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Clinical and nerve conduction features in Guillain−Barré syndrome associated with Zika virus infection in Ccuta, Colombia

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Abstract

Background and purpose

Zika virus (ZIKV) infection has been associated with an increased incidence of Guillain−Barré syndrome (GBS) but the relative frequency of acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and axonal GBS subtypes is controversial.

Methods

Twenty GBS patients diagnosed according to the Brighton criteria during the ZIKV outbreak in Cúcuta, Colombia, were evaluated clinically and electrophysiologically. The electrodiagnosis of GBS subtypes was made according to a recently described criteria set that demonstrated a high diagnostic accuracy on the basis of a single test. The electrophysiological features of 34 Italian AIDP patients were used as control.

Results

All patients had symptoms compatible with ZIKV infection before the onset of GBS and ZIKV infection was laboratory confirmed through a plaque reduction neutralization test ($PRNT_{90}$) in 100% of patients. The median time from onset of ZIKV infection symptoms to GBS was 5 days (interquartile range 1–6 days). Cranial nerve palsy was present in 85% of patients (facial palsy in 75%, bulbar nerve involvement in 60%), autonomic dysfunction in 85%, and 50% of patients required invasive mechanical ventilation. AIDP was diagnosed in 70% of patients. 40% of nerves of AIDP patients showed a prevalent distal demyelinating involvement but this pattern was not different from the Italian AIDP patients without ZIKV infection.

Conclusions

Guillain−Barré syndrome associated with ZIKV infection in Cúcuta is characterized by a high frequency of cranial nerve involvement, autonomic dysfunction and requirement of mechanical ventilation indicating an aggressive and severe course. AIDP is the most frequent electrophysiological subtype. Demyelination is prevalent distally but this pattern is not specific for ZIKV infection.

Introduction

Zika virus (ZIKV) infection was declared a Public Health Emergency of International Concern on 1 February 2016 [1]. By October 2016, 67 countries reported autochthonous transmission of the ZIKV since 2015, and 27 of these countries reported cases of congenital brain abnormalities, Guillain−Barré syndrome (GBS) or both [2]. The worldwide incidence of GBS is 0.8–1.89 cases per 100 000 persons-year [3]. However, during the ZIKV outbreak in French Polynesia a 20-fold increase in GBS incidence was observed compared with the previous 4 years and in seven countries of Tropical and Caribbean America the incidence increased from 2 to 9.8 times [4, 5].

Guillain−Barré syndrome is an immune-mediated neuropathy characterized, in the classical form, by a rapidly progressive symmetrical weakness and areflexia but the term includes also several variants and subtypes distinguished by the distribution of weakness in the limbs or cranial-nerve-innervated muscles [6, 7]. On the basis of underlying pathophysiology GBS is classified into acute inflammatory demyelinating polyneuropathy (AIDP) and axonal GBS: acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy. GBS is commonly triggered by infections or vaccinations, and the most frequently (30%) associated pathogen is *Campylobacter jejuni*. There is evidence of a molecular mimicry mechanism between the *C. jejuni* lipo-oligosaccharide and the peripheral-nerve gangliosides triggering autoantibodies and inducing the axonal subtypes of GBS [6].

The World Health Organization stated in March 2016 that there is 'scientific consensus that ZIKV is a cause of microcephaly and GBS' but the causal relationship and the pathophysiology of these disorders are still unknown [8].

Electrophysiology plays an important role in supporting the diagnosis of GBS and, taking into account the possible pitfalls and applying the appropriate electrodiagnostic criteria, indicates which component of the peripheral nerve is primarily damaged allowing an appropriate classification into demyelinating and axonal subtypes [9-11]. Electrophysiological studies in ZIKV associated GBS have provided contradictory conclusions. Studies from French Polynesia concluded that the electrophysiological findings were compatible with AMAN in all patients whereas in one series from Colombia the majority of patients had AIDP [4, 12, 13]. Here the clinical and electrophysiological features of 20 GBS patients evaluated

during the ZIKV outbreak in Cúcuta, Colombia, are described and the results are discussed in comparison with what has been previously reported.

