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EDITORIALS

Outbreaks of acute flaccid myelitis in the US

Enteroviruses are implicated, particularly D68

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The World Health Organization has declared much of the world free of polio, including the UK (1982) and the US (1979). However, acute flaccid myelitis and paralysis due to vaccine associated poliomyelitis are still evident in Papua New Guinea,[1] and large outbreaks of acute flaccid myelitis due to non-polio enteroviruses (often enterovirus A71) have occurred, particularly in South East Asia.[2]

Outbreaks of acute flaccid myelitis are currently ongoing in the US, where the Centers for Disease Control and Prevention (CDC) recently described an outbreak of a polio-like disease in children as "a mystery illness."[3] Symptoms include sudden onset of paralysis in the arms or legs and grey matter lesions in the spinal cord. By the end of November 2018, the condition had been confirmed in 116 children from 31 US states,[4] an increase of 250% from 2017, when 33 confirmed cases were recorded. This is a rare condition, with 404 confirmed cases across the US since the CDC began investigating in 2014.[4]

US outbreaks of acute flaccid myelitis occur roughly every other year,[4] a pattern similar to that of enterovirus A71 outbreaks in different settings.[5] The median age of patients involved in a recent US outbreak was 4 years, and 99% of children had symptoms of a respiratory or gastrointestinal infection in the four weeks before presenting with acute flaccid myelitis, suggesting a viral association.[6] In the CDC's 2018 report clinical specimens from 38 (54%) of the 71 patients were positive for enterovirus or rhinovirus.[6] As these two viruses (both picornaviridae) are so similar, it is difficult to differentiate them without gene sequencing. Of the 38 patients, 14 were positive for enterovirus D68 and 11 for A71.[6] Poliovirus was not detected in any specimen.

The enterovirus family includes poliovirus, enterovirus A71 (which usually causes the common childhood illness hand, foot, and mouth disease), enterovirus D68 (usually causes mild respiratory symptoms), and rhinovirus (cause of the common cold). Enteroviruses A71 and D68[7 8] have both been associated with acute flaccid myelitis, but D68 is emerging as the leading causal candidate.

Large outbreaks of enterovirus D68 infections occurred across the US, Europe, and Asia in 2014,[9] with 1153 people (mostly children) affected in the US alone.[10] At the same time, many cases of acute flaccid myelitis were reported among US children,[8] some of whom had laboratory confirmed enterovirus D68 infection.[8 11] Limb weakness or disability can persist for more than 18 months after infection among children with acute flaccid myelitis associated with enterovirus D68.[7 12]

The CDC has not attributed the current outbreak of acute flaccid myelitis to an enterovirus, because enterovirus was detected in just 10% (2/21) of available cerebrospinal fluid specimens.[4 6] However, enterovirus is not always found in cerebrospinal fluid,[7] and other evidence suggests that the current outbreak is caused by enterovirus D68.[13]

Firstly, enteroviruses typically cause outbreaks every two to three years,[5 14 15] and outbreaks of acute flaccid myelitis in the US seem to follow a two year pattern.[4] Many scientists believe this regular cycling is due to the seroprevalance of enterovirus antibodies waning in the population every two years, as new children are born without immunity.[15] Secondly, there is a temporal association between previous outbreaks of enterovirus D68 and acute flaccid myelitis,[13] for example, in the US in 2014.[8] Thirdly, enterovirus D68 infects human neurones—a recent study shows that enterovirus D68 strains, including 2014 strains, can enter and replicate in neuronal cells.[16] Finally, mice infected with enterovirus D68 develop limb paralysis, although the virus is not always detected in cerebrospinal fluid.[17]

Recognition is key to understanding the patterns of this disease, along with fast, accurate diagnostic strategies that include local or point-of-care testing. Individual responses to viral infection vary, and symptoms will differ depending on host factors (such as pre-existing conditions, immunosuppression, genetic factors), and viral factors (subtype, genetic virulence).

Confirming the diagnosis can be difficult, but confirmation should not delay use of treatments such as intravenous immunoglobulin. Commercial preparations contain high levels of neutralising antibodies against enterovirus D68,[18] but randomised clinical trials have not been done to evaluate their

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effectiveness. In one case series from Scotland, patients with D68 associated acute flaccid myelitis showed varying levels of recovery after treatment with intravenous immunoglobulin.[12] Immunoglobulin may also benefit children with enterovirus A71 infection, particularly those with more severe symptoms, including encephalitis and encephalomyelitis.[19]

Collection of these data in a more systematic manner would help inform future treatment decisions. Vaccines and antiviral agents are currently unavailable for enterovirus D68, although enterovirus A71 vaccines are being trialled.[20]

Surveillance and genotyping of enteroviruses must be enhanced and prioritised globally in order to track spread, allow evaluation of novel therapies and vaccines, and reduce outbreaks of acute flaccid myelitis. Techniques such as next generation enteroviral sequencing provide information on specific genome mutations associated with virulence and should inform vaccine design to reduce this serious threat.

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