the effects of the input currents from neural activity[5]. The implications of these findings are far-reaching, given that microtube-connected glioma cells can evade the cell death that usually arises from radiation therapy[9].

In mice and humans, the gliomas that were enriched for functional connectivity were associated with poorer survival and with cognitive decline. The study shows that gliomas hijack computational power from the brain by parasitizing neural plasticity, so as to grow at the expense of cognitive function. Cognitive decline in individuals with glioma might therefore be an independent predictor of poor survival[10]. This electrical conversation in the brain between the physiological mind and the tumour is a frankly startling and astounding concept. Through this hijacking, gliomas demonstrate a unique form of plasticity that is perhaps appropriate only for an intrinsic tumour of the mind.

These two ghosts in the machine, the mind and the tumour, whispering to each other in the dark recesses of the brain, engage in a conversation that could be well worth eavesdropping on. Doing so could lead to innovative approaches to improving the lives of people with brain tumours.

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Medical research

Childhood hepatitis outbreak under scrutiny

Frank Tacke

Since 2022, more than 1,000 cases of childhood hepatitis with no known cause have been reported. The discovery of adeno-associated virus 2 in the blood and livers of such children might provide an explanation. **See p.555, p.564 & p.574**

Paediatricians first began to report a concerning wave of acute severe hepatitis — a disease involving liver inflammation — in children in spring 2022. This spate of cases, which now numbers more than 1,000 (see go.nature.com/42dpfv4), had no known cause, unlike most cases of paediatric hepatitis. The cases were often serious, with 7.3% of affected children needing a liver transplant[1]. Three groups now independently provide evidence that infection by adeno-associated virus 2 (AAV2) is linked to this wave[2–4]. Their work is likely to spark debate, and could influence disease management.

Two previous analyses[5,6] of this wave of acute severe hepatitis found an association with human adenovirus (HAdV), particularly the HAdV-F41 strain. However, this result has puzzled clinicians because, although adenovirus-induced hepatitis is a known phenomenon, it is rare and usually restricted to people with severely compromised immune systems. Moreover, the studies identified various HAdV strains, even in children from the same geographical region, implying that a single strain could not explain these hepatitis outbreaks. Furthermore, adenovirus-induced hepatitis is characterized by virus-derived structures, called inclusions, in the nucleus — something that has not often been detected in the current outbreak[7].

Controversy therefore remained around whether the outbreak was caused by HAdV or another virus. The previous studies identified HAdV using targeted genetic-sequencing approaches. By contrast, the current studies involved an untargeted approach called clinical metagenomics, in which all nucleic acids from a sample are sequenced, to discover which viruses might be present. All three identified AAV2 — a virus known to replicate in the liver, but not known to cause hepatitis[8].

In the first of the papers, Ho *et al.*[2] (page 555) report high levels of AAV2 in blood and liver samples from 26 (81%) out of 32 affected children in the United Kingdom. By contrast, the researchers detected only low AAV2 levels in 5 (7%) of 74 members of a control group consisting of healthy children, children who had HAdV infection but not hepatitis, or children who had other diseases or other forms of acute hepatitis. The authors found that 93% of the affected group carried a gene variant that predisposes an individual to autoimmune diseases involving immune cells called T cells. Liver biopsies were available for five infected children. Analysis using a tissue-staining approach (histology) revealed AAV2 in abnormally swollen liver cells (hepatocytes) surrounded by T cells, suggesting a causative role of AAV2 in acute hepatitis.

In the second study, also from the United Kingdom, Morfopoulou *et al.*[3] (page 564) report high levels of AAV2 in 27 of 28 affected children, and only low levels of AAV2 in a control group, which included immunocompromised children who had acute hepatitis due to other causes, and children with normal immune systems who had fever. The authors used several techniques to demonstrate that the disease was not due to direct damage

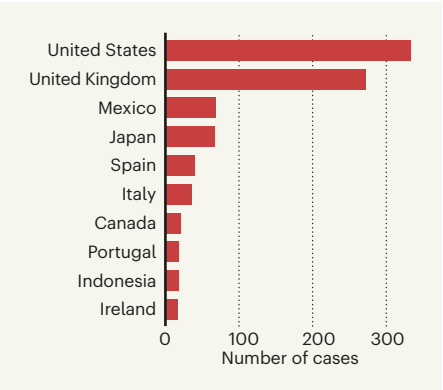

Figure 1 | Hepatitis outbreak around the world. As of July 2022, 35 countries had reported cases of severe acute paediatric hepatitis that had no known cause, according to the World Health Organization (see go.nature.com/42dpfv4). Numbers for the 10 countries with most reported cases are shown here. Three groups[2–4] now provide evidence that adeno-associated virus 2 has a role in this outbreak.

to hepatocytes (known as hepatotoxicity) caused by AAV2 alone. Because low levels of HAdV and human herpesvirus 6B (HHV-6B) were detected in the liver in most cases, the authors speculate that these viruses might enable AAV2 replication, leading to damage to hepatocytes.