Methods

Study population and design

Twenty patients with a diagnosis of GBS according to the Brighton Collaboration GBS Working Group criteria (Table S1) associated with ZIKV disease were retrospectively evaluated 14. All patients were recruited from different healthcare centers in Cúcuta, Santander, Colombia. The study period was from the epidemiological week 40, 2015 (11–17 October), to epidemiological week 30, 2016 (24–30 July). Some features of these patients have already been reported 15. The onset of ZIKV infection was defined as the day of onset of systemic symptoms and the onset of GBS symptoms as the first day of neurological symptoms.

Laboratory studies

Sera from the 20 convalescent patients were tested within a median of 96.5 days [interquartile range (IQR) 69–132] after the onset of GBS. Immunoglobulin G (IgG) and IgM antibodies against ZIKV were detected using a standardized enzyme-linked immunosorbent assay (ELISA). IgG antibodies against ZIKV were also detected using an indirect immunofluorescence (IFI) assay and a plaque reduction neutralization test ($PRNT_{90}$). Details of the methodology are reported in the Supporting information. Since Cúcuta is one of the most affected regions of Colombia for arboviruses 16, IgG and IgM against dengue and chikungunya viruses were also quantified using an ELISA from respectively Vircell (Granada, Spain) and Abcam (Cambridge, UK). Additionally, IgG against chikungunya virus and each of the four serotypes of dengue virus were assayed on serum samples using an IFI assay (Euroimmun, Luebeck, Germany).

Electrophysiological studies and electrodiagnostic criteria

Nerve conduction studies were performed with a median interval from GBS onset of 106 days (IQR 29–138) according to standardized techniques. Details of the methods are reported in the Supporting information. In three patients nerve conduction studies were repeated with an interval of 111–114 days from the first study. For the electrodiagnosis of GBS subtypes a recently reported criteria set (Table 1) was employed that at first study and in a cohort with a balanced number of AIDP and axonal GBS patients showed the highest diagnostic accuracy 11. To investigate whether in AIDP nerves there was a prevalent involvement of distal or intermediate nerve segments the criteria reported in Table 2 were employed. The control group was 34 Italian AIDP patients diagnosed, according to the criteria reported in Table 1, at the University Hospital of Chieti and with a median interval from disease onset and electrophysiological test of 28 days (IQR 13.5–34.2). These patients

had no IgG antibodies to gangliosides GM1, GM1b, GD1a, GalNAcGD1a, GD1b, GT1a and GQ1b.

Table 1. Criteria set employed for electrodiagnosis of GBS subtypes

AIDP	AMAN	AMSAN	Unexcitable	Equivocal
At least one of the following in at least two nerves: MCV < 70% LLN DML > 130% ULN dCMAP duration > 120% ULN pCMAP/dCMAP duration ratio > 130% F response latency > 120% ULN Or one of the above in one nerve, plus: absent F waves in two nerves with dCMAP >20% LLN abnormal ulnar SNAP amplitude and normal sural SNAP amplitude	None of the AIDP features in any nerve (demyelinating features allowed in one nerve if dCMAP <20% LLN) And at least one of the following in each of two nerves: dCMAP < 80% LLN pCMAP/dCMAP amplitude ratio < 0.7 (excluding tibial nerve) isolated F wave absence (or <20% persistence)	Same criteria as AMAN in motor nerves, plus: SNAP amplitudes <50% LLN in at least two nerves	Distal CMAP absent in all nerves (or present in only one with distal CMAP <10% LLN)	Abnormal findings not, however, fitting criteria specific for other subtypes

AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor and sensory axonal neuropathy; CMAP, compound muscle action potential; dCMAP, distal compound muscle action potential; DML, distal motor latency; GBS, Guillain−Barré syndrome; LLN, lower limit of normal; MCV, motor conduction velocity; pCMAP/dCMAP, ratio between proximal and distal amplitude compound muscle action potential; SNAP, sensory nerve action potential; ULN, upper limit of normal.

