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CENTRAL NERVOUS SYSTEM INFECTIONS (K BLOCH, SECTION EDITOR)

Neurological Presentation of Zika Virus Infection Beyond the Perinatal Period

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Abstract
Purpose of Review Our purpose was to summarize the current knowledge about the neurological presentation of Zika virus infection after the perinatal period. Other Flaviviruses infections, such as West Nile virus (WNV) or Japanese encephalitis virus (JEV), can result in neuroinvasive disease such as myelitis, encephalitis, or meningitis. We aimed at describing the specificities of ZV neurological infection.
Recent Findings The recent outbreaks demonstrated clearly the neurotropism of ZV. However, by contrast with other Flaviviruses, the most frequent neurological presentation of ZV infection beyond the perinatal period was Guillain-Barré syndrome, especially the demyelination form of GBS. Encephalitis and myelitis seem to occur less frequently after ZV infection than after WNV or JEV infection.
Summary The pathophysiology of neurological ZV infections is still poorly understood and no specific treatment is available. Moreover, no data is available about long-term persisting symptoms and possible impairment of patients after the acute clinical episode.

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Introduction

Zika virus (ZV) is a member of the *Flaviviridae* family. ZV was isolated for the first time in Rhesus monkey in Uganda, in 1947 [1]. In 2007, the first outbreak ever described in humans occurred in Yap Island, Malaysia [2•]. Before that, only sporadic cases had been reported and seroprevalence studies suggested that clinical disease was rare in humans. ZV is transmitted by *Aedes* mosquitoes.

In 2013, ZV reemerged in French Polynesia, resulting in an estimated 28,000 cases, and rapidly spread to the other countries of the South Pacific region (Cook Islands, Solomon Islands, Vanuatu). In the Americas, the first infections were diagnosed in Bahia, Brazil, in March 2015 and in Colombia in August 2015 [3, 4]. It was later showed that the virus spreading in South America was similar to the one responsible of the French Polynesian outbreak [3]. A major outbreak followed then, reaching most of South and Central America countries, and Florida [5]. The WHO declared the outbreak a "public health emergency of international concern" in February 2106 [6]. These unprecedented outbreaks were responsible for hundreds of thousand infections in adults and infants [5], and revealed severe clinical presentations not described before: Guillain-Barré syndrome (GBS) in adults [7, 8], and brain malformations in children born from mothers infected during pregnancy, including microcephaly [9••, 10]. Transmission through sexual intercourse, first demonstrated in 2008 [11], was confirmed during the recent outbreaks [12, 13••], as well as the potential for transmission through blood donation [14••].

Since mid-2016, the number of new cases seems to be decreasing in almost all affected countries [15]. However, new outbreaks may occur due to the worldwide repartition of the vector and the high number of people still susceptible to the infection. The first cases of ZV infection were recently identified in India [16].

Neurotropism was first demonstrated in mice in the 50s [17]. However, before the 2013 outbreak in South Pacific, there had been no report of severe neurological complications following ZV infections. In this article, we report the current knowledge about neurological infections due to ZV following the prenatal and perinatal periods. We searched PubMed and Embase, and the epidemiological report from the WHO and PAHO to retrieve significant articles and case reports to synthesize the available information.

Zika Virus Disease Brief Overview

Although the virus was isolated in various monkey species, it is unclear if some animal species play a role of reservoir in the ecological cycle of the virus [18]. ZV is transmitted by *Aedes* mosquitoes, mainly by *A. aegyti* and *A. africanus* [19]. It has been suggested that *A. albopictus* might be less competent to transmit ZV [20].

During the 2007 outbreak in Yap Island, it was estimated that 73% of the population of the island had been infected but 80% remained asymptomatic [2•]. No complications occurred among symptomatic cases. In fact, before 2013, ZV disease was considered a mild, self-limited disease, usually milder than Dengue or Chikungunya infection, but with more frequent and more pronounced rash.

The incubation period ranges from 3 to 12 days. In most cases, ZV infection presents with a maculopapular rash, fever, myalgia and arthralgia, headache, edema of the extremities, retro-orbital pain, and non-purulent conjunctivitis [2•, 3–21]. Digestive symptoms may occur. Rash was the most frequent sign in Brazil during the outbreak, reported by more than 90% of cases. By contrast, fever was present in less than 30% and conjunctivitis in 50% [22]. In a cohort of patients from Brazil, pruritus was reported as a frequent symptom affecting 79% patients, as well as prostration, although this was less frequent [23]. Severe thrombocytopenia has been reported as a rare complication [24].

