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WHAT'S NEW IN INTENSIVE CARE

Zika virus-associated Guillain–Barré syndrome: a warning for critical care physicians

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After yellow fever, dengue, West Nile and chikungunya, Zika virus opens a new chapter in the history of the threat from arbovirus.

Zika virus (ZIKV) belongs to the *Flaviviridae* family, genus *Flavivirus*. It was first identified in 1947 in rhesus monkeys in Uganda and isolated in humans in 1952. It is predominantly transmitted between human beings by *Aedes* mosquitos: *Aedes aegypti* is the main vector, but *Aedes albopictus* (the Asian tiger mosquito), a much more widely distributed mosquito in Southern Europe and the USA, might play a part too. Recent observations suggest that sexual transmission of the virus may be more common than previously thought [1]. In addition, the virus was detected in 3 % of asymptomatic blood donors in French Polynesia, suggesting the possibility of a transmission by blood products [2].

In 2007 an outbreak occurred on the island of Yap, in the Federal State of Micronesia. An estimated 73 % of the island's population were infected by the virus over a 3-year period [3]. In 2013 a larger outbreak occurred in French Polynesia with an estimation of 32,000 infected patients between October 2013 and April 2014 [4]. In early 2015, the first case of ZIKV autochthonous transmission was identified in Brazil [5]. Since then the virus has spread across the Americas, affecting 31 countries in South America, Central America and the Caribbean [6, 7], and has become a global threat, according to the World Health Organization (WHO) [8]. The most recent affected territories are in the Caribbean, including Puerto Rico [7] and the French West Indies [9], particularly in Martinique where the incidence currently reaches 120 cases for 10,000 inhabitants and where an estimated 2.5 % of the population has been infected [9].

Zika virus causes a mild illness after an incubation period of 3–12 days. Symptoms predominantly include fever, conjunctivitis, widespread maculopapular rash frequently pruritic, arthralgia and myalgia, but as many as 80 % of infections may be asymptomatic [2, 3]. The clinical presentation is close to that of dengue and chikungunya. During the acute phase, laboratory diagnosis is based on detection of ZIKV RNA by polymerase chain reaction (PCR) in blood, but the low viral load and the short duration of the viraemia, which rarely exceeds 5 days after the symptoms onset [10], limits the probability of a positive result. Detecting the virus in other body fluids, such as saliva, cerebrospinal fluid (CSF) or urine, might be a valuable alternative [11, 12]. Urinary samples seem particularly interesting, as the virus can be detected at higher titers and for a longer period than in serum sample [13]. After the acute phase, serological diagnosis is compromised because of extensive cross-reactivity between antibodies triggered by different flavivirus infections or vaccination.

Serious neurological complications have led to the WHO declaring the Zika outbreak a global emergency [8]. Like with other flaviviruses, Zika has been found to trigger Guillain–Barré syndrome (GBS) during the outbreak in French Polynesia in 2013 [14]. In a recent case control study, the role of Zika virus in patients with GBS has been convincingly established during this epidemic [10]. In total, 42 cases of GBS were recorded, among whom 98 % had antibodies against ZIKV and 100 % had neutralizing antibodies against ZIKV. Thus, the risk of GBS was estimated at 0.24/1000 ZIKV infections [10], compared to 0.25–0.65/1000 *Campylobacter jejuni* infections [15] and 0.6–2.2/1000 *Cytomegalovirus* infections [16]. Most patients (88 %) had a previous viral syndrome-associated rash (81 %), arthralgia (74 %),

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fever (58 %) and conjunctivitis (48 %), with a median time between viral syndrome and onset of neurological symptoms of 6 days (IQR 4–10). The progression of the neurological symptoms was rapid: the ascendant phase, from onset to peak, lasted a median of 6 days (IQR 4–9), and the plateau phase lasted a median of 4 days (IQR 3–10). The clinical picture comprised associated muscle weakness (86 %), facial palsy (83 %) and paraesthesia (83 %). The prevalence of swallowing troubles and respiratory disorders was 45 and 33 %, respectively. Electrophysiological findings were in favour of the acute motor axonal neuropathy (AMAN) type. Twelve (29 %) patients were mechanically ventilated. Importantly, they had a very long length of stay in the ICU of 51 days (IQR 16–70). Treatment did not differ from that of GBS from other origins: all patients were treated with intravenous immunoglobulin at a dosage of 2 g/kg over 2–5 days and one had plasmapheresis.

Confirmation of neurotropism of the virus has been reinforced by two recent observations. In Guadeloupe, French West Indies, an acute myelitis was diagnosed in a 15-year-old girl in whom high concentrations of the virus was found in blood, urine and CSF [17]. In Paris, France, an 81-year-old man was diagnosed with acute meningoencephalitis 10 days after he had returned from a 4-week stay in the South Pacific. ZIKIV was identified in the CSF by PCR and subsequently confirmed by virus growth on cellular culture [18].

These data obviously raise concerns for critical care physicians. First, given the high attack rate of ZIKV epidemics so far (73 % in Micronesia [3] and 66 % in French Polynesia [10]), we must be prepared to face a high number of patients with GBS in areas in which the ZIKIV is circulating. With 42 out of 268,270 inhabitants diagnosed with definite ZIKV-induced GBS, the extrapolation to a larger population is definitely concerning, especially as the outbreak is still spreading dramatically. In Martinique and Guadeloupe (French West Indies), six patients have been hospitalised in ICUs with GBS since 1 January 2016, among whom two had a confirmed ZIKV infection [12], whereas the rate is usually around 10 cases per year [12]. Secondly, although the ascendant phase and the plateau are relatively short in the global population, the duration of respiratory muscle weakness might be very long in some patients requiring mechanical ventilation, leading to notably longer duration of stay in the ICU. The combination of these two factors may lead to overwhelming pressure on ICUs. As an example, the French West Indies preparedness plan has expected 160 GBS cases including 40 requiring ICU admission for a global population of 800,000 inhabitants. Both critical care physicians and health policy decision makers should take this threat seriously into account in allocating appropriate resources in areas affected by the epidemic.

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