ARTICLE

Long-term outcome in neuroZika

When biological diagnosis matters

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Abstract

Objective

To characterize the full spectrum, relative frequency, and prognosis of the neurologic manifestations in Zika virus (ZIKV) postnatal infection.

Methods

We conducted an observational study in consecutive ZIKV-infected patients presenting with neurologic manifestations during the French West Indies 2016 outbreak.

Results

Eighty-seven patients, including 6 children, were enrolled. Ninety-five percent of all cases required hospitalization. Guillain-Barré syndrome was the most frequent manifestation (46.0%) followed by encephalitis or encephalomyelitis (20.7%), isolated single or multiple cranial nerve palsies (9.2%), other peripheral manifestations (6.9%), and stroke (1.1%). Fourteen patients (16.1%), including one child, developed a mixed disorder involving both the central and peripheral nervous system. Mechanical ventilation was required in 21 cases, all of whom had ZIKV RNA in at least one biological fluid. Two adult patients died due to neuroZika. Clinical follow-up (median 14 months; interquartile range, 13–17 months) was available for 76 patients. Residual disability (modified Rankin Scale score ≥2) was identified in 19 (25.0%) patients; in 6 cases (7.9%), disability was severe (modified Rankin Scale score ≥4). Among patients with ZIKV RNA detected in one biological fluid, the risk of residual disability or death was higher (odds ratio 9.19; confidence interval 1.12–75.22; $p = 0.039$).

Conclusions

NeuroZika spectrum represents a heterogeneous group of clinical neurologic manifestations. During an outbreak, clinicians should consider neuroZika in patients presenting with cranial nerve palsies and a mixed neurologic disorder. Long-term sequelae are frequent in NeuroZika. ZIKV reverse-transcription PCR status at admission can inform prognosis and should therefore be taken into consideration in the management of hospitalized patients.

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Glossary

ADEM = acute disseminated encephalomyelitis; **AIDP** = acute inflammatory demyelinating polyradiculoneuropathy; **CI** = confidence interval; **GBS** = Guillain-Barré syndrome; **GDS** = Guillain-Barré Disability Scale; **HR** = hazard ratio; **ICU** = intensive care unit; **IgG** = immunoglobulin G; **IgM** = immunoglobulin M; **IGOS** = International GBS Outcome Study; **IQR** = interquartile range; **IVIg** = IV immunoglobulin; **mRS** = modified Rankin Scale; **PAHO** = Pan American Health Organization; **PNS** = peripheral nervous system; **PRNT** = plaque reduction neutralization test; **RT-PCR** = reverse transcription PCR; **ZIKV** = Zika virus.

Zika virus (ZIKV) is a flavivirus transmitted to humans by *Aedes* genus mosquitoes. Since the first epidemic in 2007 in Yap Island, ZIKV has spread to Polynesia, South America, and the Caribbean.[1] In 2016, an epidemic in the French Caribbean islands of Guadeloupe and Martinique resulted in 66,600 people seeking medical attention with clinical manifestations of ZIKV infection. Reported neurologic manifestations of postnatal ZIKV infection following the French Polynesian epidemic in 2013/2014 include Guillain-Barré syndrome (GBS) in adults[2–7] and children.[8] Other reported neurologic manifestations include myelitis,[9–11] encephalitis,[10,12] meningo-encephalitis,[13] sensory polyneuropathy,[14] acute polyneuritis,[15] sensory neuronopathy,[16] and chronic inflammatory demyelinating polyneuropathy.[10] These studies were mostly limited to hospitalized adult patients and principally focused on GBS[2–7] or acute neuroinflammatory diseases.[10] Furthermore, biological evidence of ZIKV infection was inconsistently reported, with an absence of long-term prognostication.

To report the full spectrum and prognosis of neuroZika, and to identify predictors of poor outcome, we conducted a large population-based observational study during the French West Indies 2016 outbreak.

Methods

Patients and study design

We included all patients seen at the University Hospitals of Guadeloupe and Martinique between January 6 and September 13, 2016, with recent neurologic manifestations and documented ZIKV infection. As previously defined by the Pan American Health Organization (PAHO) and the WHO,[17] patients were considered to have confirmed ZIKV recent infection in the presence of (1) detection of viral genome in urine, plasma, or CSF samples or (2) detection of immunoglobulin M (IgM) for ZIKV and plaque reduction neutralization test (PRNT) positive for ZIKV or probable recent ZIKV infection in the presence of ZIKV IgM and no dengue IgM or suspected recent ZIKV infection within the previous month of a clinical picture consistent with ZIKV infection that we call typical ZIKV symptoms (rash with 2 or more of the following signs or symptoms: fever, arthralgia, myalgia, conjunctivitis, or edema). Patients with positive immunoglobulin G (IgG) detection for ZIKV but infectious manifestations that did not fulfill the criteria defined by the PAHO organization or positive IgG but no consistent infectious symptoms or suspected recent infection without ZIKV IgG were excluded. Historic, clinical, biologic, neurophysiologic, and neuroradiologic data were collected during the hospital stay. The acute phase has partly been described in previous publications for 2 patients with neurologic manifestations due to ZIKV infection from Guadeloupe (1 with myelitis,[9] 1 stroke[18]) and for 23 patients from Martinique (2 patients with encephalopathy[19] and 21 patients with GBS,[5] including 2 patients previously described as case reports[20]).

Standard protocol approvals, registrations, and patient consents

The local institutional review board (EREGIN, University Hospital of Guadeloupe, approval number: A11_05_07_16_ZIKA) reviewed and approved the study protocol. The study was classified as an observational study according to the rules of the French regulation. As the local ethical committee did not require written consent for this observational study, oral informed consent was obtained from all participants after providing them written explanations, and the study was performed according to the approved protocol.

Diagnosis of ZIKV infection

At admission, a diagnosis was made using reverse transcription PCR (RT-PCR, RealStar Zika Virus RT-PCR Kit 1.0; Altona Diagnostics, Hamburg, Germany) of CSF, plasma, and urine samples. Serologic testing for ZIKV and dengue virus was also performed (ELISA anti-Zika Virus IgM and IgG, Euroimmun, Germany; ELISA anti dengue virus IgM and IgG ELIT kit; Eurobio, Germany). In equivocal cases, when ZIKV RT-PCR was negative and dengue IgM antibodies were detected, the presence of neutralizing antibodies was assessed using PRNT[5] to avoid false-positive results due to cross-reactivity (done by National Reference Center for Arboviruses, Institut Pasteur de Cayenne, French Guyana, or by National Reference Center for Arboviruses, Marseille, France). In addition, for patients in Martinique, RT-PCR testing for dengue virus (Simplexa dengue RT-PCR assay; DiaSorin Molecular, Cypress, CA) and chikungunya (RealStar Chikungunya RT-PCR Kit 1.0; Altona Diagnostics) was performed on plasma at admission.

Neurologic investigations

All patients had a detailed standardized neurologic examination performed by a certified neurologist. Neurologic manifestations were classified as either involving the peripheral nervous system (PNS) only or CNS only or involving both PNS and CNS (mixed disorders). A diagnosis of GBS was

made using international Brighton criteria.[21] Patients with encephalitis or acute myelitis were diagnosed according to consensus criteria.[22,23] The severity of disability was graded using (1) modified Rankin Scale (mRS)[3] in all patients and (2) Medical Research Council score[24] and Guillain-Barré Disability Scale (GDS)[25] in patients with GBS.

Patients with clinical evidence of PNS involvement underwent EMG during the initial hospital stay. Compound muscle action potential amplitude and duration, distal motor latency, and motor nerve conduction velocity in tibial, peroneal, median, and ulnar nerve were measured. We tested for temporal dispersion and conduction block. Sensory conduction velocities and amplitude of sensory nerve action potential were measured with surface electrodes, using antidromic techniques. Absent or blocked F responses and F-wave latency were also evaluated.