Like for other Flaviviruses, ZV infection diagnosis can be challenging. ZV RNA can be detected using RT-PCR [25••]. ZV RNA has been detected in a number of clinical samples: whole blood, serum, urine, saliva, semen, vaginal secretions, breastmilk, and cerebrospinal fluid (CSF). Because the viremia is short and of low level [26••], it has been suggested that urine might be a better sample for the diagnosis in clinical practice as it may contain higher viral load for a longer duration [27, 28].

ZV RNA can usually be detected in blood and serum between 3 and 5 days after the onset of symptoms. However, in some patients, it has been detected in clinical samples up to several weeks [29••] or months [25••] after onset. In semen, ZV RNA seems to be able to persist for more than 6 months [30].

Primary serological diagnosis relies on ELISA but can be difficult in areas with co-circulation of several Flaviviruses due to cross reactivity [21]. In such situations, plaque-reduction neutralization testing (PRNT) is required to be able to distinguish between other infections, such as dengue for example. IgM appear early in the clinical course of ZV infection and last for an average of 3 months [31]. PRNT can be positive a few days after the disease onset.

No specific antiviral drug is available for the treatment of ZV infection. ZV infection treatment is mainly supportive. In the absence of complications, the disease lasts 3 to 7 days and has a favorable outcome, although arthralgia may persist [2•].

Guillain-Barré Syndrome and Zika Infection

The first GBS cases related to ZV infection were reported during the French Polynesia outbreak, in 2013 [8, 32••]. No cases had been reported during the outbreak of Yap Island in 2007 [2•]. In 2017, after the massive diffusion of the virus throughout the Pacific Islands, New Caledonia, South America, West Indies, and Puerto Rico, a total of 200 cases of GBS related to ZV infection has been reported as case series or isolated cases: 42 cases in French Polynesia [2•, 8], 44 cases in Brazil, 22 cases in Salvador, 82 cases in Columbia [7, 33], 1 case in Haïti [34], 2 cases in Martinique [35], and 1 case in Puerto Rico [36]. The analysis of the first 118 cases demonstrated the relationship between ZV and GBS, using various criteria: temporality (cases during the outbreak, no more after it ended in Polynesia), biological plausibility, strength of the association, and no other explanation for the clinical syndrome [37]. A lot of cases were reported to health authorities as sporadic cases, but strongly suggested the relationship if not causality between the ZV outbreak and the excess of GBS cases (when compared to the expected number of cases during the given period). The number of GBS cases was twice as higher as expected in Salvador, 2.5 in Dominic Republic, 2.6 in Honduras, 2.7 in Brazil, 3.1 in Columbia, 5 in Suriname, and 9.8 in Venezuela [38], and up to 20 times during the outbreak in French Polynesia. A total of 73 GBS cases have been reported at the date of 22 December, 2016, in the French West Indies, as a complication of the infection, among an estimated total number of more than 66,000 acute ZV infections [39].

The association of GBS and ZV infection was not reported in all countries. It was only reported when the circulating strain was of Asian lineage [37]. As of 1 February 2017, ZV of the Asian lineage was circulating in more than 80% of affected countries, including 48 countries in the two parts of Americas [40].

Uncini et al. estimate the overall incidence of ZV-associated GBS to 24 per 100,000 cases of ZV infection [41] but this rate may be as high as 800 per 100,000 cases of ZV infection [42].

GBS is a life-threatening neurological disease mediated by the immune system, involving sensitive and motor peripheral neurons [43]. There are three stages of the disease: palsies set up more or less rapidly during some days to 4 weeks, then the steady state lasts over 1 week to several months, and finally recovering duration is very variable. Total cure is possible, as well as the occurrence of persisting symptoms and sequelae, some being clinically severe. Infection, or rarely vaccination, is responsible for 2/3 of GBS cases. In other cases, the cause of GBS, if any, remains unknown. The most frequent infection associated with GBS is *Campylobacter jejuni* infection. Other GBS-related infections are viral (CMV, EBV, *influenza* A, hepatitis E) or bacterial (*Haemophilus influenzae, Mycoplasma pneumoniae*).

Several clinical GBS presentations are possible, depending on the involved nerves: limbs and trunk, cranial (including the Miller Fisher syndrome in case of ophtalmoplegia associated with ataxia) or scapulopharyngeal nerves. Involvement of the respiratory and oropharyngeal functions is a sign of severity of the disease and usually requires the admission of the patient in the ICU.

