



Case Report: Guillain-Barré Syndrome Secondary to Dengue Virus Infection in Northeast Mexico

**Fernando De la Garza-Salazar^{1*}, Fernando Góngora-Rivera^{1,2},
Hector Lopez-de la Garza¹, Emma Purón-González¹
and Jorge Alberto Hernandez-Portales¹**

¹*Department of Internal Medicine, Christus Muguerza Hospital Alta Especialidad, Universidad de Monterrey, Nuevo León, México.*

²*Department of the Neurology, Hospital Universitario José Eleuterio González, Universidad Autónoma de Nuevo León, Mexico.*

Authors' contributions

This work was carried out in collaboration between all authors. Author FDGS managed literature searches, wrote the first and final draft of the manuscript. Author FGR contributed to the writing and helped in the making of the final draft. Authors HLG, EPG and JAHP managed the literature searches and made manuscript corrections. All authors read and approved the final manuscript.

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Case Study

ABSTRACT

Aims: Dengue virus is a mosquito-borne viral disease that infects about 390 million people each year. The clinical manifestations are fever, arthralgia and myalgia. Guillain-Barré Syndrome (GBS) caused by dengue fever has been rarely reported.

Presentation of Case: A 46-year-old man with no relevant medical history was seen because of progressive quadriparesis, dysautonomia, dysphagia and facial paresis. Ten days before seeking medical care the patient had fever, myalgia, arthralgia, rash, thrombocytopenia, and a positive NS1 dengue antigen. GBS was suspected and immunoglobulin was started while nerve conduction studies confirmed an acute motor axonal polyradiculoneuropathy. According to Brighton criteria, the patient was classified with a level 2 diagnostic certainty, since it was decided to not perform

*Corresponding author: E-mail: fernandodelagarza@gmail.com;

lumbar puncture for CSF analysis. The patient had a good clinical response and was subsequently discharged.

Discussion: Dengue virus is arthropod-borne. It presents with high fever, rash, arthralgia, myalgia, and in rare cases, neurological complications such as GBS. In Mexico, there were 14,112 confirmed cases of non-severe dengue and 3,683 cases of severe dengue or with warning signs in 2016. There are no reported cases of GBS secondary to dengue infection in this country.

Conclusion: GBS following dengue fever should be considered in countries with a high incidence of dengue infection such as Mexico even if there are no previous manifestations of dengue fever.

Keywords: Guillain-Barré syndrome; dengue fever; flavivirus; neurological manifestations of dengue.

1. INTRODUCTION

Dengue virus causes a mosquito-borne viral disease that infects about 390 million people each year [1]. In Mexico, there were 14,112 confirmed cases of non-severe dengue and 3,683 cases of severe dengue or with warning signs in 2016. In the state of Nuevo Leon 1,373 confirmed cases of non-severe dengue and 65 cases of severe dengue or with warning signs were also reported in 2016 [2]. Clinical manifestations generally include a period of high fever accompanied by a maculopapular rash, arthralgia and myalgia. Some patients present severe complications such as respiratory distress syndrome, liver and renal failure, and neurological disorders. Few cases of Guillain-Barré syndrome (GBS) secondary to dengue fever have been reported and none have been reported in Mexico [3-8]. The following is a case of GBS secondary to dengue fever.

2. CASE REPORT

A 46-year-old man with no relevant medical history was seen because of lower limb weakness. The patient's symptoms began 10 days before with fever, myalgia, generalized arthralgia, conjunctival injection, and a generalized non-pruritic macular rash. He subsequently received medical treatment in a primary care unit where leukopenia, thrombocytopenia, and a positive NS1 dengue antigen were discovered. His symptoms improved after seven days with acetaminophen. Three days later, he experienced mild paresthesia in the palmoplantar areas accompanied by weakness in the lower limbs. On the day of admission, the patient had difficulty getting up from his bed. On physical examination, his vital signs were stable, and he was alert and oriented with a normal pupil reflex and preserved cranial nerve function. His muscle strength in the upper limbs was 4/5 and in the lower limbs 1/5. Deep tendon reflexes were

absent in the lower limbs and normal muscle reflexes were found in the upper limbs; there were no sensory abnormalities and the Babinski reflex was negative. Abdominal exploration revealed a distended bladder so a Foley catheter was inserted. The rest of the physical examination was normal.

