.

In the five patients in Israel, "The adenovirus stain was negative in all, and the histologic features [under the microscope] were not suggestive of adenovirus hepatitis. Three patients had adenovirus PCR performed from whole blood, and in one, it was positive. However, as the liver histology was not suggestive of adenovirus infection, we did not consider it as the culprit for the hepatitis."

As to the mechanism of injury, the authors suggested that damage to the immune system from COVID is likely the cause, and considerable effort is needed to understand these complex processes. It is all the more necessary that public health authorities stop being obstructionists, heed the weight of the evidence that has already been presented, and acknowledge the dangers posed by COVID and the reckless "herd immunity" policy that exposes children to unnecessary harm.

Dr. Lisa Iannattone stated bluntly on Twitter, "Anyone putting forth the hypothesis that there are two novel pediatric liver failure outbreaks caused by two different viruses happening at the same time is not someone to be taken seriously. I don't care what 'very serious institution' they work for. This is absurd. It's COVID."