

Zika Virus–Associated Neurological Disease in the Adult: Guillain–Barré Syndrome, Encephalitis, and Myelitis

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Abstract

Zika virus (ZIKV) has caused a major infection outbreak in the Americas since 2015. In parallel with the ZIKV epidemic, an increase in cases of neurological disorders which include Guillain–Barré syndrome (GBS), encephalitis, and myelitis have been linked to the infection. We reviewed the evidence suggesting a relationship between ZIKV and neurological disorders in adults. A search of the literature supporting such link included databases such as PubMed and the World Health Organization (WHO) surveillance system. Through June 1, 2016, 761 publications were available on PubMed using the search word “Zika.” Among those publications as well as surveillance reports released by the WHO and other health organizations, 20 articles linked ZIKV with neurological complications other than microcephaly. They corresponded to population and surveillance studies ($n = 7$), case reports ($n = 9$), case series ($n = 3$), and case–control studies ($n = 1$). Articles were also included if they provided information related to possible mechanisms of ZIKV neuropathogenesis. Evidence based on epidemiological and virological information supports the hypothesis that ZIKV infection is associated with GBS. Although cases of encephalopathy and myelitis have also been linked to ZIKV infection, the evidence is scarce and there is a need for virological, epidemiological, and controlled studies to better characterize such relationship.

Keywords

- ▶ ZIKV
- ▶ GBS
- ▶ encephalitis
- ▶ myelitis
- ▶ adult

Zika virus (ZIKV) is a mosquito-borne flavivirus phylogenetically related to other well-known neurotropic flaviviruses, such as Japanese encephalitis and West Nile virus.¹ In 2007, the Yap State of the Federal States of Micronesia presented the first known outbreak of ZIKV infection affecting 73% of the local population, with an estimated of 900 cases reported. At that time, the illness was self-limited being characterized by fever, rash, conjunctivitis, and arthralgia, with no major neurological complications described.²

As ZIKV continued to spread across regions of the Pacific in 2013 to 2014, a temporal relationship in the onset of ZIKV infection outbreak and an increased number of Guillain–Barré syndrome (GBS) cases and other neurological disorders was described in French Polynesia.^{3,4} Such observation gave

origin to the hypothesis that ZIKV infection was associated with neurological complications. A similar temporal relationship was noted in early 2015 when a significant increase in the number of microcephaly^{5–7} and GBS cases was observed in parallel with the ZIKV infection outbreak in the northeast of Brazil.⁸ By April 2016, a total of 13 countries affected by the ZIKV epidemic had reported increased incidence of GBS and/or GBS cases with laboratory confirmed ZIKV infection.^{9,10} The occurrence of other neurological disorders such as encephalitis and myelitis linked to ZIKV infection was also reported.^{4,9,11}

Through June 2016, there has been accumulated evidence supporting the role of ZIKV infection in the development of GBS, but a causal relationship remains to be established. Although

there is no agreement yet regarding the role of ZIKV in other neurological disorders in adults, there are early observations which may suggest such possibility. This review summarizes the current evidence that supports the association between ZIKV infection and neurological disease in the adult.

Methods

We conducted a search of articles on ZIKV published up until June 1, 2016, in public electronic databases, including PubMed and the surveillance system of the World Health Organization (WHO), the Pan American Health Organization (PAHO), and the European Centre for Disease Prevention and Control (ECDC). We selected studies providing evidence on a link between ZIKV and neurological disorders in adults including GBS, encephalitis, myelitis, and other neurological syndromes. We summarized the relevant studies highlighting the evidence used to support the link to ZIKV in each one.

Results

As of June 1, 2016, PubMed listed 761 publications with the search word “Zika.” After excluding review articles, comments, and editorials, we found 16 articles that provided new information about ZIKV-related neurological disease in the adult. Four surveillance reports from WHO, PAHO, and ECDC were also relevant. We included population and surveillance studies ($n = 7$), case reports ($n = 9$), case series ($n = 3$), and case-control studies ($n = 1$). Out of the 20 articles, 17 were related to GBS, 2 discussed a link with encephalitis/encephalopathy, and only 1 referred to myelitis. **Table 1** summarizes the relevant studies. Articles were also included if they provided information related to possible mechanisms of ZIKV pathogenesis in the nervous system.