Table 2. Criteria employed to define the pattern of prevalent demyelinating involvement in nerve segments

Distal	Intermediate	Diffuse	Unclassifiable

Distal	Intermediate	Diffuse	Unclassifiable
DML > 130% ULN and/or dCMAP duration > 120% ULN *and* MCV > 70% LLN and pCMAP/dCMAP duration ratio < 130%	MCV < 70% LLN and/or pCMAP/dCMAP duration ratio > 130% *and* DML < 130% ULN and dCMAP duration < 120% ULN	DML > 130% ULN and/or dCMAP duration > 120% ULN *and* MCV < 70% LLN and/or pCMAP/dCMAP duration ratio > 130%	Normal nerve, unexcitable nerve or that does not reach the cut-offs for demyelination in distal and/or intermediate nerve segments

DML, distal motor latency; LLN, lower limit of normal; MCV, motor conduction velocity; pCMAP/dCMAP, ratio between proximal and distal amplitude compound muscle action potential; ULN, upper limit of normal.

Statistical analysis

Univariate analysis was applied to determine the distribution of clinical and electrodiagnostic findings. Generalized additive models were used to estimate the $PRNT_{90}$. Statistical analysis was performed in the R statistical software version 3.3.2 [17]. The chi-squared test was employed to determine statistically significant differences between Colombian and Italian AIDP patients. A *P* value <0.05 was considered statistically significant.

Ethical approval

This study was performed in compliance with Act 008430/1993 of the Ministry of Health of the Republic of Colombia, which classified it as minimal-risk research. All patients agreed to participate in the study by signing the informed consent document. The institutional review board of the Universidad del Rosario approved the study design.

Results

Demographic characteristics, clinical features and electrodiagnosis of GBS subtypes are summarized in Tables 3 and 4. The main individual findings are reported in Table S2.

Table 3. Demographic and clinical characteristics of 20 patients with Guillain−Barré syndrome and previous Zika virus infection

Characteristics	*n* (%), median (IQR)
Female	13 (65)
Age (years)	42 (27.0–50.7)
ZIKV infection symptoms	
Fever	15 (75)
Rash	16 (80)
Arthralgia	15 (75)
Conjunctivitis	12 (60)
Previous ZIKV infection	
Epidemiological link	20 (100)
$PRNT_{90}$ ≥ 128 and positive IgG against ZIKV	20 (100)
Interval from onset of ZIKV infection symptoms and onset of GBS (days)	5 (1–6)
GBS diagnostic certainty according to Brighton criteria	
Level 1	6 (30)
Level 2	14 (70)
Level 3	0

GBS, Guillain−Barré syndrome; IgG, immunoglobulin G; PRNT, plaque reduction neutralization test; ZIKV, Zika virus.

Table 4. Clinical and electrodiagnostic findings of 20 patients with Guillain−Barré syndrome and previous ZIKV infection

Neurological features, *n* (%)	
Symmetrical weakness	19 (95)
Lower limb weakness	20 (100)
Upper limb weakness	19 (95)
Symmetrical areflexia	20 (100)
Areflexia or reduced reflexes lower limbs	20 (100)
Areflexia or reduced reflexes upper limbs	18 (90)
Paresthesias	18 (90)
Cranial neuropathies	
Any	17 (85)
Oculomotor nerve (III)	1 (5)