Neurophysiologic criteria were used to diagnose GBS and its variants.[26] MRI were performed using a neuro-optimized 1.5T scanner (Philipps Brillance, Best, the Netherlands). 3D T1, 3D fluid-attenuated inversion recovery, and 3D T1 gadolinium and axial T2 sequences were acquired for brain MRI. Sagittal T1, short time inversion recovery, and T1 gadolinium sequences were acquired for MRI of the spinal cord.

Investigations and assessments performed at the initial consultation were repeated at follow-up visits from 8 months after the onset of neuroZika. For patients with GBS, the Overall Neuropathy Limitations Scale[27] was also performed.

Statistical analysis

Quantitative variables were summarized as median with interquartile range (IQR) and compared across groups using Mann-Whitney nonparametric test. Categorical data were expressed as percentages and compared between groups using χ^2 test or Fisher exact test, depending on the sample size. Cox models were used to identify factors associated with the need for mechanical ventilation during hospitalization. The survival period was calculated from the date of admission to the date of mechanical ventilation or of discharge from hospital. Logistic regression model was used to identify factors associated with long-term residual disability (mRS ≥ 2) or death due to neuroZika. In both analyses, factors investigated were the general characteristics and the clinical or biological data related to dengue and ZIVK infection, mRS at admission, and neurologic symptoms. For the presence of long-term residual disability or death due to neuroZika, the duration of hospital stay and the need for mechanical ventilation during hospitalization were added. In patients with GBS, we also analyzed the GDS. Statistical analyses were performed using SPSS (v. 21, IBM SPSS Statistics, Chicago, IL); significance was considered at the 5% level.

Data availability statement

In each participating center (Martinique and Guadeloupe), data collection was carried out by simple input into an electronic case report form implemented under Ennov Clinical (Clinical Data Management System). Some data will be made available from the corresponding author, upon reasonable request. The data are not publicly available because they contain information that could compromise the privacy of our patients.

Results

In 2016, 87 patients with ZIKV postnatal recent infection presented to hospital in Guadeloupe and Martinique with neurologic manifestations (figure 1A). According to the PAHO criteria, 65 cases were confirmed ZIKV infection. Eleven cases were probable ZIKV infection. Eleven cases were suspected ZIKV infection and also had ZIKV IgG.

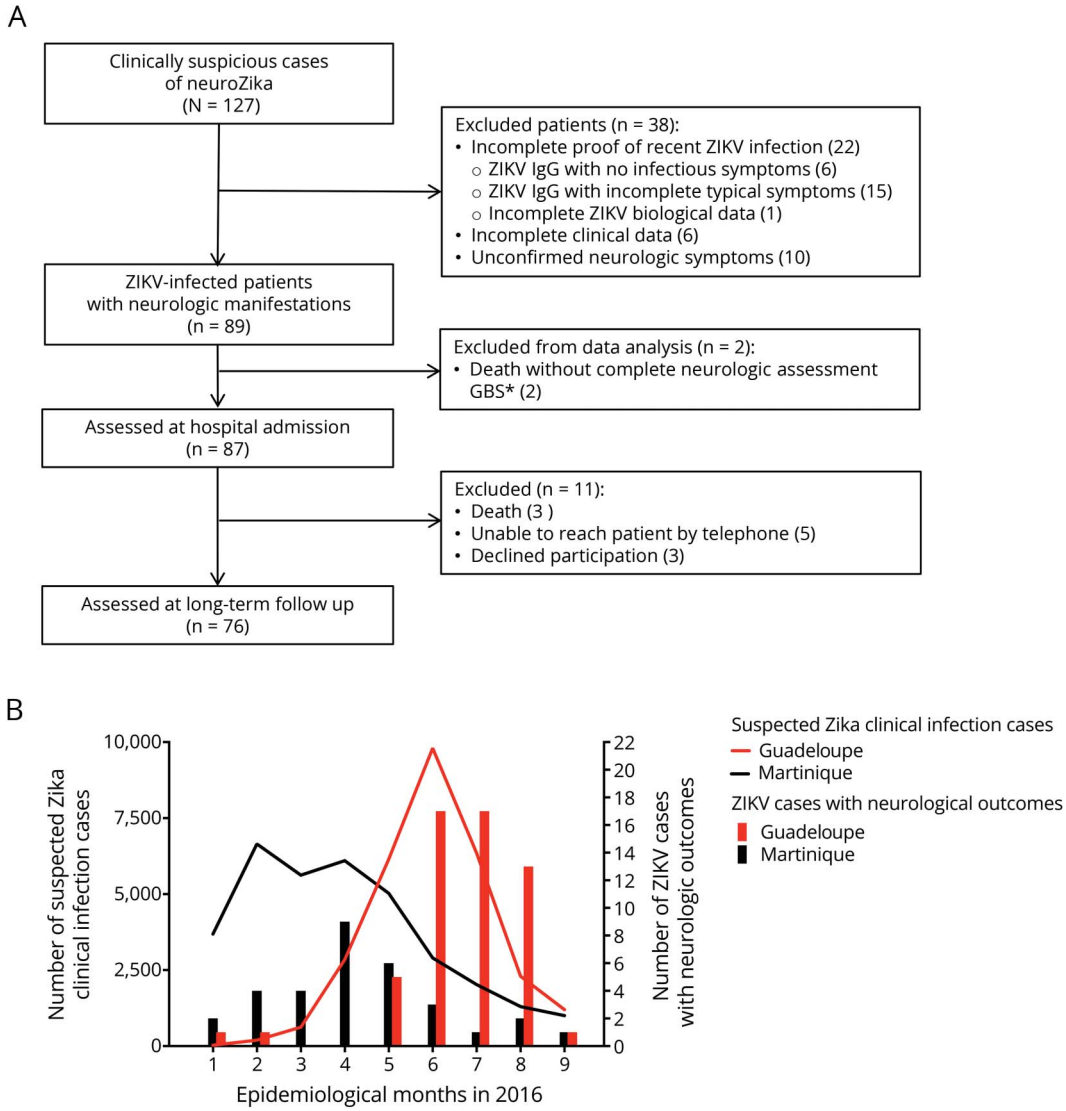
The majority of these 87 cases were diagnosed between March and June in Martinique (22 cases out of 32), and between June and August in Guadeloupe (47 cases out of 55) (figure 1B). The distribution of ZIKV cases with neurologic manifestations fits the epidemic curve of each island (figure 1B). ZIKV RNA was detected in at least one biological fluid (plasma, urine, or CSF) in the majority of cases (64 cases out of 87, 73.6%, table 1 and table S1, doi.org/10.5061/dryad.35q1p98). Of the 23 patients with no evidence of ZIKV RNA, plasma IgM for ZIKV was detected in 12 (13.8%). Finally, plasma ZIKV IgG was found in the last 11 cases, who had ZIKV typical symptoms within the previous month but with no evidence of ZIKV RNA or IgM (12.6%). Chikungunya RT-PCR was negative in the plasma of patients from Martinique (performed in 31 of 32 patients) where co-circulation was low (only one confirmed case over the study period). Testing was not performed in Guadeloupe during this period due to the absence of chikungunya virus circulation. Finally, of the 87 ZIKV-infected patients with neurologic manifestation, nearly all (92.5%) presented with plasma IgG for dengue virus consistent with a history of dengue infection (table S2, doi.org/10.5061/dryad.35q1p98). Dengue RT-PCR was negative in the plasma of patients from Martinique (performed in 31 of 32 patients).

