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NEWS ANALYSIS

Hepatitis in children: What's behind the outbreaks?

Cases of idiopathic hepatitis in children have been reported around the world. **Elisabeth Mahase** looks at what we know so far

Elisabeth Mahase

How many children have been affected?

The World Health Organization has so far reported 169 cases of acute hepatitis of unknown origin from 11 countries in Europe and the US, as of 21 April 2022.¹

In the UK, where the increase in cases was first noted at the start of 2022, 114 cases have been confirmed, followed by 13 in Spain, 12 in Israel, nine in the US, six in Denmark, five in Ireland, four in the Netherlands and in Italy, two in Norway and in France, and one in Romania and in Belgium. Ages of the affected children range from 1 month to 16 years.

Japan's health ministry (25 April) has reported its first possible case in a child under the age of 17 who has been admitted to hospital.²

Is this higher than normal?

It seems to be. Will Irving, professor of virology at the University of Nottingham, told *The BMJ* that there had always been a background but low incidence of severe hepatitis in young children without a known cause but that now the numbers had risen fivefold to 10-fold. These cases are referred to as non-A-E hepatitis, because although the patients are known to have hepatitis, all the markers for the usual suspects—hepatitis A, B, C, and E—are negative.

Irving said, “Normally a paediatric haematologist in, say, Birmingham, at one of the big UK centres, might see one or two cases a month. For many years we've wondered whether there was another virus that's causing non-A-E hepatitis. There's always a background level there, but now Birmingham, for example, has seen 40 cases in three months.”

How serious is it?

Most children seem to be recovering well. However, WHO has confirmed that at least one child has died so far, while 17 children (around 10% of the total known cases) have needed a liver transplantation.

Simon Taylor-Robinson, consultant hepatologist at Imperial College London, said, “Treatment is usually supportive, with hydration and management of temperature, because the problem normally resolves. The liver has an amazing ability to regenerate itself after an insult. Generally, within a few days or weeks, things settle back down with this supportive treatment. If blood tests are significantly abnormal, treatment would be in a specialised hospital, as in rare cases the liver injury can require more specialised medical intervention.”

Why is it happening?

While there is no certain cause, the current hypothesis relates to adenovirus type 41, because many of the children with hepatitis have tested positive for this virus. Adenovirus 41 is known to infect children and cause symptoms such as diarrhoea, vomiting, and fever, although it has not previously been linked to hepatitis.

In its latest report the UK Health Security Agency said it believed that there was a “cofactor affecting young children which is rendering normal adenovirus infections more severe or causing them to trigger immunopathology.”³ The report listed several possible cofactors, including susceptibility arising from lack of prior exposure during the pandemic; a prior infection with SARS-CoV-2 or another infection; a coinfection with SARS-CoV-2 or another infection; or a toxin, drug, or environmental exposure.

The agency suggested some other possible causes, although it noted that these did not fit as well with the current evidence. These included a novel variant of adenovirus, with or without a contribution from a cofactor as listed above; a drug, toxin, or environmental exposure; a novel pathogen either acting alone or as a coinfection; or a new variant of SARS-CoV-2.

Commenting on the current theories, Zania Stamataki, associate professor in viral immunology at the University of Birmingham, said, “The rising incidence of children with sudden onset hepatitis is unusual and worrying. If an adenovirus is to blame, this could be a new variant of adenovirus that may cause liver injury in children with naïve or immature immune systems. But we need to know more to be sure.

“Alternatively, if adenovirus is the culprit for hepatitis in children who are otherwise well, we ought to look for other infections and environmental causes that could exacerbate adenoviral inflammation.”

Might the pandemic have played a role?

Irving said that the covid pandemic could have had an effect, notably through the reduction in social mixing and virus spreading. “It is conceivable that whatever it was that was causing the odd case before is now, like all of the other viruses, simply circulating more widely because of the effects of lockdown and then the release from lockdown.

“That's an alternative hypothesis: that there's always been a non-native virus that we haven't yet identified and that that's simply circulating at greater levels

than it used to, because of the effects of the pandemic,” he told *The BMJ*.

- 1 Multi-country: Acute, severe hepatitis of unknown origin in children. WHO. Apr 2022. <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON376>.
- 2 Possible case of mysterious child hepatitis found in Japan. Nippon.com. Apr 2022. <https://www.nippon.com/en/news/yjj2022042501132>.
- 3 UK Health Security Agency. Investigation into acute hepatitis of unknown aetiology in children in England: technical briefing. Apr 2022. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1071116/acute-hepatitis-technical-briefing-1_3_.pdf.