

Emerging clues to unexplained pediatric hepatitis

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Earlier this year, physicians in the United Kingdom raised alarm over an apparent surge in cases of unexplained severe acute hepatitis in children.

By late June, the U.K. reported 258 cases, 12 of which required liver transplants, up from about 20 in a normal year.

As of mid-July, 35 countries reported more than 1000 probable cases, including 22 deaths, with most of those cases occurring in Europe.

Canada reported 23 as of mid-August, two of which required liver transplants. An expert told *CMAJ* that's roughly the number you would expect to see given the size of Canada's population.

It's not unusual for the causes of severe liver inflammation in children to be unknown — by some estimates, up to half of such cases are unexplained. And it's still unclear whether the numbers reported globally reflect a true uptick in unexplained cases rather than increased attention to the issue.

Adenovirus, SARS-CoV-2 initially suspect

Early investigations suggested a link with adenoviruses, a group of more than 50 viruses known to cause cold symptoms, pink eye, gastroenteritis, and other common illnesses.

The United States Centers for Disease Control and Prevention (CDC) reported evidence of adenovirus infection in 45% of children with unexplained hepatitis from October 2021 to June 2022, with adenovirus 41 being the most common. Meanwhile, a U.K. study found adenovirus infection in 90% of cases.

Adenoviruses are known to cause hepatitis in immunocompromised children,

but most of those with unexplained hepatitis were otherwise healthy. That raised questions about whether an adenovirus mutated or interacted with another virus to cause the inflammation.

Another hypothesis links the unexplained hepatitis cases to SARS-CoV-2 infection or some sort of delayed immune response related to COVID-19. About 10% of affected children had an active SARS-Cov-2 infection while up to one-third previously had COVID-19, according to the CDC.

However, there is no evidence of a link with any SARS-CoV-2 vaccine, as most of the unexplained severe acute hepatitis cases have been in children who were too young to receive the shots.

Multiple factors likely contributing

"Most likely with acute hepatitis, it will be more than one thing contributing," says Tehseen Ladha, an Edmonton-based pediatrician and assistant professor at the University of Alberta.

More recent investigations from the U.K. suggest multiple viruses may be behind the mystery.

In two small preprint studies, researchers from Scotland and England detected an adeno-associated virus called AAV2 in the blood and livers of children with unexplained severe acute hepatitis. Notably, the Scottish study did not detect AAV2 in controls who had adenovirus without liver inflammation, or who had hepatitis from a known cause.

AAV2 typically requires a second "helper" virus to replicate, and both of the studies detected evidence of adenovirus and herpesvirus — two common

helper viruses — in children with unexplained hepatitis.

Many of the children with unexplained hepatitis also had a certain type of human leukocyte antigen linked with a genetic predisposition to autoimmune liver inflammation.

This type of human leukocyte antigen is more common in people of European ancestry, which could explain the concentration of unexplained pediatric hepatitis cases in Europe and North America.

The authors of the two studies also hypothesize that COVID-19 lockdowns may have contributed to reduced immunity and larger numbers of children being infected for the first time with AAV2 and its helper viruses when restrictions dropped, which in turn may have triggered hepatitis in those with a genetic predisposition.

Larger peer-reviewed studies are needed to investigate the relationship between AAV2, helper viruses, and human leukocyte antigen type.

Researchers are also exploring other hypotheses, including drug, toxin, or environmental exposures.

Early diagnosis is essential

Astute clinicians are key to solving the mystery, as they're usually the ones bringing cases of pediatric hepatitis to the attention of public health, said John Ward, a senior scientist at the CDC and director of the Coalition of Global Hepatitis Elimination, at a recent talk.

According to Ontario's science table, the uncertainties surrounding pediatric hepatitis and the incomplete workup of most cases to date highlight the need for more robust surveillance and testing of potential cases.

Physicians should look out for specific symptoms like jaundiced skin or eyes, dark urine, pale stool, and hepatic encephalopathy — a decline in brain function that occurs when the liver can't remove toxins from the blood.

Ladha says it's also important to have a lower threshold for testing children with prolonged, nonspecific symptoms, such as nausea, vomiting, loss of appetite, joint or muscle pain, fever, and fatigue.

While severe acute hepatitis is rare in Canadian children, the severity of the illness warrants alarm, Ladha says.

Early diagnosis is especially important because of the difficulty of arranging liver transplants, says Sylvie Lebel, a pediatric gastroenterologist at BC Children's Hospital.

Any jaundice outside the neonatal period, with or without abnormal coagulation, should trigger a call to a pediatric hepatologist, Lebel says.

A recent practice article in *CMAJ* recommends that children with an ALT level of more than 500 IU/L or an INR of 1.5 or higher require referral.

"We do not have technology anywhere in the world to support a failing liver, so being in a transplant centre at the earliest possible time is of the essence," Lebel says. "The worst thing to do is sit on a case like this."

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