Patients' characteristics at hospital admission

Patients, 51% of whom were male (n = 44), had a median age of 54 years (IQR 38–66, table 1). Ninety-three percent (n = 83) required hospitalization (table 1), 6 of whom (6.9%) were children aged 10 months to 16 years (table S3, doi.org/10.5061/dryad.35q1p98). Fifty-four patients (62.1%) had PNS involvement (GBS, cranial nerve palsy, or other peripheral disorders). Nineteen (21.8%) patients had CNS involvement (encephalitis, myelitis, encephalomyelitis, or stroke). Fourteen (16.1%) patients had a mixed disorder.

Patients with ZIKV infection confirmed by RT-PCR (73.6%) presented earlier to hospital after onset of neurologic signs (median of 2 days, IQR 1–4 [table 1]; compared to 4 days, IQR 2–9, in others; $p = 0.008$). This finding is consistent with

Figure 1 Enrollment and outcome in the neuroZika study performed in the French territories of Martinique and Guadeloupe



(A) Flow chart of the selection process. *Cases described in Rozé et al.[5] GBS = Guillain-Barré syndrome; IgG = immunoglobulin G. (B) Monthly cases of patients with suspected Zika virus (ZIKV) clinical infection consulting general practitioners and ZIKV patients with neurologic manifestations in Guadeloupe and Martinique between January and September 2016.

the relatively short time period for ZIKV RNA clearance in body fluids after symptom onset (maximum 14 days).[28–30] Patients with positive ZIKV RT-PCR in urine or in any fluid (plasma, urine, CSF) presented with more severe disability as assessed by mRS (positive ZIKV RT-PCR: urine: $p = 0.027$; any fluid: $p = 0.016$; table S1, doi.org/10.5061/dryad.35q1p98). ZIKV genome was detected in the CSF of 5 patients (26.3%) with CNS involvement (encephalitis), 3 patients (5.6%) with PNS involvement (1 with GBS and 2 with other peripheral disorders), and 1 (7.1%) with a mixed disorder (table 1).

PNS involvement

GBS was diagnosed in 40 (74.1%) of the 54 patients with PNS involvement, of whom 28 (70.0%) had a Brighton level 1, 4 had a Brighton level 2, 1 had a Brighton level 3, and 7 had a Brighton level 4. Twenty-one of these patients were graded as severe (GDS and mRS ≥ 4): wheelchair-bound or bedridden at the time of examination (table 1 and table S4, doi.org/10.5061/dryad.35q1p98). All patients with GBS received IV immunoglobulin (IVIg) at a median of 4 days (IQR 2–7) following onset of neurologic symptoms (table 1). Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) was the most frequent neurophysiologic diagnosis (table S5, doi.org/10.5061/dryad.35q1p98). Among the 12 patients who had MRI (2 brain MRI, 3 spinal MRI, 7 both), 5 had enhancement of the facial nerve (figure 2I), and 4 had enhancement of the lumbar roots post contrast injection (figure 2J).

Table 1 Characteristics and management of patients presenting with recent Zika virus (ZIKV) infection and acute neurologic manifestations

		PNS involvement			CNS involvement		
	Total	GBS	Cranial nerve palsy	Other peripheral disorders	Encephalitis-myelitis	Stroke	Mixed disorder
N	87 (100.0)	40 (46.0)	8 (9.2)	6 (6.9)	18 (20.7)	1 (1.1)	14 (16.1)
Inclusion							
Male	44 (50.6)	23 (57.5)	3 (37.5)	2 (33.3)	10 (55.6)	1 (100.0)	5 (35.7)
Age, y, median (IQR)	54 (38–66)	58 (48–69)	41 (37–46)	41 (29–59)	49 (31–56)	0	58 (47–69)
Children (≤16 y)	6 (6.9)	2 (5.0)	—	—	2 (11.1)	1 (100.0)	1 (7.1)
Diabetes mellitus	13 (14.9)	9 (22.5)	—	1 (16.7)	1 (5.6)	—	2 (14.3)
No viral symptoms	12 (13.8)	12 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ZIKV typical symptoms[a]	42 (48.3)	17 (42.5)	5 (62.5)	4 (66.7)	10 (55.6)	1 (100.0)	5 (35.7)
ZIKV diagnosis, positive RT-PCR[b]	64/87 (73.6)	26 (65.0)	5 (62.5)	4 (66.7)	15 (83.3)	1 (100.0)	13 (92.9)
Plasma	12/85 (14.1)	2/40 (5.0)	1/8 (12.5)	1/5 (20.0)	4/17 (23.5)	1/1 (100.0)	3/14 (21.4)
Urine	58/83 (69.9)	25/40 (62.5)	4/7 (57.1)	4/6 (66.7)	14/17 (82.4)	0/1 (0.0)	11/12 (91.7)
CSF	9/83 (10.8)	1/39 (2.6)	0/7 (0.0)	2/5 (40.0)	5/18 (27.8)	0/1 (0.0)	1/13 (7.7)
Positive IgM in plasma[c]	12 (13.8)	6 (15.0)	3 (37.5)	1 (16.7)	1 (5.6)	—	1 (7.1)
Positive IgG + typical symptoms[d]	11 (12.6)	8 (20.0)	—	1 (16.7)	2 (11.1)	—	—
Time between viral symptoms and neurologic manifestations, d, median[e] (IQR)	5 (2–8)	6 (4–8)	3 (2–25)	3 (1–6)	4 (1–6)	6	6 (2–8)
Time between neurologic manifestations and admission (d) median (IQR)	3 (1–5)	3 (2–6)	3 (1–10)	2 (2–2)	1 (0–3)	0	3 (0–4)
In ZIKV, positive RT-PCR	2 (1–4)	3 (2–5)	3 (3–8)	2 (1–3)	1 (0–2)	0	2 (0–3)
Time between viral symptoms and sample collections, d, median (IQR)	8 (5–12)	9 (5–14)	11 (8–27)	5 (4–7)	7 (1–10)	6	8 (6–13)
In ZIKV, positive RT-PCR	7 (4–11)	8 (4–12)	11 (6–28)	5 (4–7)	6 (1–10)	6	13 (7–25)
Modified mRS score							
1	19 (21.8)	3 (7.5)	7 (87.5)	5 (83.3)	3 (16.7)	—	1 (7.1)
2–3	29 (33.3)	11 (27.5)	1 (12.5)	1 (16.7)	10 (55.6)	—	6 (42.9)
4–5	39 (44.8)	26 (65.0)	—	—	5 (27.8)	1 (100.0)	7 (50.0)
Hospitalization	83 (95.4)	40 (100.0)	6 (75.0)	4 (66.7)	18 (100.0)	1 (100.0)	14 (100.0)
Children	6	2			2	1	1
IV immunoglobulin treatment	59 (67.8)	40 (100.0)	2 (25.0)	1 (16.7)	4 (22.2)	—	12 (85.7)
Corticosteroids treatment	20 (23.0)	4 (10.0)	5 (62.5)	1 (16.7)	5 (27.8)	—	5 (35.7)
Admission in ICU	32 (36.8)	21 (52.5)	—	—	7 (38.9)	—	4 (28.6)
Children	2	1			1		
Duration of stay in ICU, d, median (IQR)	10 (7–26)	13 (7–21)	—	—	10 (5–30)	—	9 (5–46)
Death during stay in ICU	2 (2.3)	1 (2.5)	—	—		—	1 (7.1)
Children	0						

Continued

Table 1 Characteristics and management of patients presenting with recent Zika virus (ZIKV) infection and acute neurologic manifestations *(continued)*