In the third paper, Servellita *et al.*[4] (page 574) report similar findings from the United States. They detect AAV2 in 13 of 14 cases, compared with only 4 of 113 controls. All 14 cases also tested positive for HAdV. In the 13 children infected with AAV2, the authors found co-infection with a 'helper' virus that might promote AAV2 replication — either Epstein–Barr virus (EBV) or HHV-6. Thus, most of the cases had a triple infection (AAV2, HAdV and either EBV or HHV-6). The fact that these authors examined only children who were infected with HAdV might explain why they detected more concomitant viral infections than did the other groups.

All three studies make the same observation of AAV2 in children with unexplained acute hepatitis. That the studies took place on two continents adds to their value, given the global nature of the outbreak (Fig. 1). However, a note of caution is needed — these studies were all conducted retrospectively, rather than being gold-standard prospective trials, in which subjects are selected for study, with data being subsequently collected over time. The case numbers are relatively small, and the number of liver samples even smaller. The studies report limited clinical information (such as ethnic background, whether the children were born by caesarean section and whether they could have been exposed to viruses during day care), which is needed to reveal potential factors or co-factors in disease development. Such data would be essential to exclude the possibility that AAV2 is a harmless bystander.

Direct evidence for how AAV2 might cause hepatitis is limited. Ho and co-workers' genetic and histological analyses imply that the disease is rooted in abnormal immune responses, rather than in a hepatotoxic role for AAV2. Morfopoulou and colleagues provide support for this conclusion, finding that liver samples were enriched in adaptive immune cells and immune-related proteins, but contained no detectable HAdV or AAV2 proteins, or viral particles.

Further evidence for the idea that this rash of cases is immune-related comes from gene-therapy trials. AAV is perhaps the most commonly used viral vector for delivering genes to people for gene therapy[9]. Hepatotoxicity has been observed in trials that involve AAV-based approaches, but it is rare, and generally not fatal[9]. If AAV2 directly caused hepatitis, one would expect more cases to have been reported.

Going forward, in-depth immunological analyses will be eagerly awaited. In addition, analysis of any direct toxic effects of AAV2 on liver cells — using 3D cultures called liver organoids, for instance — will be needed to understand how AAV2 infection (with or without helper viruses) might affect hepatocyte metabolism and viability[9]. This distinction between immune-mediated and hepatotoxic effects is highly relevant, because it will dictate whether this disease should be managed through immunosuppression or directed antiviral drugs.

The three studies cannot rule out the possibility that COVID-19 is a contributory factor, because the timing of the hepatitis outbreak meant that antibodies against the SARS-CoV-2 virus were prevalent in all groups. The children often reported symptoms of viral infection, including fever and gastrointestinal problems, suggesting that a SARS-CoV-2 reservoir might be present in the intestine or in bile-duct cells called cholangiocytes (these cells express high levels of the protein ACE2, which mediates infection by SARS-CoV-2)[10]. Researchers should investigate the possibility that SARS-CoV-2 proteins act as 'superantigens', triggering a powerful immune response to HAdV-F41 or AAV2 in a host whose immune system has been sensitized.

Even if a direct involvement of SARS-CoV-2 can be ruled out, the timing of the hepatitis outbreak in relation to the COVID-19 pandemic is striking. The wave of hepatitis in spring 2022 coincided with the relaxation of COVID-19 measures around the globe, and cases rapidly tailed off (although scattered new cases are still being reported). As such, the timing of the outbreak might be explained by the fact that children were suddenly exposed to a barrage of viruses after lockdowns, or had poorly trained immune systems that led to an increased susceptibility to otherwise harmless viruses.

Although the current studies report few follow-up data, the acute hepatitis apparently resolved without the need for long-term immunosuppression in most cases. Prospective, properly controlled follow-up investigations are now needed, to determine the extent to which AAV2 infection can cause, or contribute to, acute hepatitis in children. Until then, surveillance for AAV2 (and related viruses) in such cases is to be advised.

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Electrochemistry

An organic catalyst for chlorine production

Thomas Turek

The industrial process for making chlorine uses a vast amount of energy globally. An organic catalyst has been developed that could form the basis of a more energy-efficient process, replacing expensive inorganic catalysts. **See p.519**

Chlorine is required for the manufacture of an enormous variety of products in the chemical industry. Most of this chlorine is made using a process called chlor-alkali electrolysis, which requires energy equivalent to about 1% of worldwide electricity production, and is therefore responsible for huge carbon dioxide emissions. Any improvement in the energy efficiency of the process would thus be of great economic and environmental importance. On page 519, Yang *et al.*[1] report an organic catalyst with extremely high activity and selectivity for chlorine production in the chlor-alkali process, which could help to reduce its energy demands.

The chlor-alkali process is carried out in a reactor known as a membrane cell, which is divided into two chambers. In the conventional process, concentrated sodium chloride solution is passed through the first chamber, where the salt's chloride ions (Cl^-) are converted to chlorine at the cell's anode.