ZIKV and Guillain-Barré Syndrome

GBS is an acute progressive paralytic neuropathy usually preceded by a recent immune stimulation, often with sensory and cranial nerve involvement that proceeds to its peak of clinical symptoms in 2 to 4 weeks.^{12,13} Weakness pattern tends to be symmetric and develop rapidly. Cranial and autonomic nerve involvement is frequent with 20 to 30% of cases being affected with respiratory failure.¹³ The incidence of GBS ranges between 0.8 and 1.9 cases per 100,000 people per year.^{14,15} The pathophysiology of GBS includes an abnormal immune response targeting peripheral nerves and spinal roots generally 1 to 2 weeks after a preceding infection, out of which the best characterized organism is *Campylobacter jejuni*, described to have molecular mimicry with peripheral nerve antigens.^{12,13,15}

The observation of temporal occurrence of GBS cases during ZIKV infection outbreaks has pointed toward a possible relationship of such infection with the development of GBS. During a ZIKV infection outbreak in French Polynesia in 2013, 26 cases of GBS were initially reported over the course of 8 weeks, exceeding the GBS baseline incidence estimated to be 3 to 8 cases per year.³ A similar temporal pattern of increase of GBS cases has been documented since 2015 in some countries in the Americas affected by the ongoing ZIKV outbreak.⁹

Presently, six surveillance and population-based studies supporting a relationship between GBS and ZIKV infection have been published. An analysis of the surveillance for acute flaccid paralysis (AFP) in the Pacific Islands between 2013 and 2015 reported sporadic cases of GBS in patients with ZIKV infection diagnosed clinically. There was one case in which the ZIKV infection was confirmed in New Caledonia; however, only Solomon Islands had a statistically significant increase in AFP correlated with the emergence of the ZIKV outbreak.¹⁶ From May 2015 to May 2016, the WHO reported clusters of GBS during the most recent ZIKV outbreak in the Americas and the Caribbean.⁹ Surveillance systems from Brazil⁸ initially described 11 cases of GBS preceded by probable ZIKV infection in May 2015. Since then Brazil, Puerto Rico,¹⁷ Colombia, Dominican Republic, El Salvador, French Guiana, French Polynesia, Haiti, Honduras, Martinique, Panama, Suriname, and Venezuela reported at least one GBS case with positive ZIKV reverse transcription polymerase chain reaction (RT-PCR). Among those countries, eight reported a total increase in the incidence of GBS during the most recent ZIKV outbreak.⁹ Paraguay reported an increase in GBS cases with no ZIKV laboratory confirmation.¹¹

We found six case reports, two case series, and one case-control study about ZIKV-related GBS. The presence of anti-flavivirus antibodies was used to demonstrate a recent ZIKV infection in cases of GBS in French Polynesia¹⁸ (2013), Haiti¹⁹ (2016), and Spain²⁰ (2016). In the context of the current ZIKV outbreak, the infection has been confirmed by RT-PCR in urine and/or serum samples of GBS cases in Brazil^{21,22} (2014; 2016), Martinique²³ (2016), and in an imported case in the Netherlands^{24,25} (2016). Among those cases, one was reported to be ZIKV positive by RT-PCR in cerebrospinal fluid (CSF).²¹

During the epidemic in French Polynesia in 2013, a total of 42 cases of GBS were diagnosed^{4,26} and analyzed retrospectively in a case-control study.²⁷ ZIKV diagnosis was done based on serology assays. Out of the 42, 88% reported history of a viral syndrome compatible with ZIKV infection, with a median of 6 days before the neurological symptoms. GBS was characterized by a rapid progression pattern and a high frequency of facial palsy (64%). An acute motor axonal neuropathy subtype of GBS was found by electrophysiology testing. Seroprevalence for anti-flavivirus antibodies was significantly different between the GBS group and the control group 1 (nonfebrile illness population). The resulting association measure (odds ratio) between ZIKV infection exposure and GBS was 59.7 (95% confidence interval: 10.4–∞). None of the GBS cases were ZIKV RT-PCR positive. Dengue virus (DENV) immunoglobulin M (IgM) was positive in 19% of GBS cases where ZIKV-IgM was also positive; those were considered positive for recent ZIKV infection as DENV positivity was related with cross-reactivity.²⁷