		PNS involvement			CNS involvement		
	Total	GBS	Cranial nerve palsy	Other peripheral disorders	Encephalitis-myelitis	Stroke	Mixed disorder
Mechanical ventilation	21 (24.1)	15 (37.5)	—	—	4 (22.2)	—	2 (14.3)
Children	1				1		
Duration of mechanical ventilation, d, median (IQR)	9 (6–20)	9 (6–19)	—	—	14 (3–26)	—	33 (2–64)
Outcomes	79 (90.8)	35 (87.5)	7 (87.5)	6 (100.0)	17 (94.5)	1 (100.0)	13 (92.8)
Children	6	2			2	1	1
Admission in rehabilitation center	42 (52.5)	25 (69.4)	—	—	6 (37.5)	—	11 (84.6)
Children	2	1					1
Duration of stay in rehabilitation center, d, median (IQR)	47 (31–80)	53 (32–83)	—	—	80 (57–174)	—	44 (28–47)
Duration of work incapacity, d, median (IQR)	42 (0–92)	57 (35–90)	0 (0–92)	—	30 (15–65)	—	149 (99–590)

Abbreviations: GBS = Guillain-Barré syndrome; ICU = intensive care unit; IgG = immunoglobulin G; IgM = immunoglobulin M; IQR = interquartile range; mRS = modified Rankin Scale; PNS = peripheral nervous system; RT-PCR = reverse transcription PCR.
When not specified, results are n (%).
[a] Rash with 2 or more of the following signs or symptoms: fever, arthralgia, myalgia, conjunctivitis, or edema.
[b] RT-PCR-positive for ZIKV in urine, plasma, or CSF.
[c] Negative RT-PCR for ZIKV in urine, plasma, and CSF and detection of IgM for ZIKV in plasma.
[d] Negative RT-PCR for ZIKV in urine, plasma, and CSF and detection of IgG for ZIKV in plasma without detection of IgM for ZIKV in plasma.
[e] Identical to the time from onset of viral symptoms and the collection of samples.

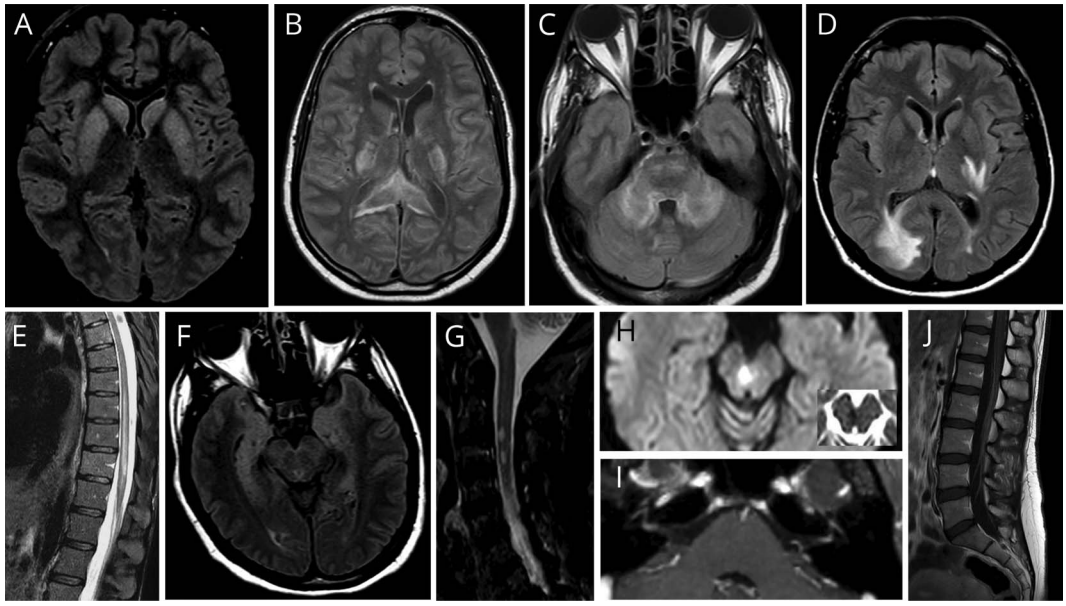
Two other types of PNS manifestations were observed in adults:

1. Cranial nerve palsies were identified in 8 patients at a median of 3 days (IQR 2–25) post infectious symptoms (table 1): isolated unilateral (n = 3) or bilateral (n = 1) facial palsy or multiple cranial nerve palsy (n = 4). Enhancement of the facial nerve was observed on MRI brain in 2 patients who had an MRI. Multiple cranial nerve palsies (n = 4) involved the facial and vestibulocochlear cranial nerve (hypoacousis in one case and vestibular syndrome in another). One patient developed facial hypoesthesia associated with vertigo, hypoacousis and dysphagia related to bilateral glossopharyngeal, vagus, and accessory cranial nerve palsies; another had an ocular motor nerve palsy with involvement of the oculomotor and trochlear cranial nerve.
2. Six patients developed unclassified peripheral manifestations characterized by paresthesia (6/6), neurogenic pain (4/6), dysautonomia (2/6), areflexia (2/6), and hypopallesthia/ataxia (2/6) without muscular weakness (table S4, doi.org/10.5061/dryad.35q1p98) at a median of 3 (IQR 1–6) days following the infectious symptoms (table 1). The functional consequence was mild, and usually consisted of proprioceptive ataxia and pain of the lower limbs. Electrophysiologic examination was normal in all patients as well as CSF analysis.

CNS involvement

Among the 19 patients with CNS involvement, encephalitis was observed in 13 adults and 2 children (5 and 16 years old), encephalomyelitis in 2, myelitis in 1, and stroke in 1. Clinical manifestations included cognitive dysfunction (aphasia, memory loss, frontal syndrome) (n = 9), confusion (n = 9), cranial nerve palsy (n = 6), seizures (n = 6, including 1 status epilepticus), motor weakness (n = 5), nuchal rigidity (n = 3), vestibular dysfunction (n = 2), cerebellar dysfunction (n = 2), unilateral visual loss (n = 2), hearing loss (n = 1), upper limb tremor (n = 1), and parkinsonism (n = 1) (table S4, doi.org/10.5061/dryad.35q1p98). Meningitis was identified in 12 patients (median leukocyte count of 62.5 × 10^9/L, IQR 24.5–175; range 8–380). In these cases, CSF was purely or predominantly lymphocytic (56%–100%; n = 5), or with a neutrophil polynuclear predominance (70%–91%; n = 5), and indeterminate in 2 cases with a leukocyte count at 8 × 10^9/L and 9 × 10^9/L. Among the 19 patients with CNS involvement, MRI brain (n = 18) or MRI spine (n = 11) was performed during the first week after the onset of neurologic manifestations in patients. Among patients with encephalitis (n = 16), brain imaging was normal in 8 (50%). Brain lesions (T2 hyperintensities) were mainly asymmetric (n = 6), located in supratentorial regions: the frontal cortex (n = 4), the white matter (n = 4) (figure 2D), the striatum (figure 2A) (n = 3), and the hippocampic cortex (n = 1) (figure 2F). In one case, supratentorial lesions (figure 2B) were associated

Figure 2 MRI findings in encephalitis, encephalomyelitis, Guillain-Barré syndrome (GBS), and mixed central and peripheral disorder complicating infection by Zika virus (ZIKV)