Facial nerve (VII)	15 (75)
Bulbar nerves (IX, X)	12 (60)
Dysautonomia	
Any	17 (85)
Blood pressure variability	15 (75)
Arrhythmia	7 (35)
Pupillary dysfunction	1 (5)
Diaphoresis	4 (20)
Bladder dysfunction	9 (45)
Ileus	7 (35)
Severity	
ICU admission	16 (80)
Respiratory failure	12 (60)
Invasive mechanical ventilation	10 (50)
Non invasive mechanical ventilation	2 (10)
Hughes' disability scale at hospital leave	
1	1 (5)
2	3 (15)
3	3 (15)
4	12 (60)
5	1 (5)
6	0 (0)
Treatment	
None	3 (15)
Intravenous immunoglobulin	16 (80)
Plasmapheresis	0 (0)
Intravenous immunoglobulin and plasmapheresis	1 (5.0)
GBS subtypes	
Acute inflammatory demyelinatiing polyradiculoneuropathy	14 (70.0)
Acute motor axonal neuropathy	0 (0)
Acute motor and sensiry axonal neuropathy	1 (5.0)
Equivocal	3 (15.0)
Unexcitable	1 (5.0)
Normal	1 (5.0)

GBS, Guillain−Barré syndrome; ICU, intensive care unit; ZIKV, Zika virus.

Zika virus and other arbovirus infections

All 20 patients had a history of ZIKV infection preceding the onset of GBS. The most frequent symptoms of ZIKV infection were fever, rash and arthralgia (Table 3). All patients had neutralizing antibodies by $PRNT_{90}$ with a titre ≥128 and IgG antibodies for ZIKV by ELISA and IFI assay. IgM against ZIKV by ELISA was found in one patient.

Concerning other arboviruses, all patients were positive for IgG anti-dengue virus, whereas only 20% were positive for IgM antibodies; 70% of patients were positive for IgG anti-chikungunya virus and none had IgM antibodies.

Neurological features and cerebrospinal fluid examination

The median time interval between the onset of the ZIKV infection and the onset of GBS was 5 days (IQR 1–6). Clinical presentation was characterized by rapidly progressive bilateral symmetrical weakness and paresthesias (Tables 4 and S2). A high percentage (85%) of patients had cranial nerve involvement: 75% had facial palsy and 60% swallowing difficulties. Because of Colombian guidelines for GBS treatment the great majority of patients were admitted to the intensive care unit and 50% of patients required invasive mechanical ventilation. Autonomic dysfunction was present during the disease course in 85% of

patients. Median hospitalization time was 31 days (IQR 12–42) and at hospital leave 65% of patients were bedridden or chair bound (grades 4 and 5 of the GBS disability scale) [18].

Cerebrospinal fluid analysis was performed in seven patients (35%). Albuminocytological dissociation, indicated by increased protein levels (>52 mg per decilitre) in the absence of pleocytosis (<50 cells/mm^3), was present in six patients.

Treatment

Treatment consisted of intravenous immunoglobulins in 80% of patients. One patient received immunoglobulins and plasmapheresis. Twelve patients received treatment within 7 days from the onset of neurological symptoms and five patients after 7 days.

Electrodiagnosis

Acute inflammatory demyelinating polyradiculoneuropathy was diagnosed in 14 (70%) patients. Acute motor and sensory axonal neuropathy was diagnosed in only one patient by a study performed 67 days after onset. One patient had a normal study 7 days after onset, another had unexcitable nerves and three patients had an equivocal pattern. In AIDP patients 81 nerves were classified according to the prevalent electrophysiological pattern of demyelination (Table 5). The most frequent pattern was distal (40.7%), followed by the diffuse (14.8%) and intermediate (4.9%) patterns. 39.5% of nerves were normal, unexcitable or did not reach the cut-offs required for demyelination and were unclassifiable. However, the frequencies of patterns did not differ from the frequencies obtained in 142 nerves of 34 Italian AIDP patients (Table 5, chi-squared test).

