Mysterious Children's Hepatitis Finally Has Some Answers

New studies offer evidence that an unexpected virus plays a role—but it needs a helper.

July 26, 2022 By Liz Highleyman

Recent studies have shed more light on the unexplained cluster of acute hepatitis cases among children first reported this spring. But there are still no simple answers. It appears that two or more viruses must collaborate to trigger liver inflammation, and genetic susceptibility may also play a role.

> Looks like a pretty major breakthrough in the investigation of paediatric hepatitis with unknown cause
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> Adeno-associated virus 2 (AAV2) detected in the plasma of all 9 cases (and liver of the 4 available to test), and in zero matched controls
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> 1/https://t.co/RZNeawi9cr
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> — Alasdair Munro (@apsmunro) July 25, 2022

As we previously reported, the cluster was first detected in the United Kingdom in April. At that time, 73 cases were under investigation, mostly among children ages 2 to 5. Soon thereafter, nine cases were reported in Alabama, dating back to last fall. Once health officials and doctors knew what to look for, more reports began flooding in from around the world.

As of July 8, more than 1,000 probable cases of severe acute hepatitis of unknown cause had been identified dating back to the fall of 2021, according to the World Health Organization. While most of the children recovered, about 5% required a liver transplant, and 22 died. The Centers for Disease Control and Prevention (CDC) is investigating more than 350 possible cases in the United States.

But after the initial burst, case reports began to level off. It is still unclear whether pediatric hepatitis actually became more common over the past year or whether it truly represents a new medical condition. A recent CDC review of four medical databases did not turn up evidence of increased hepatitis-related pediatric emergency room visits, hospitalizations or liver transplants. "Current data do not suggest an increase in pediatric hepatitis or adenovirus type 40/41 above pre-COVID pandemic baseline levels," the study authors wrote.

Multiple causes of the mysterious malady have been proposed, including an adenovirus (in particular, adenovirus type 41); SARS-CoV-2, the coronavirus that causes COVID-19; a novel virus; or perhaps multiple pathogens acting in concert. Some suspected kids might be more susceptible due to "immunity debt" during COVID lockdowns. Others blamed the coronavirus more directly, suggesting it might be damaging the liver, triggering inflammation or impairing immune defenses; some called it a manifestation of long COVID.

Some causes have been ruled out. The affected children tested negative for well-known hepatitis viruses (A, B, C, D and E). No common exposure to drugs, toxins or environmental factors could be identified. And while some social media commentators seem convinced COVID vaccines are the culprit, most of the affected children were too young to be eligible for vaccination. (The adenoviruses used as vectors in some COVID vaccines are inactivated so they won't cause disease.)

What We Know Now

Two case series published in The New England Journal of Medicine two weeks ago, one looking at nine children with unexplained acute hepatitis in Alabama and the other at 44 children in the U.K., appear to support the adenovirus 41 hypothesis, though the data are not entirely convincing. While most of the kids tested positive for adenovirus using various blood assays (8 of 9 in Alabama and 27 of 30 in the U.K.)—and those with more severe illness had higher levels, on average—adenovirus usually could not be detected in liver tissue.

More than 50 types of adenovirus can cause infection in humans. Though this virus family is best known for causing the common cold, adenovirus 41 is typically associated with gastrointestinal illness. There have been prior reports of adenoviruses causing hepatitis, especially in immunocompromised people, but this appears to be rare.

Now, two new preprints, one from researchers in England and the other from a team in Scotland, describe a more complex picture. They suggest that a different virus, dubbed adeno-associated virus type 2 (AAV2), could be the culprit, but it needs the help of another virus, which could be adenovirus 41.

Together with @UCLchildhealth, we've supported @UKHSA to investigate the recent global hepatitis spike in children. We've been busy analysing samples in our specialised labs and are sharing our results today, along with another study from @UofGlasgow https://t.co/BxQR5nXOBq pic.twitter.com/95kxwMrcC1

— Great Ormond Street Hospital (@GreatOrmondSt) July 25, 2022

Adeno-associated virus 2 is a dependoparvovirus, meaning it is dependent on another helper virus for its replication (similar to the way hepatitis D virus can only replicate in the presence of hepatitis B virus). High levels of AAV2 were found in both blood and liver tissue, along with adenoviruses or herpesviruses. In the two studies together, all but one of the children with acute hepatitis had detectable AAV2, compared with less than 5% of those in a control group comprised of healthy children, kids with adenovirus infection but no liver inflammation and kids with a known cause of liver inflammation.

The studies also found that genetic susceptibility appears to play a role. While only about 16% of the Scottish population carries a particular genetic variant (class II HLA-DRB1*04:01 allele) associated with an aggressive immune response, 8 of 9 children with unexplained hepatitis in the Scottish study and 4 of 5 children who required a liver transplant in the English study had the mutation.

The proportion of children with acute hepatitis who had antibodies against SARS-CoV-2 was similar to that of the general pediatric population, indicating that the coronavirus itself probably isn't causing the mysterious illness.

However, the researchers suggested that when COVID restrictions were lifted, many children may have been exposed to multiple viruses at once, leading to a temporary rise in acute hepatitis cases. In addition, many children were exposed later in life, when viruses may cause more severe disease.

"During the lockdown period when children were not mixing, they were not transmitting viruses to each other. They were not building up immunity to the common infections they would normally encounter," Judith Breuer, MD, of University College London and Great Ormond Street Hospital, the

senior author of the English study, told the BBC. "When the restrictions were lifted, children began to mix, viruses began to circulate freely—and they suddenly were exposed with this lack of prior immunity to a whole battery of new infections."

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