(A) Fluid-attenuated inversion recovery (FLAIR) imaging demonstrates symmetric bilateral striatal hyperintensities in a 16-year-old patient with encephalitis (headache, fever, and seizures). (B, C) Hyperintensities of corticospinal tracts and the splenium of the corpus callosum (B) and hyperintensity of the middle cerebellar peduncle and the pons (C) in a 53-year-old man with epileptic seizure and febrile coma Glasgow Coma Scale 4, neutrophil-predominant meningitis (180 leukocytes/mm^3, 88% polynuclear leukocytes) with normal glycorrhachia, hyperproteinorrachia (117 mg/dL), and no oligoclonal bands; a stereotactic biopsy performed on day 37 in the corpus callosum revealed large macrophage infiltrates and a few perivascular lymphocytes, but no signs of vasculitis; ZIKV was not detected by real-time PCR in brain tissue. (D, E) MRI findings (FLAIR sequences) in acute encephalomyelitis with radiculitis in a 47-year-old woman (patient 12, table 2): (D) white matter FLAIR hyperintensity in the right temporo-occipital region, in the left lenticular and internal capsule, and (E) extensive T2 hyperintensity in the lower thoracic spinal cord. (F) Axial FLAIR in a 46-year-old woman with left hemiparesis shows bilateral hippocampal hyperintensities. (G, H) MRI findings in a 68-year-old woman with encephalomyelitis and radiculitis (patient 13, table 2) shows spotty hyperintensities in the cervical spinal cord in short time inversion recovery sequences and a centromesencephalic hyperintensity in diffusion-weighted imaging sequence was positive with a low apparent diffusion coefficient (vignette). (I, J) T1 sequences with gadolinium in two 35-year-old patients with GBS with facial diplegia showing (I) bilateral enhancement of the facial nerve and (J) regular and intense enhancement of the lumbar nerve roots.

with infratentorial involvement (figure 2C). Longitudinally extensive T2 hyperintensities were observed on spinal MRI in patients with myelitis or encephalomyelitis (n = 3) (figure 2E and figure S1A, doi.org/10.5061/dryad.35q1p98). In one patient with encephalomyelitis and optic neuritis, contrast enhancement of the right optic nerve was observed (figure S1D, doi.org/10.5061/dryad.35q1p98).

Mixed disorders

Fourteen patients presented mixed PNS and CNS disorders. Their detailed characteristics are provided in table 2.

Mechanical ventilation requirement as prognosis for severity

A total of 32 (36.8%) patients were admitted to the intensive care unit (ICU) for a median duration of 10 days (IQR 7–26) (table 1). Mechanical ventilation was required in 21 (table S3, doi.org/10.5061/dryad.35q1p98). Of these 21 cases, 15 patients had GBS, 4 had encephalitis (including 1 child), and 2 had a mixed disorder. ZIKV was detected by RT-PCR in all patients who required mechanical ventilation. In univariate analysis, diabetes, mRS 4–5, and a diagnostic of isolated GBS significantly increased the risk of mechanical ventilation (table 3). When these 3 factors were considered, only mRS 4–5 remained significantly associated with a greater risk of mechanical ventilation (hazard ratio [HR] 6.25; confidence interval [CI] 1.77–22.10; p = 0.004). Similarly, among patients with GBS, mRS 4–5 was identified as the only risk factor for mechanical ventilation after adjustment for diabetes (HR 9.63; 95% CI 1.26–73.73; p = 0.029).

Clinical characteristics at long-term follow-up and identification of predictors for disability or death

Long-term evaluation was conducted in 76 patients, after a median delay of 14 months (IQR 13–17 months). Three adults died before long-term evaluation and 8 were lost to follow-up (figure 1A).

The patients who died were aged 59, 81, and 76 years, respectively. All 3 were admitted to the ICU and the 2 men required mechanical ventilation. Two died during the stay in the ICU (table 1). The 59-year-old man had a mixed disorder comprising encephalitis and polyradiculoneuropathy (patient 10, table 2). The 81-year-old man had GBS. Death occurred at 79 days and 22 days, respectively, following the onset of neurologic symptoms. The 76-year-old woman died 7 months after the acute period due to an unrelated cause.

Table 2 Individual features of 14 Zika virus (ZIKV) patients presenting with mixed CNS and peripheral nervous system involvement

Patient (age, y/sex)	Neurologic features at admission	mRS	CSF WCC/ protein, g/L	MRI findings	Neurologic diagnosis	Medical care	Follow-up mRS (mo)
1 (66/F)	Tetraparesis and axial weakness, paresthesia, areflexia, swallowing dysfunction, bilateral facial palsy, unilateral Babinski sign, GCS 15, AIDP	3	0/1.33	Normal	Polyradiculoneuropathy with pyramidal signs	IVIg	2 (20)
2 (71/M)	Paresthesia, areflexia, bilateral facial palsy, and bilateral Babinski sign, GCS 15, EMG nonworkable	1	20/2.26 L 60%	Not done	Polyradiculoneuropathy, subclinical meningitis, pyramidal signs	IVIg	1 (15)
3 (52/M)	Tetraparesis, paresthesia, areflexia, lasegue sign, lower back pain, swallowing dysfunction, unilateral facial palsy, bilateral Babinski sign, constipation, GCS 15, AIDP	4	2/1.64	CE of lumbar roots and VII bilateral	Polyradiculoneuropathy with pyramidal signs	IVIg	1 (13)
4 (56/M)	Tetraparesis and axial weakness, paresthesia, areflexia, swallowing dysfunction, ineffective cough, GCS 15, EMG nonworkable	5	0/1.70	Medullary cone HS, CE of VII bilateral	Polyradiculoneuropathy and myelitis	IVIg	Loss of follow-up
5 (77/F)	Tetraparesis and axial weakness, paresthesia, areflexia, swallowing dysfunction, ineffective cough, GCS 15, AIDP	3	5/2.18	Cervical HS (C6-7), CE of VII bilateral	Polyradiculoneuropathy and myelitis	ICU, V, IVIg	2 (16)
6 (38/M)	Tetraparesis and axial weakness, paresthesia, areflexia, ataxia, bilateral facial palsy, breathing dysfunction, dysautonomia, urinary incontinence, GCS 15, AIDP	2	7/1.16	Medullary cone HS, CE of lumbar roots and VII bilateral	Polyradiculoneuropathy, subclinical meningitis, and myelitis	IVIg, MP	1 (12)
7 (37/F)	Tetraparesis and axial weakness, paresthesia, areflexia, lower back pain, swallowing and breathing dysfunction, ineffective cough, T8 sensory level, GCS 15, AIDP	4	50/1.90 L 75%	Medullary cone HS and CE of lumbar roots	Polyradiculoneuropathy, subclinical meningitis, and myelitis	ICU, IVIg, MP	0 (14)
8 (69/F)	Areflexia, paresthesia, GCS 15, sensory neuropathy	2	1/0.32	Cervical (C3-C4) HS	Sensory polyneuropathy and myelitis	IVIg	1 (14)
9 (80/F)	Tetraparesis and axial weakness, paresthesia, areflexia, bilateral Babinski sign, constipation, confusion, GCS 14, AIDP	4	5/1.18	Normal	Polyradiculoneuropathy and encephalitis	IVIg	1 (14)
10 (59/M)	Confusion, nystagmus, ataxia, tremor, GCS 14, areflexia, urinary retention, AIDP	5	3/1.72	CE of VII bilateral and left VIII	Polyradiculoneuropathy and encephalitis	ICU, V, IVIg	Death (3)
11 (57/F)	Paresthesia, ataxia, unilateral facial palsy GCS 15	3	29/0.63 L 100%	CE of VII bilateral	Polyradiculoneuropathy, subclinical meningitis, and encephalitis	IVIg	2 (13)
12 (47/F)	Left homonymous hemianopsia, diplopia, dizziness, nystagmus, ataxic gate, dysuria, genital and anal anesthesia, tactile hypoesthesia of the left leg, GCS 15	2	470/0.73 L 100%	Subcortical brain white matter HS (figure 3D), 3 extensive lesions (C2-C4, T1-T3, T9-T11) (figure 3E), CE of lumbar roots	Encephalomyelitis, meningitis, and radiculitis	MP	1 (12)
13 (68/F)	Bilateral cerebellar syndrome, left hemiparesis, muscle weakness of the left leg, urinary retention, GCS 15	4	4/0.60	Spotty HS in the cervical cord (figure 3G), bilateral pyramidal tracts and centro-mesencephalic HS (figure 3H), CE of lumbar roots	Encephalomyelitis and radiculitis	ICU, IVIg, MP	2 (12)
14 (15/F)	Left hemiparesis, lower back pain, paresthesia, sensory level T2 left, T4 right, dysuria and urinary retention, bilateral Hoffman sign, GCS 15, normal EMG	4	3/0.30	Cervical (C4-C7) and thoracic (T5-T8) HS, CE of lumbar roots	Myeloradiculitis	MP	2 (20)