Because of the patient's initial presentation and local epidemiology, the acute lower limb weakness and findings compatible with dysautonomia led to the consideration of common viral and bacterial diseases with an antigenic capacity that would lead to the appearance of an autoimmune neuropathy. Such is the case of Zika virus, dengue and Epstein-Barr virus (EBV) and infections caused by enterobacteria such as *Campylobacter jejuni* and *Yersinia pestis*. In this case, the patient had no gastrointestinal symptoms.

A complete blood count, biochemical profile, C-reactive protein, erythrocyte sedimentation rate and creatine phosphokinase were within normal range. Anti-zika IgG was positive and IgM negative. Anti-dengue IgG and IgM were positive. Antinuclear and heterophile antibodies were negative.

GBS was suspected as a first possible diagnostic consideration due to the patient's clinical characteristics, the compatible findings on physical examination and the serological results. Therapy was started for this condition and complementary diagnostic tests were also performed for confirmation.

The patient was treated with intravenous fluids, gastric protection and strict monitoring of vital signs. Immunoglobulin was started at 0.4 g/kg/day (30 g/day) at an infusion rate of 10 g/hour for 5 days. Nerve conduction studies confirmed an acute motor axonal polyradiculoneuropathy with an abolished H reflex and the absence of an F wave in the lower

and upper limbs. Anti-ganglioside antibodies (GD1b IgG, GD1b IgM and GQ1b IgG) were negative. According to Brighton criteria (Table 1) the patient was classified with a level 2 diagnostic certainty, since it was decided to not perform a lumbar puncture for CSF analysis. The patients' weakness increased causing dyspnea and dysphagia for liquids and solids, poor control of oral secretions, oxygen desaturation and heart rate variations. Because of this, the patient was transferred to the intensive care unit and managed with non-invasive ventilation (CPAP). In the following 72 hours, the motor and dysautonomic symptoms improved. Dysphagia and dyspnea disappeared and on the 10th day of hospitalization, the patient was discharged. A month and a half after discharge the patient was contacted and referred that he was ambulatory with minimal support and that facial muscle function had improved.

3. DISCUSSION

Dengue virus is a member of the Flaviviridae family. Vectors are female *Aedes aegypti* and *Aedes albopictus*, which have a wide geographic distribution and a preference for tropical and subtropical areas due to the characteristics of the life cycle of the mosquito. In recent years, the number of cases has increased with most epidemics developing in Asia and America [2]. In Mexico, confirmed cases of non-severe dengue and severe dengue or with warning signs have been reported with an incidence rate of 4.71. Also, cases of non-severe dengue and severe dengue or warning signs have been reported in the state of Nuevo Leon, but no cases of GBS associated with dengue fever [2]. There are four viral serotypes (1 to 4) classified according to the surface antigens. Mexico is a geographic area where all serotypes are found circulating at the same time. This is known as hyperendemicity, a transition that has caused local epidemics and high rates of dengue hemorrhagic fever and dengue shock syndrome [9]. All serotypes have the ability to cause serious manifestations although serotypes 2 and 3 have been most frequently associated with neurological symptoms. Exposure to a serotype confers lifelong immunity but heterotypic infection may occur [10]. This has even been associated with an increased likelihood of developing severe disease [11]. Clinical manifestations generally begin after an incubation period of 3 to 7 days. The first period of the disease includes high fever (up to 40°C), malaise, a maculopapular rash, arthralgia, myalgia, hepatomegaly, petechial

lesions, leukopenia, lymphopenia, thrombocytopenia, and moderate elevation of transaminases. Subsequently, a small subset of patients may enter a critical phase characterized by clinical manifestations suggestive of plasma leakage and hemorrhage. The third and last phase is spontaneous recovery, which lasts approximately 2-3 days with a gradual resolution of symptoms. There are several complications associated with dengue fever such as respiratory distress syndrome, bronchiolitis, liver failure, renal failure and various neurological complications [12]. The incidence of neurological involvement ranges from 0.5 to 6.2% according to different descriptive reports. There have been studies in humans that have shown an elevation of IgM against dengue virus in cerebrospinal fluid (CSF) as indirect evidence of viral neurotropism [13,14]; Viral invasion of CNS cells in mice has also been demonstrated. In a 2004 article, Carod *et al.* classified the neurological manifestations of dengue infection based on the form of presentation (Table 2) [12]. Among the neurological complications, encephalitis and encephalopathy represent 95%, although these manifestations are very infrequent. The most frequent manifestation of the peripheral nervous system, although extremely rare, is GBS [4]. GBS is characterized by acute, progressive flaccid paralysis that begins in the lower limbs and is accompanied by areflexia, and in some cases, cranial nerve palsy and sensorial and autonomic dysfunction [1]. The main pathophysiological mechanism of the disease begins with an immunological stimulus (usually an infection) that generates an aberrant immune response with the creation of autoantibodies directed against the myelin of the axons of Schwann cells, although other epitopes have also been described [15].