Electromyographical (EMG) features demonstrate demyelination acute inflammatory demyelinating polyneuropathy (AIDP), or axonal lesions acute motor axonal neuropathy (AMAN), or acute sensory motor axonal neuropathy (ASMAN). The immune mechanism is probably different in these various electrophysiological presentations. Antiganglioside antibodies are probably involved in axonal presentation, and an immune mechanism, not so well defined, in case of demyelination. In all cases, the treatment includes intravenous immunoglobulins or plasmapheresis combined with supportive care, as usual for paralyzed patients in the ICU.

Main clinical, electrophysiological, and prognosis features of GBS-complicating ZV infections were reported in two major case series: 42 cases in French Polynesia [32••, 44], and 68 cases in Columbia [7]. The reported data were confirmed by another cohort of 29 cases, from Cucuta district in Columbia [40]. The mean delay between the onset of the early infection and the onset of neurological symptoms was 6–7 days (IQR 4–10). This early occurrence of GBS onset after ZV infection strongly suggests that the mechanisms related to the infection itself are responsible of the GBS, rather than post-infection immune process [7]. Early neurological symptoms were limb-ascending motor deficit, restricted to the lower limbs in 40% of cases, combined with sensitive disorders and facial palsy in 1/3 to 2/3 of cases. Swallowing disorders were reported in 25% of cases. Tendon reflexes were impaired or missing in 75% of cases. The mean duration for the complete paralysis set up was 6 days (IQR 4–9). At the steady-state stage of the disease, 2/5 to 2/3 of patients have been hospitalized in the ICU and 50 to 75% required mechanical ventilation. A bilateral facial palsy was observed in 50 to 75% of cases, and dysautonomia in 33% of cases. All patients of the Polynesian cohort were treated with non-specific immunoglobulins. The duration of their steady-state stage was 4 days (IQR 3–10), and no death were reported [32••]. In the Columbian cohort, 3 patients died [7]. The long-term outcome is still unknown, but will probably be similar to standard GBS cases, which means that 20% of cases may need assistance for walking during an average of 6 months after the onset of the disease [43].

The CSF biological characteristics of ZV-related GBS, reported in the Columbian cohort, were non-specific: high protein level in 82–93% of cases, no pleiocytosis. The mean leucocytes count in CSF in the Polynesian cohort was 5.5/mm^3 (0–28).

Electrophysiological features were not similar in Polynesian and Columbian patients: 78% of Columbian GBS patients presented with AIDP (demyelination), whereas AMAN syndrome was present in 50% of Polynesian patients allowing the complete recovery of the distal motor conduction alterations during follow-up [44]. This topic is still a matter of debate, but the best matching of EMG data obtained in ZV-associated GBS with the updated EMG data-based classification of polyneuropathies strongly suggest that demyelination mechanism as encountered in AIDP is the predominant pathophysiological process [41, 45].

Brain or spinal MRI was rarely performed in ZV-associated GBS patients. When available, authors reported contrast enhancement of cranial nerves or nerve roots [44].

ZV RT-PCR in CSF, when performed, was negative in all Polynesian patients. In the Columbian cohort, ZV RT-PCR was positive in 40% of tested patients, considering all biological fluids tested, mainly in urines (67% of cases) and CSF (10%) [7].

IgM antibodies against ZV were evidenced in 93% of cases. An IgM cross-reaction between dengue virus and ZV was suspected in 19% of cases, as they were positive to both viruses. Combined identification of IgG and IgM was considered as a ZV infection and 100% of GBS patients had neutralizing antibodies against ZV [32]. IgG antibodies against ZV and dengue were observed in 100% of cases and against Chikungunya in 69% of cases, in the Cucuta Columbian cohort [46]. GBS was significantly associated with previous *Mycoplasma pneumoniae* infection (OR 3.95, 95% CI 1.44–13.01) but not with *C. jejuni*, EBV, and CMV infection [46].

From a pathophysiological point of view, although a lot of data has been published in the field of virus-host interactions [47], no direct pathological way has been demonstrated linking ZV infection with disorders of the peripheral nervous system. As with other infections triggering GBS, like *Campylobacter jejuni*, a molecular mimicry phenomenon between some viral antigens and the molecular components of the axons and myelin sheath, especially at the node of Ranvier site is highly likely.

In the French Polynesia study, antiganglioside antibodies have been found in 31% of the patients during the initial phase of the disease, increasing to 48% at 3 months [32••]. The targeted gangliosides were mainly GA1, GD1a, GD1b, GM1, and GM2. In the same way, the finding of antiganglioside antibodies against GM1 or GT1b in 7 cases (24%) of the Cucuta's cohort and the similarity of the course of the disease following ZV infection with the classic clinical forms of the GBS argue for a common pathophysiology [46, 48, 49].