Abbreviations: AIDP = acute inflammatory demyelinating polyradiculoneuropathy; CE = contrast enhancement; HS = hypersignal; GCS = Glasgow Coma Scale score; ICU = intensive care unit; IVIg = IV immunoglobulin; L = lymphocytes; MP = methylprednisolone 1 g/d for 5 days; mRS = modified Rankin Scale; V = mechanical ventilation; WCC = white cell count (/μL).

Table 3 Univariate Cox proportional hazard model predicting mechanical ventilation (n = 21) for neurologic complications in Zika virus (ZIKV) infection

	All patients (n = 87)			Isolated GBS (n = 40)		
	N	Crude HR (95% CI)	*p*	N	Crude HR (95% CI)	*p*
Sex						
Male	44	1		23	1	
Female	43	0.50 (0.20–1.25)	0.139	17	0.94 (0.33–2.63)	0.901
Age at acute phase, y						
<50	38	1		13	1	
≥50	49	2.29 (0.84–6.26)	0.106	27	3.49 (0.79–15.48)	0.100
Diabetes mellitus						
No	74	1		31	1	
Yes	13	3.06 (1.23–7.61)	0.016	9	3.09 (1.09–8.78)	0.034
Dengue IgG						
Negative	6	1		0	Nonestimable as all patients are dengue-positive	
Positive	74	22.99 (0.02–28,659.56)	0.389	40		
Time between neurologic manifestations and admission, d						
≤2	39	1		12	1	
>2	48	0.56 (0.23–1.32)	0.185	28	0.45 (0.16–1.26)	0.130
ZIKV RT-PCR[a]						
Negative	23	1		14	1	
Positive	64	34.18 (0.61–1902.17)	0.085	26	49.77 (0.71–3,505.76)	0.072
Modified Rankin Scale[b]						
1	19	0.00 (0.00–∞)	0.962	3	0.00 (0.00–∞)	0.986
2–3	29	1		11	1	
4–5	39	5.38 (1.58–18.31)	0.007	26	7.93 (1.04–60.46)	0.046
Neurologic symptoms						
PNS only	54	1				
CNS only	19	0.70 (0.23–2.12)	0.531			
Mixed disorder	14	0.36 (0.08–1.58)	0.175			
Isolated GBS						
No	47	1				
Yes	40	3.07 (1.19–7.93)	0.020			
GDS[c]						
1				2	0.00 (0.00–∞)	0.987
2–3				17	1	
4–5				21	2.55 (0.81–8.03)	0.109

Abbreviations: CI = confidence interval; GBS = Guillain-Barré syndrome; GDS = Guillain-Barré Disability Scale; HR = hazard ratio; IgG = immunoglobulin G; PNS = peripheral nervous system; RT-PCR = reverse transcription PCR.
[a] RT-PCR: positive for ZIKV in urine, plasma, or CSF.
[b] 0: No symptoms at all; 1: no significant disability despite symptoms; able to carry out all usual duties and activities; 2: slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance; 3: moderate disability; requiring some help, but able to walk without assistance; 4: moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5: severe disability; bedridden, incontinent, and requiring constant nursing care and attention.
[c] Specific to GBS. 0: healthy state; 1: minor symptoms and capable of running; 2: able to walk 5 meters or more without assistance but unable to run; 3: able to walk 5 meters across an open space with help; 4: bedridden or chair-bound; 5: requiring assisted ventilation for at least part of the day.

Of the 76 patients followed up, 19 (25.0%) had residual disability (mRS ≥ 2) (table 4). Among the 19 cases with residual disability, 3 (out of 18 analyzed) had ZIKV RNA in CSF at admission (table S1, doi.org/10.5061/dryad.35q1p98). Patients with positive ZIKV RT-PCR in urine, plasma, or CSF presented with more severe residual disability ($p = 0.043$).

Seventy-eight patients were included in the analysis of predictors of disability or death: the 76 patients with a follow-up visit and the 2 patients in whom death was related to neuroZika. In univariate analysis, older age, mechanical ventilation, hospital stay >10 days, and positive ZIKV RT-PCR were significantly associated with the persistent functional disability or death (table 5). In multivariate analysis, following a stepwise descending procedure, only ZIKV detected by RT-PCR remained significantly associated with a long-term residual disability (odds ratio [95% CI] 9.19 [1.12–75.22]; $p = 0.039$). Restricting the analysis to patients with GBS, only ZIKV detected by RT-PCR remained significantly associated with long-term disability.

Characteristics of postnatal neuroZika in children

Two children had GBS, 3 had CNS involvement, and 1 had a mixed disorder. Their detailed characteristics are provided in table S3 (doi.org/10.5061/dryad.35q1p98). A 15-year-old girl with a mixed neurologic disorder and a 10-month-old boy with a stroke were graded as severe (GDS and mRS ≥4). The latter case presented 6 days after viral symptoms a right hemiparesis due to an ischemic stroke, 8 leukocytes in the CSF, and ZIKV RNA detected in plasma. Two children aged 6 and 13 years had GBS (AIDP), with ataxia, bilateral motor weakness, and areflexia. Both received IVIg with fast recovery. None had long-term sequelae. The 2 remaining children (5 and 16 years) had meningoencephalitis with generalized seizures. CSF count revealed 160 and 380 white cells, respectively, predominantly neutrophil polynuclear. Two children were admitted to the ICU. The first one eventually did not need mechanical ventilation. The other child was ventilated during 24 hours in the context of convulsive status epilepticus. Two out of the 6 children required prolonged rehabilitation. After a median delay of 14 months (IQR 12–17), 5 children had no disability, whereas 1 (a 15-year-old girl with myeloradiculitis) had neuropathic pain, lower limbs paresthesia, left hemihypoesthesia, mild ataxia, bladder dysfunction, and hyposmia.

Discussion

This study highlights the heterogeneous clinical spectrum observed in children and adults with neuroZika. It describes the relative proportion of each neurologic manifestation among patients with recent postnatal ZIKV infection and emphasizes the existence of mixed neurologic disorders. We also provide information on the long-term outcome of neuroZika and identify biological viral detection as a predictor of poor long-term outcome.