The French Polynesia case-control study provided the highest level of epidemiological evidence to date of a link between ZIKV and GBS. Surveillance data describing a temporal correlation of ZIKV and GBS cases also support the association. However, well-designed controlled studies with stronger and consistent results are required to

Table 1 Studies linking ZIKV with neurological disorders in adults

Study type	Clinical features	Ancillary studies	Place, year	Association to ZIKV
GBS				
Case report ¹⁸	40 y old female; tetraparesis, facial palsy, and dysautonomia	CSF with ACD; AIDP in EMG	French Polynesia, 2013	Positive ZIKV IgM/IgG and PRNT ₉₀ in serum
Case report ²¹	24 y old female; febrile illness followed by paraparesis	Normal CSF, EMG, and MRI	Brazil, 2014	Positive ZIKV RT-PCR in serum, CSF, saliva, and urine
Case report ²²	51 y old female; viral syndrome preceding facial palsy and paraparesis	AIDP in EMG; CSF with ACD; enhancement in nerve VI and spinal roots	Brazil, 2016	Positive ZIKV RT-PCR in serum and urine
Case report ¹⁹	35 y old male; Miller-Fisher syndrome variant	CSF with ACD; normal brain MRI	Haiti, 2016	Positive serum and CSF anti-ZIKV IgM (PRNT ₉₀)
Case report ²⁴	60 y old female; tetraparesis and facial palsy	CSF and EMG consistent with GBS	The Netherlands, 2016	Positive ZIKV RT-PCR in serum and urine
Case report ²⁰	28 y old pregnant female; febrile illness preceding tetraparesis and bulbar nerves compromise	CSF with ACD; AIDP in EMG	Spain, 2016	Positive ZIKV serology
Case series (n = 2) ²³	Young patient and older adult with gait disturbance and cranial nerves involvement	CSF with ACD; EMG with demyelination pattern; normal spinal cord MRI	Martinique, 2016	Positive ZIKV RT-PCR in urine
Case-control ^{4,26,27}	42 GBS cases; control group 1 (n = 98), population with nonfebrile illness	CSF with ACD in 93% of cases; AMAN in EMG	French Polynesia, 2013	98% cases had anti-ZIKV antibodies and 36% in control group 1; OR: 59.7 (p < 0.0001)
Surveillance ⁸	7 GBS cases reported in Rio Grande and 4 GBS cases reported in Pernambuco	Not reported	Brazil, 2015	History of febrile illness (Rio Grande); positive ZIKV RT-PCR (Pernambuco)
Surveillance ¹⁷	One case of GBS with confirmation of ZIKV infection	Not reported	Puerto Rico, 2016	Positive ZIKV RT-PCR
Ecologic ¹⁶	Sporadic cases of GBS in New Caledonia, Solomon Islands, and New Zealand; Solomon Islands had an increase in AFP during the ZIKV epidemic	Not reported	Pacific Islands, 2013–2016	History of febrile illness. ZIKV infection confirmed in one New Caledonia case; epidemiological association
Surveillance ^{4,9–11}	Countries with increased incidence of GBS (cases): Brazil (1,708); Colombia (298); El Salvador (178); Venezuela (578); Dominican Republic (11); Honduras (74); French Polynesia (42); Suriname (19)	Not reported	Thirteen countries worldwide, 2013–2016	Eight countries with increase GBS incidence during ZIKV circulation; five countries with at least one ZIKV positive GBS case; 25 cases had positive ZIKV RT-PCR
Myelopathy				
Case report ³³	15 y old female; headaches, conjunctivitis, hemiparesis, urinary retention, and a T4 sensory level	Spine MRI: cervical and thoracic hyperintensities in T2; normal EMG and CSF	Guadeloupe, 2016	Positive ZIKV RT-PCR in serum, CSF, and urine
Surveillance ⁸	2 cases of ADEM diagnosed in state of Pernambuco	Not reported	Brazil, 2015	Positive ZIKV RT-PCR in either urine or CSF
Encephalitis/encephalopathy				
Case report ³⁰	81 y old male; fever, altered mental status, and rash after a 4-wk cruise in the Pacific	Brain MRI: ischemic foci and meningitis; CSF with pleocytosis and elevated protein; normal EEG	France, 2016	Positive ZIKV RT-PCR in CSF
Case series (n = 2) ³¹	Adult with seizures preceded by viral syndrome; adult with acute confusion, facial palsy, aphasia, conjunctivitis, and arthritis	Case 1: normal MRI, EEG, and CSF; Case 2: normal for age; EEG: abnormal left frontotemporal slowing; normal CSF	Martinique, 2016	Positive ZIKV RT-PCR in serum, urine, and CSF

