Starting in April, young children with mysterious cases of acute liver inflammation began to attract scientific—and media—attention in the United Kingdom and elsewhere. Most would recover, some after liver transplants, but a few died. Physicians could find no evidence in the children of viruses that typically cause hepatitis, but researchers homed in on an unexpected suspect: adenovirus, a family of cold-causing viruses common in kids. Now, a sweeping genetic search of these patients instead implicates another virus, one previously thought to be completely harmless.

In two independent, preliminary studies, U.K. researchers found high adeno-associated virus 2 (AAV2) levels in the blood or liver cells in 24 of 25 children with unexplained hepatitis. In a group of kids without this condition, almost none had AAV2, even those with adenovirus. The young hepatitis patients were also much likelier to have a genetic variant that may make their immune systems overreact to viruses.

The preprints, one posted on medRxiv on 19 July and the other just submitted there, offer new clues to the mystery pediatric hepatitis, which now numbers more than 1000 probable cases in 35 countries and has caused at least 22 deaths.

But outside researchers are cautious about the studies, which haven't been peer reviewed. "It's intriguing for sure, but it's a very small number of cases and controls. It could be associations and not causation," says Saul Karpen, a pediatric gastroenterologist at Emory University School of Medicine.

Severe hepatitis in children is rare and often goes unexplained. But alarm bells went off in the spring after hospitals in the United Kingdom reported a rise in cases—now up to 272—that are not linked to the usual causes, such as a hepatitis A, B, or C virus. Another 334 such unexplained cases have been reported in the United States, but the Centers for Disease Control and Prevention said in June that these are not above usual levels.

Still, a spring spike in adenovirus infections in the United Kingdom lent credibility to a hepatitis surge there. And last week in two papers in *The New England Journal of Medicine*, teams in Birmingham, England, and Birmingham, Alabama, reported adenovirus 41, a specific type that causes gastrointestinal illness, in the majority of nine U.S. and 30 U.K. cases tested.

But the London and Glasgow, Scotland, teams behind the two preprints wanted to make sure some new virus or viral variant wasn't emerging. They used DNA and RNA sequencing of tissue samples from U.K. cases to look for about 200 different virus families. AAV2 jumped out. It was in liver or blood samples in all nine Scottish cases examined and 15 of 16 separate cases from all over the United Kingdom, according to the studies. In contrast, almost none of 158 controls, which included healthy children and children with hepatitis for known reasons, had AAV2.

The viral family to which AAV2 belongs was initially discovered in samples that contained adenoviruses—AAVs need a protein from a distant viral relative, usually adenovirus or herpesvirus, to replicate. Many people are infected by AAV2 by age 10, but the virus can lie dormant in cells until that helper virus comes along and activates it.

Most of the patients also had adenovirus, usually the 41 type. But AAV2 never turned up in a control group of 12 Scottish children who had an adenovirus infection but no hepatitis. The authors of the preprints also ruled out SARS-CoV-2, an early suspect, partly because its infection rates weren't higher than average in the Scottish hepatitis patients.

The pandemic could, however, indirectly explain the rise of pediatric hepatitis in the United Kingdom. Relaxed COVID-19 restrictions meant children may have been exposed to a "cocktail of viruses" all at once versus gradually, according to Emma Thomson, an infectious diseases specialist at the MRC-University of Glasgow Centre for Virus Research and a leader of the Scottish study.

Both studies also found that all but two of 14 sick children tested carried a specific version of a type of gene called *HLA* that helps shape the body's response to pathogens. The variant is particularly common in northern Europeans—16% of Scottish people carry it, and it is known to be linked to some autoimmune disorders, Thomson notes.

Although the researchers found genetic material from AAV2 in patients' liver cells, they did not detect viral proteins or actual copies of the virus. That suggests instead of directly damaging liver cells, AAV2 may provoke an immune response that harms the organ. That theory is supported by the link with *HLA* type and that some kids had gastrointestinal illnesses many weeks before they developed hepatitis, said a leader of the London team, virologist Judy Breuer of Great Ormond Street Hospital and the University College London Great Ormond Street Institute of Child Health, at a press briefing Monday.

A pathogenic role for AAV2 "goes against everything we know" about the virus, says virologist Eric Kremer of the Institute of Molecular Genetics of Montpellier. Looking at the type of antibodies to AAV2 in the children, he notes, could support its guilt by distinguishing between a long-ago infection, or a more recent one timed with the onset of hepatitis. Those studies are planned, Thomson says.

The good news for U.K. parents in all this: Pediatric hepatitis cases have dropped in recent weeks to "almost … background," said Meera Chand of the UK Health Security Agency, which expects to release its own study of adenoviruses in these cases this week.

At the same time, the studies raise questions about delivering therapeutic genes with AAVs, as many groups are trying to, Kremer notes. Although the viruses are further modified so they can't replicate even if a helper virus is around, they have sometimes caused liver inflammation—which in rare cases may have contributed to deaths. Stanford University gene therapy researcher Mark Kay says the field may want to explore whether *HLA* type can predict whether an AAV gene therapy patient will experience liver toxicity.

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