The strengths of this study are as follows: (1) the large sample size; (2) concomitant evaluation of ZIKV in plasma, CSF, and urine using molecular and serologic assays; (3) comprehensive documentation of all neurologic manifestations following recent ZIKV infection, without any a priori hypothesis regarding manifestation type; (4) the inclusion of children; and (5) long-term follow-up of 90% of patients. Consistent with prior data acquired from French Polynesia, New Caledonia, and the America and other Caribbean islands,[1–7] our study strongly suggests a link between ZIKV and neurologic manifestations, based on clinical, virologic, and epidemiologic arguments. The annual incidence rate of GBS in the general population of Guadeloupe and Martinique during the ZIKV outbreak increased 6-fold (total: 10.2/100,000; Martinique: 9.5/100,000[5]; Guadeloupe: 10.7/100,000 [database of the program for the medicalization of information systems, Guadeloupe Hospital]), compared with 1.77/100,000 over the 2011–2013 period.[31] It was 3-fold higher than in 2014 during concomitant chikungunya and dengue outbreaks (3.45/100,000),[31] providing an epidemiologic argument for causality. The annual rate of encephalitis and myelitis in 2016 in Guadeloupe was 4.3 higher than in 2012–2013 and 2015 (1.77/100,000) outside any epidemic context of arbovirosis, and 2.4-fold higher (3.2/100,000) than in 2014 during concomitant chikungunya and dengue outbreak (database of the program for the medicalization of information systems, Guadeloupe Hospital). In contrast with several studies from Latin America[11,32] in which coinfection of ZIKV with chikungunya and dengue virus was described, our data strongly suggest the absence of dual infection involving these 2 viruses in our neuroZika cases of Martinique.

Our study has limitations. First, the sample is hospital-based, which probably reflects the underlying severity of these cases. Second, due to our strict selection criteria based on ZIKV virology and serology, 22 potential cases with neurologic manifestations were excluded. Third, as we did not systematically perform comprehensive additional investigations to exclude other potential triggering infections with other pathogens such as *Campylobacter jejuni* and cytomegalovirus,[33,34] we cannot definitely rule out the possibility of dual or multiple coinfections.

Consistent with other series,[2–7] GBS was the most frequent neurologic manifestation (46.0% of our patients); it manifested with symmetrical limb weakness (85%, nonambulating in 61%) with areflexia (77.5%) and paresthesia (95%). In keeping with previous reports, the median delay between acute infectious symptoms and GBS was short (6 days) and about 15% of patients had no history of viral illness prior to neurologic manifestations.[2–7] In 88.9% of our patients with GBS, clinical and electrophysiologic findings were consistent with AIDP, a sensorimotor form of GBS that is often accompanied by cranial nerve deficits and pain.[35] AIDP was previously identified as the main GBS subtype complicating flavivirus infection.[36] These data contrast with those of French Polynesia,[2] where GBS following ZIKV infection has been

Table 4 Clinical characteristics of the 76 patients at the follow-up visit

		PNS involvement			CNS involvement		
	Total	GBS	Cranial nerve palsy	Other peripheral disorders	Encephalitis-myelitis	Stroke	Mixed disorder
Death before follow-up visit	3	1	0	0	1	0	1
N with follow-up visit	76	34	7	6	16	1	12
Male	36 (47.4)	19 (55.9)	2 (28.6)	2 (33.3)	9 (56.3)	1 (100.0)	3 (25.0)
Age, y, median (IQR)	52 (37–66)	58 (47–68)	40 (35–43)	41 (29–59)	43 (27–54)	0	62 (43–70)
Time between neurologic manifestations and evaluation, mo							
Median (IQR)	14 (13–17)	16 (13–17)	14 (13–16)	14 (14–16)	13 (12–15)	16	14 (13–16)
Range	8–27	8–21	12–21	12–17	11–27		12–20
Symptoms at the time of evaluation							
Paresthesia	29 (38.2)	20 (58.8)	3 (42.9)	3 (50.0)	0 (0.0)	0 (0.0)	3 (25.0)
Ataxia	24 (34.8)	10 (33.3)	1 (14.3)	2 (40.0)	1 (7.1)	0 (0.0)	10 (83.3)
Persistent cranial nerve palsy	23 (30.3)	14 (41.2)	1 (14.3)	0 (0.0)	4 (25.0)	0 (0.0)	4 (33.3)
Facial palsy	14 (21.9)	10 (34.5)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	3 (27.3)
Neuropathic pain	21 (27.6)	12 (35.3)	1 (14.3)	2 (33.3)	0 (0.0)	0 (0.0)	6 (50.0)
Sensory deficit	19 (26.8)	12 (38.7)	1 (16.7)	1 (20.0)	2 (12.5)	0 (0.0)	3 (25.0)
Postparetic facial hemispasm	9 (14.3)	8 (27.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Phonation disorders	11 (14.5)	8 (23.5)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (16.7)
Swallowing disorders	4 (5.3)	3 (8.8)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)
Areflexia	13 (19.1)	8 (26.7)	0 (0.0)	2 (40.0)	2 (14.3)	0 (0.0)	1 (8.3)
Other	3 (4.8)	0 (0.0)	1 (20.0)	0 (0.0)	2 (14.3)	0 (0.0)	0 (0.0)
Modified Rankin Scale score							
0–1	57 (75.0)	25 (73.5)	6 (85.7)	6 (100.0)	12 (75.0)	1 (100.0)	7 (58.3)
2–3	13 (17.1)	6 (17.6)	1 (14.3)	0 (0.0)	1 (6.3)	0 (0.0)	5 (41.7)
4–5	6 (7.9)	3 (8.8)	0 (0.0)	0 (0.0)	3 (18.8)	0 (0.0)	0 (0.0)
Abnormal muscular strength (MRC scale <60)[a,b]		5 (16.7)					
GDS scale ≥1[a]		18 (58.1)					
ONLS scale ≥1[a]		15 (44.1)					

Abbreviations: GBS = Guillain-Barré syndrome; GDS = Guillain-Barré Disability Scale; IQR = interquartile range; MRC = Medical Research Council; ONLS = Overall Neuropathy Limitations Scale; PNS = peripheral nervous system.
When not specified, results are n (%).
[a] Specific to GBS.
[b] 0: Complete paralysis; 1: minimal contraction; 2: active movement with gravity eliminated; 3: weak contraction against gravity; 4: active movement against gravity and resistance; 5 normal strength.

characterized as acute motor axonal neuropathy in most cases. This suggests that the type of ZIKV-related GBS may be influenced by geographical factors.[37] Frequency of poor outcomes was higher in our patients with GBS with ZIKV-RT-PCR positive in any fluid (plasma, urine, CSF). We compared outcome of GBS in our series with that of the GBS prospective cohort from the International GBS Outcome Study (IGOS)[38] (n = 909), comprising 78.7% of patients from Europe or America.[37] The proportion of patients who required mechanical ventilation in our series was higher (37.5%) than in the IGOS cohort (19%).[37] Diabetes mellitus, a factor classically considered as predictor of respiratory

Table 5 Logistic regression analysis model predicting long-term residual disability (modified Rankin Scale ≥2) or death