Abbreviations: ACD, albuminocytological dissociation; ADEM, acute demyelinating encephalomyelitis; AFP, acute flaccid paralysis; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; CSF, cerebrospinal fluid; EEG, electroencephalogram; EMG, electromyogram; GBS, Guillain-Barré syndrome; IgG, immunoglobulin G; IgM, immunoglobulin M; OR, odds ratio; PRNT, plaque reduction neutralization testing; RT-PCR, reverse transcription polymerase chain reaction; ZIKV, Zika virus.

demonstrate a causal relationship. In addition, caution must be exercised when interpreting serology results in regions of the world with high incidence and circulation of DENV or other flaviviruses, as there is known cross-reactivity of anti-flavivirus antibodies. Even plaque reduction neutralization testing cannot reliably establish the difference. Currently, the

only way to accurately diagnose ZIKV infection is through detection of RNA genome using RT-PCR techniques.²⁸

ZIKV and Encephalitis/Encephalopathy

Encephalopathy refers to a clinical state of altered mental status or other cognitive impairment with or without brain

inflammation, while encephalitis implies underlying inflammation.²⁹ There has not been an increased encephalitis incidence reported with the current or previous ZIKV outbreaks. We found no population-based studies. However, sporadic cases of encephalitis and encephalopathy with confirmed ZIKV infection by RT-PCR in CSF have been published in the context of the 2015 to 2016 outbreak. Carreaux et al³⁰ reported a case in France of an 81-year-old man who had been, 10 days prior to presentation, on a cruise to New Caledonia, Solomon Islands, and New Zealand. The patient presented with fever, rash, and altered mental status, followed by coma and hemiplegia. His brain magnetic resonance imaging (MRI) was suggestive of ischemic foci and meningitis. CSF analysis was inflammatory with pleocytosis and elevated protein. He tested positive for ZIKV by RT-PCR in the CSF, while negative in the serum. ZIKV was isolated from the CSF and cultured showing cytopathic changes in infected cells. Two cases of encephalopathy were also reported in the Caribbean Island of Martinique.³¹ The first one was a young adult with fever, arthralgia, asthenia, and headache followed by seizures and a low level of consciousness. Brain MRI, electroencephalogram (EEG), and CSF analysis were normal. The second case was a patient in their late 70s with acute mental confusion, dysarthria, right facial palsy, and aphasia associated with conjunctivitis, bilateral hands edema, and peripheral arthritis at the time of presentation. Brain MRI showed nonspecific white matter disease and CSF analysis was normal. EEG showed abnormal left frontotemporal slow waves. Both cases had positive ZIKV RT-PCR in serum, CSF, and urine. Other infectious causes for encephalitis were ruled out by PCR.

Even though cases of encephalitis have been mentioned as potentially related with ZIKV infection,⁴ there are not enough fully characterized cases or well-controlled studies making the association still presumptive.