Table 5. Pattern of prevalent segmental nerve involvement in 14 AIDP patients associated with ZIKV infection and in 34 Italian AIDP patients

	ZIKV associated AIDP *n* (%)	**Italian AIDP *n* (%)**
Nerves	81	142
Distal	33 (40.7)	68 (47.8)
Intermediate	4 (4.9)	5 (3.5)
Diffuse	12 (14.8)	19 (13.4)
Unclassifiable	32 (39.5)	50 (35.2)

AIDP, acute inflammatory demyelinating polyradiculoneuropathy; ZIKV, Zika virus.

In three AIDP patients electrophysiology was repeated with an interval of 111–114 days and the distal demyelinating involvement, albeit improved, was still evident in at least two motor nerves.

Discussion

The incidence of GBS in Cúcuta increased 4.4 times during the ZIKV outbreak [15]. In the patients reported here the median interval between ZIKV infection and the onset of neurological symptoms was 5 days, similar to the interval reported in a larger Colombian cohort in which 48% of patients had an onset of neurological symptoms during the viral syndrome associated with the ZIKV infection [13]. This para-infectious onset seems to be too rapid to represent an autoimmune reaction to a first exposure to a virus and is different from the post-infectious profile described in classical GBS usually developing up to 4 weeks after an infection [19]. The reason for the para-infectious onset is uncertain but a hyperacute immune response, possibly favoured by previous infections (e.g. other flaviviruses) or a direct viral neuropathogenic mechanism could be hypothesized.

In the cohort reported here the frequency of cranial nerve involvement (85%) and the need for invasive mechanical ventilation (50%) are higher than in a large European GBS cohort (36% and 28%, respectively) [20]. Facial palsy (often bilateral) is a characteristic feature of ZIKV associated GBS, being present in 75% of patients reported here and described in up to 79% of French Polynesian patients [4]. Autonomic dysfunction and especially the potentially life threating blood pressure instability and arrhythmia were also frequent in the cohort reported here and dysautonomia was identified as the main risk factor of poor prognosis in a previous analysis from Cúcuta [15]. Although there are still no conclusive data about the burden of GBS associated with the ZIKV outbreak in Colombia, this is estimated to be relevant because of the high rate of respiratory failure, dysautonomia or medical complications [21]. Overall GBS associated with ZIKV infection seems, at least in Cúcuta, to have an aggressive and severe course that should be carefully monitored.

The electrophysiological results were consistent with the AIDP subtype in 70% of patients similarly to the percentages reported in Colombian and Brazilian cohorts and in contrast with the AMAN diagnosis in all the patients from French Polynesia [4, 12, 13, 22]. The different pathological and electrophysiological GBS subtypes may be due to mutations of the virus spreading from the South Pacific to America or to different host-dependent factors in the two geographic areas. Anyway, a simpler explanation can be hypothesized by examining the electrophysiological data. In the two reports from the French Polynesia, 37 patients were studied in the first week of disease and at 4 months [4, 12]. The mean electrophysiological values were reported but not the classification of individual patients. In the first week mean distal motor latencies (DMLs) were greatly increased (203%–335% of the upper limit of normal, ULN). The mean distal compound muscle action potential (CMAP) duration was also increased (128%–155% of ULN, with individual values up to 320% of ULN) [12]. No conduction block or substantial mean conduction slowing in the intermediate nerve segments was

reported (although the lowest reported conduction velocities ranged from 24.7 m/s to 29.9 m/s) 12. Studies repeated at 4 months in 19 patients showed an improvement of mean CMAP amplitudes but DMLs remained substantially prolonged. The authors concluded that the electrophysiology was consistent with AMAN with reversible conduction failure prevalently of distal nerve segments 4, 12. The diagnosis of AMAN was reinforced, according to the authors, by the not significantly decreased mean sensory nerve action potential (SNAP) amplitudes of radial and sural nerves although the lower limits of the range of values reported were decreased and 83% of patients had paresthesias.