	All patients (n = 78)				Isolated GBS (n = 35)			
	N	N (%)	Crude OR (95% CI)	*p*	N	N (%)	Crude OR (95% CI)	*p*
Sex								
Male	38	8 (21.1)	1		20	5 (25.0)	1	
Female	40	13 (32.5)	1.81 (0.65–5.02)	0.257	15	5 (33.3)	1.50 (0.34–6.56)	0.590
Age at acute phase, y								
<50	36	5 (13.9)	1		12	1 (8.3)	1	
≥50	42	16 (38.1)	3.82 (1.23–11.83)	0.020	23	9 (39.1)	7.07 (0.77–64.58)	0.083
Diabetes mellitus								
No	67	16 (23.9)	1		27	7 (25.9)	1	
Yes	11	5 (45.5)	2.66 (0.72–9.87)	0.145	8	3 (37.5)	1.71 (0.32–9.11)	0.527
Dengue IgG								
Negative	4	1 (25.0)	1		0	—	Nonestimable as all patients are dengue-positive	
Positive	67	18 (26.9)	1.10 (0.11–11.29)	0.935	35	10 (28.6)		
Time between neurologic manifestations and admission, d								
≤2	36	11 (30.6)	1		11	2 (18.2)	1	
>2	42	10 (23.8)	0.71 (0.26–1.94)	0.504	24	8 (33.3)	2.25 (0.39–12.97)	0.364
Need for mechanical ventilation								
No	59	11 (18.6)	1		22	4 (18.2)	1	
Yes	19	10 (52.6)	4.85 (1.59–14.77)	0.005	13	6 (46.2)	3.86 (0.83–17.94)	0.085
Duration of hospital stay, d								
<10	32	4 (12.5)	1		10	1 (10.0)	1	
≥10	46	17 (37.0)	4.10 (1.23–13.72)	0.022	25	9 (36.0)	5.06 (0.55–46.68)	0.152
ZIKV RT-PCR[a]								
Negative	21	1 (4.8)	1		12	0 (0.0)	1	
Positive	57	20 (35.1)	10.81 (1.35–86.60)	0.025	23	10 (43.5)	11.44 (1.57–∞)	0.013
Modified Rankin Scale								
1	18	1 (5.6)	0.21 (0.02–1.88)	0.161	3	0 (0.0)	0.00 (0.00–∞)	0.999
2–3	27	6 (22.2)	1		11	2 (18.2)	1	
4–5	33	14 (42.4)	2.58 (0.83–8.06)	0.103	21	8 (38.1)	2.77 (0.47–16.21)	0.259
Neurologic symptoms								
PNS only	48	11 (22.9)	1					
CNS only	17	4 (23.5)	1.04 (0.28–3.83)	0.959				
Mixed disorder	13	6 (46.2)	2.88 (0.80–10.38)	0.105				
Isolated GBS								
No	43	11 (25.6)	1					
Yes	35	10 (28.6)	1.16 (0.43–3.17)	0.767				

Continued

Table 5 Logistic regression analysis model predicting long-term residual disability (modified Rankin Scale ≥2) or death *(continued)*

	All patients (n = 78)				Isolated GBS (n = 35)			
	N	N (%)	Crude OR (95% CI)	*p*	N	N (%)	Crude OR (95% CI)	*p*
GDS[b]								
1					2	0 (0.0)	0.00 (0.00–∞)	0.999
2–3					15	4 (26.7)	1	
4–5					18	6 (33.3)	1.38 (0.31–6.20)	0.679

Abbreviations: CI = confidence interval; GBS = Guillain-Barré syndrome; GDS = Guillain-Barré Disability Scale; IgG = immunoglobulin G; OR = odds ratio; PNS = peripheral nervous system; RT-PCR = reverse transcription PCR; ZIKV = Zika virus.
[a] RT-PCR: positive for ZIKV in urine, plasma, or CSF.
[b] Specific to GBS.

failure in GBS,[39] increased the risk of mechanical ventilation in our GBS group. Despite the fact that they were more frequently ventilated, the proportion of our patients with GBS who died (2.5% vs 6.7%) or remained unable to walk after 9–12 months (8.8% vs 19.3%) was lower than that observed in the IGOS cohort.[37] Because of the relative small size of our sample (n = 35), referral bias, differences in hospital level practices, and the potential influence of geographic factors, studies in larger cohorts of GBS—ideally comparing ZIKV-infected individuals and non-ZIKV matched controls—are needed to definitely establish whether the predictors of poor outcome and the prognosis of GBS are influenced by the related ZIKV infection.

We identified several ZIKV cases with isolated cranial nerve involvement (9.2%). Our series thus reveals isolated unilateral or bilateral facial palsy (4.6%) or isolated multiple cranial nerve palsy (4.6%) is part of the neuroZika spectrum. Of note, infections represent about 10% of all causes of multiple cranial nerve palsies and are notably associated with *Mycoplasma pneumoniae* infections in children.[40] ZIKV should also be considered as a possible cause of cranial nerve palsies in areas concerned by ZIKV circulation, particularly in cases of facial or multiple cranial nerve palsies. Evidence of contrast enhancement on MRI may be a useful clue to the diagnosis in this setting.[10,41]

Consistent with previous studies,[14,15,42] we identified 6 cases of ZIKV-associated sensory polyneuropathies or acute polyneuritis, which we classified here as "other peripheral manifestations." Our isolated cases of peripheral manifestations resemble those from Nascimento et al.[15] and do Rosário et al.,[42] and may reflect a very mild form of GBS that does not fill the criteria. By contrast, our cases differ from the case report of Medina et al.[14] as they had a normal EMG. Sensory manifestations (paresthesia, ataxia, neuropathic pain) persisted in 3 of them 14 months after the acute phase.

CNS disorders identified in our population included encephalitis, myelitis, encephalomyelitis (20.7%), and stroke (1.1%). The proportion of encephalitis was similar to that observed in a previous prospective series.[10] In our study, the presence of the viral genome in the CSF in 5 cases with CNS manifestations strongly suggests ZIKV neuroinvasion in these cases. In the present study, 2 cases with lesions involving both the brain subcortical and central white matter, corpus callosum, cerebellum, brainstem, and the spine fulfilled radiologic criteria of acute disseminated encephalomyelitis (ADEM),[43] suggesting that an autoimmune mechanism may also contribute to CNS manifestations of ZIKV. However, the median delay of 4 days between infectious signs and neurologic manifestations was shorter than the 3 weeks that would have been expected in typical ADEM[44] and the high cell count in CSF (180 with 88% neutrophils) in one case would not be consistent with ADEM.

In our series, 14 cases presented with mixed CNS and PNS disorders, mostly in the form of acute polyradiculoneuropathy associated with myelitis or encephalitis. Myeloradiculitis has previously been reported as a complication of West Nile,[44] chikungunya infections,[11] and coinfections of ZIKV and chikungunya.[11] Our results suggest that ZIKV alone may simultaneously affect the CNS and PNS, raising the possibility that a combination of direct infection or autoimmunity may underlie some of the clinical patterns that are emerging. The presence of contrast enhancement of lumbar roots and cranial nerve in 4 of our cases as early reported[41] is a similar finding to what has been observed in West Nile virus infection. This supports the hypothesis of neuroinvasion as a mechanism for ZIKV in at least some of the postnatal infections. Our findings are also important for clinical practice. The detection of mixed disorders should prompt the clinician to perform MRI brain and spinal cord imaging in GBS with ZIKV infection as the identification of additional CNS involvement.

We found a proportion of 48% of patients presenting ZIKV typical viral symptoms in our neuroZika cohort (42 out of 87 patients), which is in line with the rate of symptomatic Zika in uncomplicated Zika infection.[45–47] It has been proposed that

immunization for dengue virus induced greater ZIKV replication, thereby enhancing the severity of ZIKV infection.[5,48,49] In our neuroZika group, we found that 92.5% (74 of 80) of patients had anti-dengue IgG. This high rate is comparable to the background rate of dengue IgG of 93.5% (91.5; 95.1) in adult blood donors of Guadeloupe and Martinique in 2011.[49] In addition, our univariate analysis shows that dengue IgG changed neither the risk of mechanical ventilation nor disability or death outcome, suggesting that past dengue is unlikely to be a predictor of severity and poor outcome. Because of the small size of our neuroZika group, further studies are needed to investigate the possible influence of past arboviral infections on the course of neuroZika.

During an epidemic or in endemic regions, ZIKV testing in urine, plasma, and CSF should be considered in the diagnostic workup of peripheral, CNS and PNS, acute or subacute neurologic manifestations in both adults and children, including those with facial or multiple cranial nerve palsies. A positive ZIKV RT-PCR in any fluid was the best predictor of severity in our series, as all patients requiring mechanical ventilation were positive and positive RT-PCR was the sole predictor of long-term sequelae.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix *(continued)*

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