ZIKV and Myelitis

Myelitis is a focal inflammatory disorder of the spinal cord resulting in motor, sensory, and autonomic dysfunction.³² There has been limited information regarding myelitis as a possible complication of ZIKV. In the initial reports from the surveillance system in Brazil, Araujo et al⁸ described two cases of acute demyelinating encephalomyelitis with positive detection of ZIKV by RT-PCR in the state of Pernambuco (2015). Clinical profile and imaging were not reported, as well as the type of biological sample used for ZIKV testing. There has been only one case reported of myelitis associated with ZIKV that is fully characterized. It corresponds to a 15-year-old woman from Guadeloupe³³ with a prodromal syndrome of headaches and conjunctivitis for 7 days followed by left hemiparesis and paresthesia, urinary retention, and a T4 sensory bilateral level. Lesions were demonstrated in the cervical and thoracic spinal cord by MRI in T2-weighted images. Electromyographic and CSF analysis were normal. ZIKV was detected in serum, urine, and CSF by RT-PCR on the second day of admission. She improved with methylprednisolone 1 g daily for 5 days and was able to walk unaided after such treatment.

It is unclear if there are more myelitis cases that are not being reported or described in detail. The association of ZIKV with myelitis is still presumptive.

ZIKV and Other Neurological Complications

In the surveillance systems scrutinized, there are few reports of other neurological syndromes associated with ZIKV that are not fully characterized including isolated facial paralysis⁴ (French Polynesia, 2014) and cerebellitis¹¹ (Panama, 2016).

Evidence for ZIKV Infection and Neuropathogenesis in Adults

Early experiments with animal models of infection were performed soon after the ZIKV was discovered. In 1952, Dick³⁴ described the pathological properties of ZIKV. The virus showed a high degree of neurotropism in the brain of young mice when directly inoculated causing degeneration of the neural cells, mainly at the hippocampus. Later, Bell et al³⁵ described the impact of ZIKV infection in the developing mouse brain. The virus infected both neurons and astrocytes causing marked glial activation; a special predilection for the pyriform cells in the hippocampus was remarkable. Intracytoplasmic inclusions consistent with autophagy vesicles were described in ZIKV infected neurons as a mechanism upregulating ZIKV replication *in vitro*.³⁵⁻³⁷

Recently, murine models of ZIKV infection during pregnancy have further supported the neurotropism. Fetuses of ZIKV infected mothers have shown ZIKV infection in the brain which lead to intrauterine growth restriction-like syndrome³⁸ and microcephaly.^{39,40} Further experiments with human-derived induced pluripotent stem cells (iPSC) modeled neurospheres suggest that the target of ZIKV infection is neuronal progenitor cell population in which the virus induced cell death and impaired neurodevelopment.^{41,42}

The adult animal models on ZIKV neurotropism have involved either direct brain viral inoculation or the use of knockout mice. So far, there are no experimental studies recapitulating the natural course of infection that demonstrates ZIKV neurotropism in adults. However, the detection of the virus by RT-PCR in CSF, the proven replicative capacity of isolated virus in cell cultures, and the high titers of anti-ZIKV antibodies in CSF of infected people, as described earlier, support the neurotropism of ZIKV as a potential explanation for neurological complications. Despite causality criteria still need to be fulfilled, the determination of a link between ZIKV with neurological disorders in adults specially GBS has come from various lines of evidence which together support a potential causal association.⁴³

Mechanisms of ZIKV-Related Guillain-Barré Syndrome in the Adult

ZIKV infection appears to be a critical mechanism in the pathogenesis of GBS cases observed during recent outbreaks in the Americas and other areas of the world affected by mosquito-borne flaviviruses (—Fig. 1). Despite the growing evidence of association of ZIKV infection with GBS, there is still uncertainty about the mechanisms involved in pathogenesis. Classically, GBS is thought of as being immune mediated