The GBS is not the only a peripheral nervous system complication due to ZV infection. Two cases of *myasthenia gravis* have been described during the outbreak in New Caledonia. Those 2 cases occurred 8–10 days after the acute infection. Both were positive for antiacetylcholine receptor antibodies at high level. They were also found to have a thymoma suspected as a longstanding host predisposition for a MG possibly triggered by the ZV infection [50].

Encephalitis and Encephalopathy

Only few cases responding to the case definition of encephalitis have been so far published in the literature with details. Some epidemiological reports mentioned other cases of encephalitis and myelitis without giving any details [51, 52]. However, these clinical presentations remain far less frequent than GBS.

Encephalitis

The first reported case occurred in early 2016, in a male patient aged 81 years old [53••]. The patient presented with encephalitis on return from a 3-week travel in South Pacific islands. The patient was admitted 10 days after his return with hemiplegia and scored 6 on GCS. During his hospitalization, a rash was observed during a short period. MRI displayed signs evocative of encephalitis and multiple small lesions suggesting ischemic foci. The CSF showed a mild pleiocytosis (41 WBC/mL) and a slightly elevated protein level (76 mg/dL). A confirmed diagnosis of ZV encephalitis was achieved in this patient with positive RT-PCR and positive viral culture on CSF. After sedation was interrupted, the patient was disoriented and experienced hallucinations but fully recovered and was considered cured at D38.

A second case published in Brazil had a different medical history and outcome: a 47-year-old woman had ZV infection with rash and arthralgia [54]. On day 4 of illness, she presented with confusion, speech impairment, and weakness of lower limbs. The CSF analysis revealed a low pleiocytosis (10 WBC) but a significantly elevated protein level (100 mg/dL). The condition of the patient deteriorated and she showed signs of brain swelling and areflexia, and finally died. ZV infection was diagnosed by RT-PCR on urine but RT-PCR remained negative on serum and CSF. On a second CSF sample, intrathecal synthesis of antibodies was demonstrated.

Another case of encephalitis was described in a 32-year-old female patient returning from an epidemic area [30]. She presented with fever and a rash and was admitted the following day with muscle weakness and marked cognitive impairment (processing speed, verbal and non-verbal memory disorders, and attention deficit). MRI and EEG were normal but an elevated protein level and pleiocytosis were detected on CSF. ZV infection was diagnosed by positive RT-PCR on CSF and on a number of other clinical specimens. She was treated with polyvalent immunoglobulins. On D16, her situation had improved but memory disorders were persisting. On D60, she had no longer neurological deficits.

In Colombia, during a global study on neurological presentation of ZV infections in adults, 3 cases of encephalitis were enrolled (vs 6 cases of myelitis, see below, and 29 cases of GBS, see above) [46]. The 3 encephalitis cases were young patients below 35 years of age. They had their neurological onset a mean 8 days after their other symptoms of ZV infection. Two patients had to be admitted in the ICU.

Although the small number of cases probably does not allow giving a complete picture of encephalitis due to ZV, it is of notice that patients of various ages were affected by encephalitis, but all during adultness. It is also remarkable that RT-PCR on CSF analysis was not contributive for all of them, suggesting the need to search the virus RNA in CSF during a specific time-window. It should also be noted that the delay between ZV general infection and the neurological onset is variable (from 1 to 8 days in these patients).

Although one patient died following brain edema and lesion of the brainstem, all others apparently recovered with no sequelae or persisting symptoms, by contrast with encephalitis caused by other Flaviviruses like West Nile virus or Japanese encephalitis virus. However, a comprehensive neuropsychological assessment would be necessary to confirm this finding. Another marked difference was the absence of neurological motor impairment during the course of the disease.

Encephalopathy

By contrast with encephalitis, encephalopathy may not be associated with brain inflammation [55].

In Martinique island, 2 cases of encephalopathy related to ZV infection were reported in early 2016 [56]. The first one experienced generalized seizures within hours of his onset of ZV symptoms. The patient had a rapid favorable evolution and could be discharged home 3 days later, but still experienced joint pain and headache 45 days later. The second patient was admitted in hospital with neurological symptoms (confusion, speech disorders, and facial palsy). He also had a very favorable outcome and was discharged home.

Both patients experienced short favorable course of their neurological signs, and both had a normal MRI for their age and normal results on CSF analysis. The second patient had non-specific abnormalities on the EEG. In the 2 of them, ZV infection was diagnosed by positive RT-PCR on CSF, urine, and serum.

We are not aware of any other encephalopathy cases. However, it is highly possible that other cases occurred during the outbreak but were not hospitalized or not diagnosed due to a favorable evolution in a few days.