In our opinion the greatly increased values of DMLs and distal CMAP duration reported in the French Polynesian cohort are indeed more in line with a de-remyelinating process as in AIDP. AMAN with reversible conduction failure is characterized by recovery within a few weeks of slightly prolonged DMLs, conduction slowing, reduced distal CMAP amplitudes and conduction block in intermediate nerve segments without the development of excessive temporal dispersion of CMAPs 9-11. Moreover the 'normal' radial and sural SNAP amplitudes in most patients of the French Polynesian cohort can be explained by the fact that in AIDP these nerves, when tested in intermediate segments, are usually less affected than the distal segments of median and ulnar sensory nerves 23. Overall, although the French Polynesian data do not allow the classification into subtypes of the individual patients, it is deemed that most patients actually had AIDP.

In our cohort 40% of nerves had evidence of prevalent distal demyelination. However, a similar pattern was found in Italian AIDP patients not associated with ZIKV infection indicating that the prevalently distal pattern is not specific and re-emphasizing the well-known notion that in AIDP the distal nerve terminals, where the blood–nerve barrier is deficient, are preferentially affected. Finally, to corroborate our opinion is the only histopathological evaluation of peripheral nerves reported that shows demyelination and mononuclear cell inflammation with some axonal degeneration consistent with the classical AIDP picture 24, 25.

One limit of our study was that the interval elapsed between GBS onset and the electrodiagnostic test was very variable. Nonetheless, as the great majority of cases were AIDP, the characteristic electrophysiological features were clearly evident even at long intervals from disease onset.

In conclusion GBS associated with ZIKV infection in Cúcuta shows an aggressive and severe course and is mostly demyelinating in nature just as GBS associated with other flavivirus infections 26. Extensive data acquisition and, when possible, serial studies are recommended for a better understanding of the pathogenesis of GBS associated with ZIKV infection through electrophysiology. These should be followed by the electrodiagnostic characterization of the individual patient rather than cohort analysis, which is likely to introduce inaccuracies in the conclusions.

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Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Filename	Description
ene13552-sup-0001-TableS1-S2.docx Word document, 58.6 KB	**Table S1.** Level of certainty of Brighton criteria for the diagnosis of Guillain−Barré syndrome.**Table S2.** Demographic data**,** main clinical features and electrophysiological findings of patients with Guillain−Barré syndrome associated with ZIKV infection.

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References

1 Sharma S, Tandel K, Dash PK, *et al*. Zika virus: a public health threat. *J Med Virol* 2017; **89**: 1693–1699.

2 World Health Organization. Situation report. Zika virus, microcephaly, Guillain−Barré syndrome 20 October 2016; 2016. http://apps.who.int/iris/bitstream/10665/250590/1/zikasitrep20Oct16-eng.pdf (accessed 01/06/2017).

3 Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain−Barré syndrome: a systematic review and meta-analysis. *Neuroepidemiology* 2011; **36**: 123– 133.

4 Cao-Lormeau V, Blake A, Mons S, *et al*. Guillain−Barré syndrome outbreak associated with Zika virus infection in French Polynesia: a case−control study. *Lancet* 2016; **387**: 153– 159.

5 Dos Santos T, Rodriguez A, Almiron M, *et al*. Zika virus and the Guillain−Barré syndrome − case series from seven countries. *N Engl J Med* 2016; **375**: 1598– 1601.

6 Yuki N, Hartung HP. Guillain−Barré syndrome. *N Engl J Med* 2012; **366**: 2294– 2304.

7 Wakerley BR, Uncini A, Yuki N, the GBS Classification Group. Guillain−Barré and Miller Fisher syndromes new diagnostic classification. *Nat Rev Neurol* 2014; **10**: 537– 544.

8 World Health Organization. Zika situation report. Zika virus, microcephaly and Guillain−Barré syndrome. 31 March 2016. http://www.who.int/emergencies/zika-virus/situation-report/31-march-2016/en/ (accessed 24/05/2017).