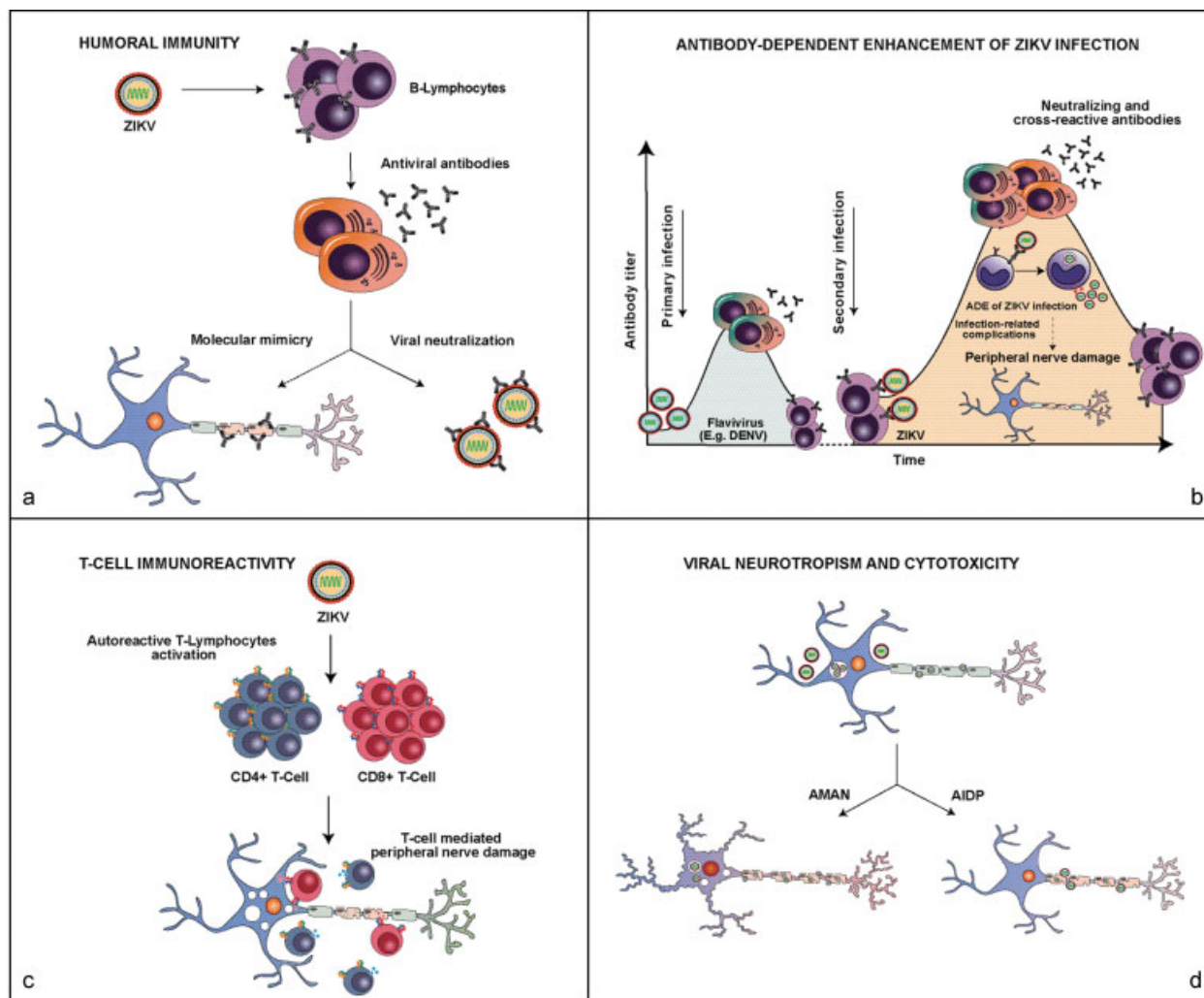


Fig. 1 Postulated ZIKV mechanisms underlying Guillain–Barré syndrome. (a) A humoral response in which ZIKV antigen determinants resemble host nerves components (molecular mimicry) may trigger humoral immune responses in which ZIKV-induced neutralizing antibodies cross-react with the peripheral nerves proteins with subsequent immune-mediated damage of nodal and paranodal structures of the nerve as well as myelin. (b) ZIKV (secondary infection) triggers a memory immune response in those subjects who have been exposed to other flavivirus (primary infection, e.g., dengue). ZIKV-induced cross-reactive antibodies drive ADE of ZIKV infection; ADE has been linked to severity of secondary infections and complications. (c) Autoreactive T lymphocytes activation induced by ZIKV mediates peripheral nerves damage. (d) Direct ZIKV infection of lower motor neurons, peripheral nerve, and/or Schwann cells inducing cytopathic changes and direct cytotoxicity. ADE, antibody-dependent enhancement; ZIKV, Zika virus.

involving both cellular and humoral immune responses.⁴⁴ One of the main postulated pathogenic mechanisms is molecular mimicry between certain pathogens and the peripheral nervous system.¹³ In the case of ZIKV-related GBS, several hypotheses including molecular mimicry have been postulated as possible pathogenic mechanisms. ZIKV polyprotein has been shown to resemble human proteins linked to myelination, axonal function, and neurodevelopment.⁴⁵ Therefore, ZIKV-induced neutralizing antibodies may cross-react with the peripheral nerve proteins resulting in an immune-mediated damage (►Fig. 1a).⁴⁵ However, ZIKV infection could trigger GBS by other suggested mechanisms. As described for DENV, antibody-mediated enhancement (ADE) of ZIKV infection is believed a potential mechanism associated with ZIKV neurological complications. Despite genetic difference between ZIKV and DENV by around 40%, a high neutralizing antibodies cross-reactivity between

them has been demonstrated.⁴⁶ In regions of the world affected by the recent ZIKV outbreaks and where DENV is endemic, immunological memory response against DENV may enhance ZIKV replication by ADE mechanism which may lead to complications such as GBS (►Fig. 1b) and eventually, a subsequent amplification of antigenic viral stimulation to the immune system in the form of a secondary flavivirus infection. Another hypothetical mechanism may involve T cell responses triggered by ZIKV which may target neural, axonal, myelin, or Schwann cell antigens (►Fig. 1c). This hypothesis is derived from observation of perineural T cell infiltrates in nerve tissues from autopsies of GBS cases associated with other pathogens, which support the role of a cell-mediated immunity in GBS.