Myelitis and Acute Disseminated Encephalomyelitis

Myelitis and acute disseminated encephalomyelitis (ADEM) following ZV have also been rarely described. By contrast with encephalitis and encephalopathy, only young adult patients were reported with myelitis or ADEM following ZV.

A case of ADEM was reported in Brazil in early 2016 [57]. The patient, a 26-year-old man, experienced non-specific symptoms evocative of Zika virus only 1 day before the neurological onset. On D3, presenting with tetraparesis and respiratory failure, he was placed under invasive mechanical ventilation. At that time, CSF analysis revealed pleiocytosis with predominant mononuclear cells and elevated CSF proteins. ZV infection was confirmed on D7 on urine and CSF by RT-PCR. After sedation was stopped, encephalitis symptoms (decreased consciousness, confusion) were noted in addition to myelitis symptoms. Lesions of the subcortical and deep white matter were demonstrated by MRI, as well as lesions of the thalamus, medial cerebellar peduncles and ventral horns along the spinal cord. The patient improved significantly under methylprednisolone and immunoglobulins, but flaccid paraparesis persisted on follow-up. Increased levels of IL-6 and IL-8 were demonstrated during the acute phase of tetraplegia and respiratory failure.

Another case of ADEM was diagnosed in Brazil 3 weeks after RT-PCR confirmed ZV infection in a 19-year-old patient [58••]. Lesions of the white matter were visible on MRI in the brain and spinal cord. The patient's condition improved with methylprednisolone.

In the USA, an 18-year-old patient returning from the outbreak zone presented a maculopapular rash 2 weeks after return [59]. She was diagnosed with ZV infection. Six weeks later, she experienced numbness of the legs, that later extended up to the trunk, with neurological deficit in both hands. Myelin basic protein was elevated in CSF. MRI showed lesions of the spinal cord compatible with ADEM, and CSF showed a low pleiocytosis (10 WBC). At that time, RT-PCR for ZV was negative but IgM results were positive.

Myelitis has been rarely reported following ZV infection. In Columbia in 2016, a man aged 23 years old presented with transverse myelitis characterized by urinary retention, abdominal pain, flaccid paraplegia, and increased reflexes [60]. Two weeks before, he had experienced fever associated with conjunctivitis and arthralgia. Cranial CT scan was normal but abnormal MRI FLAIR and T2 images were visible all along the spinal cord, with marked lesions on anterior horns. CSF showed pleiocytosis. ZV RT-PCR was positive on serum. The patient's condition improved following plasmapheresis.

In Guadeloupe island, a female patient, 15 years of age, presented with pain in the upper left limb, headaches, and conjunctivitis but no fever and no neurological signs [61]. She was admitted 7 days later with a clinical presentation compatible with myelitis: hemiparesis, weakness, and later urinary retention and positive Hoffman sign. MRI showed lesions in cervical and thoracic spinal cord, associated with edema. Results from EMG and CSF analysis were normal. ZV infection was diagnosed by RT-PCR on CSF, urine and serum on D2 of hospitalization. The patient was successfully treated with methylprednisolone.

Six more cases of ZV-associated myelitis are mentioned in a case-control study carried out in Colombia [46]. Their ages ranged from 17 to 32 years old, and they had their neurological onset between 13 and 96 days after the acute systemic symptoms of ZV infection. Two had to be admitted in the ICU.

Conclusions

Zika virus is now widely distributed in various parts of the world, but still a number of areas are inhabited by susceptible populations exposed to *Aedes* mosquito bites and other major outbreaks may occur. Therefore the knowledge gathered in South Pacific and the Americas, together with further research, may benefit these populations in case of emergence of the virus in their countries. Moreover, education about the prevention of mosquito bites and ensuring widely available healthcare access in countries affected in the future will be major challenges.

ZV infection was previously described as mild and self-limited, but the recent data revealed severe clinical presentations, most frequently neurological. These presentations are various with regards to symptoms (GBS, brain disorders) and to pathophysiology (infection vs post infection immune disorders). Therefore, in such instance, the biological diagnosis may be tricky, and CSF might not always be the best clinical sample to test.

Moreover, neurological involvement does not affect all patients, and no risk factor has been identified so far. It is very likely that not all cases were diagnosed and reported, still encephalitis and myelitis following ZV virus seem to occur less frequently than with other Flaviviruses (West Nile, Japanese encephalitis, or TBE viruses). By contrast, GBS unexpectedly emerged as a severe and frequent complication of ZV.

More research is needed to understand the pathophysiology of this viral infection and its complications, and to develop efficient drugs and vaccines.

Compliance with Ethical Standards

Conflict of Interest Drs De Broucker, Mailles, and Stahl declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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