9 Uncini A, Manzoli C, Notturno F, Capasso M. Pitfalls in electrodiagnosis of Guillain−Barré syndrome subtypes. *J Neurol Neurosurg Psychiatry* 2010; **81**: 1157– 1163.

10 Uncini A, Kuwabara S. Electrodiagnostic criteria for Guillain−Barré syndrome: a critical revision and the need for an update. *Clin Neurophysiol* 2012; **123**: 1487– 1495.

11 Uncini A, Ippoliti L, Shahrizaila N, Sekiguchi Y, Kuwabara S. Optimizing the electrodiagnostic accuracy in Guillain−Barré syndrome subtypes: criteria sets and sparse linear discriminant analysis. *Clin Neurophysiol* 2017; **128**: 1176– 1183.

12 Watrin L, Ghawché F, Larre P, *et al*. Guillain−Barré syndrome (42 cases) occurring during a Zika virus outbreak in French Polynesia. *Medicine (Baltimore)* 2016; **95**: e3257.

13 Parra B, Lizarazo J, Jiménez-Arango JA, *et al*. Guillain−Barré syndrome associated with Zika virus infection in Colombia. *N Engl J Med* 2016; **375**: 1513– 1523.

14 Sejvar JJ, Kohl KS, Gidudu J, *et al*. Guillain−Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2011; **29**: 599– 612.

15 Anaya J-M, Rodríguez Y, Monsalve DM, *et al*. A comprehensive analysis and immunobiology of autoimmune neurological syndromes during the Zika virus outbreak in Cúcuta, Colombia. *J Autoimmun* 2017; **77**: 123– 138.

16 Padilla J, Rojas DP, Sáenz-Gómez R. Dengue en Colombia: epidemiología de la reemergencia a la hiperendemia. First edn, 2012. Bogota, Colombia, https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/INEC/INV/Dengue%20en%20Colombia.pdf
(accessed 22/05/2017).

17 R Core Team. A Language and Environment for Statistical Computing. Vienna, Austria: Foundation for Statistical Computing, 2016. https://www.R-project.org/ (accessed 05/06/2017).

18 Hughes RA, Newsom-Davis JM, Perkin GD, Pierce JM. Controlled trial prednisolone in acute polyneuropathy. *Lancet* 1978; **2**: 750– 753.

19 Hadden RD, Karch H, Hartung HP, *et al*. Preceding infections, immune factors, and outcome in Guillain−Barré syndrome. *Neurology* 2001; **56**: 758– 765.

20 Fokke C, van den Berg B, Drenthen J, *et al*. Diagnosis of Guillain−Barré syndrome and validation of Brighton criteria. *Brain* 2014; **137**: 33– 43.

21 Mahecha MP, Ojeda E, Vega DA, Sarmiento-Monroy JC, Anaya JM. Guillain−Barré syndrome in Colombia: where do we stand now? *Immunol Res* 2017; **65**: 72– 81.

22 Ferreira da Silva IR, Frontera JA, Bispo de Filippis AM, Moreira-do-Nascimento OJ. Neurologic complications associated with the Zika virus in Brazilian adults. *JAMA Neurol* 2017; **74**: 1190– 1198.

23 Al-Shekhlee A, Robinson J, Katirji B. Sensory sparing patterns and the sensory ratio in acute inflammatory demyelinating polyneuropathy. *Muscle Nerve* 2007; **35**: 246– 250.

24 Ritter JM, Martines RB, Zaki SR. Zika virus: pathology from the pandemic. *Arch Pathol Lab Med* 2017; **141**: 49– 59.

25 Asbury AK, Arnason BG, Adams RD. The inflammatory lesion in idiopathic polyneuritis. *Medicine* 1969; **48**: 173– 215.

26 Uncini A, Shahrizaila N, Kuwabara S. Zika virus infection and Guillain−Barré syndrome: a review focused on clinical and electrophysiological subtypes. *J Neurol Neurosurg Psychiatry* 2017; **88**: 266– 271.