⁴⁷ Similarly, as seen in DENV, ZIKV might induce a polyclonal B lymphocytes activation contributing to an exacerbated immune response involving the nervous system.⁴⁸ Besides the indirect effect of ZIKV in

pathogenesis of neurological disease through the immune system, a direct neurotropic pathogenic damage of the peripheral nervous system has also been proposed. Direct viral effect on neurons or glial cells may be a possible mechanism in cases of encephalitis, myelitis, or even GBS although such evidence is scarce and based only on observations in experimental mouse (–Fig. 1d).^{35,39} An overlap between immune-mediated and direct-viral mechanisms is plausible, but the lack of neuropathological evidence from human biopsy or autopsy study hinders any conclusion on such possibility.

Since none of these postulations have been elucidated, further research efforts are required for a comprehensive understanding of the neuropathogenic mechanisms of ZIKV infection in the adult central and peripheral nervous system. Viral, host, and environmental factors will need to be included also in future studies of such mechanisms.

Conclusion

The spectrum of ZIKV-related neurological complications is still unknown; however, GBS, encephalitis, and myelitis have been linked to recent ZIKV outbreaks. One case–control study described earlier provides the highest support toward linking ZIKV with GBS. Most available data are derived from epidemiological surveillance systems regarding temporal relationship of GBS clusters during ZIKV epidemics, as well as case reports of patients with encephalitis or myelitis along with ZIKV detection in biological samples. With the limited current evidence, causality cannot yet be established to link ZIKV with neurological disorders in adults. Mechanisms underlying the potential pathophysiology of ZIKV in the nervous system are still unclear. Global action needs to be taken to drive well-designed prospective studies to evaluate such relationship; meanwhile, health authorities should be aware of the potential risks of neurological disorders derived from ZIKV infection such as GBS, encephalitis, and myelitis.

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