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Zika virus and Guillain-Barré syndrome

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TITLE Guillain-Barré syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study

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SUMMARY

Zika virus (genus Flaviviridae, family Flavivirus) was first identified in a sentinel rhesus monkey in Uganda in 1947.[1] Cases in Brazil were first reported in early 2015.[2] and resulted in the announcement by the World Health Organization of a Public Health Emergency of International Concern. Among many unanswered questions regarding Zika infection is the role of the virus in neurological diseases, particularly Guillain-Barré Syndrome (GBS). Several related flaviviruses, including Japanese encephalitis virus and dengue, are known to cause acute flaccid paralysis either by direct infection of anterior horn cells or by a post-infectious immune-mediated mechanism.[3,4]

This retrospective case-control study was performed during the outbreak of Zika virus in French Polynesia between October 2013 and April 2014, during which 32,000 patients were assessed for suspected Zika infection.[5]

Forty-two patients with GBS were diagnosed according to the Brighton Criteria.[6] There were two control groups: a group of hospital controls with non-febrile illness (age, sex and geographically matched) who had blood samples taken within 7 days of the matching case; and an age matched control group with RT-PCR confirmed Zika virus infection, without neurological complications.

The median age of the GBS patients was 42 (interquartile range 36–56); there were more males (31, 74%) than females, as found in GBS generally.[7] In total, 88% of GBS patients had a preceding viral syndrome, a median 6 days before onset of the neurological manifestations (which is more rapid than the 2–8 weeks typically seen in GBS). Rash, arthralgia and fever were the most common symptoms. Most patients had a rapid progression (median 6 days) to maximum weakness (which is shorter than the usual 2–3 weeks). Nearly half the patients were unable to walk at admission, facial weakness was common (64%), and just over a third were admitted to intensive care, with one quarter needing ventilatory support. All were treated with intravenous immunoglobulin and survived. Three months after discharge, 24 (57%) could walk unaided.

All the GBS patients were negative for Zika virus by PCR, unlike the 70 Zika controls. Serological evidence of Zika infection was therefore assessed, though this was complicated by the high prevalence of dengue antibodies, following recent dengue I and III outbreaks. A total of 41 (98%) of the GBS patients had IgM or IgG antibody against Zika, compared with 35 (36%) of the hospital controls (OR 59.7 [95% CI 10.4 -+ ∞] p < 0.0001). Serological tests for other common infectious causes of GBS were negative.

Nerve conduction studies were consistent with acute motor axonal neuropathy in all cases; 13 (31%) of GBS patients showed positive reactivity against glycolipids, particularly glycolipid GA1, a lower proportion than expected in acute motor axonal neuropathy.[8]

The authors concluded that there was growing evidence for a link between the Zika virus and GBS, and that GBS might be mediated by unknown autoantibodies, other unknown neurotoxic factors or viral neurotoxicity. An accompanying editorial commentary was circumspect, pointing out that the virus was not detected in any GBS patients, and highlighting the difficulties of interpreting Zika virus serological results in the context of the high prevalence of dengue antibodies.[9] Although it is likely that these patients had been recently infected with Zika virus, it is possible that GBS, at least in some patients, was due to dengue or might possibly have been unrelated to flavivirus infection. This was especially challenging given that the original serological samples

were collected weeks after the initial febrile illness, and that only one sample was collected per patient.

OPINION

In 2013, during the Zika outbreak in French Polynesia, an estimated 20-fold increase in the incidence of GBS was reported.[10] A similar increase in GBS incidence now seems to be occurring in Brazil, where the Government has reported 1,708 cases nationwide between January and November 2015, a significant increase in cases compared to the previous year, particularly in northern states where the Zika virus has been more prevalent.

Until recently, just one GBS case from the outbreak in French Polynesia had been described in more detail.[10] This case-control study therefore adds significantly to the evidence for a link between Zika infection and GBS. However, there are several challenges inherent to retrospective studies such as this.

First, the study is vulnerable to bias through systematic deviations in the sampling of cases (ascertainment bias), or inaccurate retrospective reporting of clinical data (recall bias). All case patients were referred to a reference hospital: the Centre Hospitalier de Polynésie Française, where the diagnosis was confirmed. However, the criteria for referral to this centre were not clear.

Second, tests for Zika virus infection are time-critical, and unless thorough testing is performed at presentation there may be significant diagnostic doubt, especially in the context of other circulating flaviviruses. In an environment where other flaviviruses are prevalent, IgM and IgG antibody tests for an individual flavivirus are known to be non-specific. It is therefore necessary to test for neutralising antibodies which provide higher specificity for individual viruses. Further, 19% of the GBS cases in this study also had anti-Dengue IgM, and 17% of the hospital controls had anti-Zika virus IgM. All of the cases and 56% of the hospital controls had neutralising antibody against Zika virus; however many also had neutralising antibody against the dengue virus. Only one GBS patient showed the standard criterion of neutralisation titres to Zika virus that are four-fold or higher than the titre to the dengue viruses.[9] It is therefore unclear whether the remaining cases were truly associated with Zika infection.

Finally, confirming the diagnosis of GBS retrospectively is challenging because of the vital importance of accurate clinical history and examination, as well as investigations which may not have been performed or documented. A table of clinical data given in the paper raises some questions about diagnostic accuracy. For example, it shows that at the nadir of illness, only 48% of cases had areflexia or decreased reflexes, a feature usually required for diagnosis according to the Brighton Criteria.[6]

Carefully designed prospective case-control studies are now urgently needed to establish beyond doubt the relative risk of GBS associated with Zika infection, and determine the role of any other risk factors such as co-infection. Those studies should include all the diagnostic approaches currently available, including RT-PCR for Zika in urine, where the virus may remain detectable for substantially longer.[11–13] One case report has recently demonstrated that it is possible to detect Zika virus acutely in GBS, by testing serum, cerebrospinal fluid and urine using PCR.[14] Zika serology should be performed in parallel with PRNT, in areas where co-infection with different flaviviruses is common. Multiple time-separated samples should be acquired. Upcoming studies must be powered to explore variables which may increase the risk of GBS in the setting of Zika, such as previous exposure to other flaviviruses or vaccination.

In addition, emerging reports suggest that the neurological consequences of Zika may not be limited to GBS.[15,16] Future studies should be designed to capture additional sequelae, including meningoencephalitis, myelitis and neuropathies, as well as additional, unexpected, neurological complications associated with this emerging pandemic.

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