Diagnosis is based on clinical findings, cerebrospinal fluid (albumin-cytological dissociation) and nerve conduction studies [15]. The aforementioned are included in Brighton's criteria (Table 1), which in turn subclassifies patients into 4 groups according to the level of diagnostic certainty. The present case occupied level 2 since lumbar puncture was not performed but results were obtained from GBS compatible nerve conduction studies. The Brighton criteria have limitations given the heterogeneous nature of GBS and depending on the time elapsed since the onset of the disease and results of some complementary studies. According to a study conducted in the Netherlands with a cohort of 567 patients [16], there was a high variability in

the severity of limb weakness at the nadir of the disease. Using the Medical Research Council Sum Score, with a nadir median of 38 points and an interquartile range of 24-48 points; up to 9% had normal osteotendinous reflexes in affected limbs. All patients reached the nadir of the disease within the first 6 weeks; 474 (96%) patients underwent lumbar puncture, with the

Table 1. Brighton's diagnostic criteria

Diagnostic criteria	Level of diagnostic certainty			
	1	2	3	4
Bilateral and flaccid weakness of limbs	+	+	+	±
Decreased or absent deep tendon reflexes in weak limbs	+	+	+	±
Monophasic course and time between onset-nadir 12 hours to 28 days	+	+	+	±
CSF cell count <50/μl	+	+ ^a	-	±
CSF protein concentration >normal value	+	± ^a	-	±
NCS findings consistent with one of the subtypes of GBS	+	±	-	±
Absence of alternative diagnosis for weakness	+	+	+	+

(+): present; (-): absent; (±): present or absent.

NCS= nerve conduction studies; GBS= Guillain-Barré syndrome, CSF: cerebral spinal fluid.

^aif CSF is not collected or results not available, nerve electrophysiology results must be consistent with the diagnosis of GBS

Table 2. Definitions of complications associated with dengue proposed by Carod et al.

Highly suggestive or confirmed diagnosis of dengue as recommended by World Health Organization plus one of the following categories:

1. Dengue involvement of the CNS

At least one of the following: disruption of consciousness (for ages 5+ a Glasgow coma scale score ≤ 14 points), neck stiffness, neurological targeting or seizures.

1.1) Dengue encephalopathy

- Dengue with involvement of the CNS plus:
- Presence of any of the following complications: hepatic failure, metabolic acidosis, severe hyponatremia, prolonged shock, ICD, cerebral hemorrhage, and in addition:
- Normal CSF (in cerebral hemorrhage there may be erythrocytes present)

1.2) Dengue encephalitis

- Dengue with involvement of the CNS plus:
- Presence of RNA, IgM or NS1 in CSF and:
- CSF with pleocytosis without another neuroinvasive microorganism explaining it

1.3) Involvement of the immune mediated CNS

1.4) Unspecified CNS involvement

2. Dengue associated with neuromuscular complications

2.1) Guillain-Barre syndrome

2.2) Rhabdomyolysis

2.3) Other unspecified peripheral neuromuscular complications

3. Dengue associated with neurophthalmic complications

- One of the following clinical symptoms: blurred vision, phosphenes, myodesopsia, decreased visual acuity, scotomas, red eye, metamorphosis o micropsy and:
- Eye examination with at least one of the following: optic neuropathy (hyperemia or optic disc edema), maculopathy (edema or hemorrhages), retinal vasculitis, retinal hemorrhage, exudative retinal detachment, signs of uveitis or iridocyclitis
- Highly suspected dengue: positive IgM in serum or IgG positive sample in serum sample with titers of 1280 or more. Dengue confirmed: PCR positive; positive viral culture; seroconversion of IgM in matched samples; increased IgG >4 fold in paired samples.

Abbreviations: CNS: central nervous system, ICD: ischemic cerebrovascular disease, RNA: ribonucleic acid, PCR: protein chain reaction, NS1: non-structural protein 1

finding of a protein increase in CSF being dependent on the time elapsed since the onset of weakness (88% >14 days). Nerve conduction studies were performed in 440 (89%) patients, with acute demyelinating polyneuropathy being the predominant subtype, but only 48% met all diagnostic criteria. Finally, in the classification according to Brighton criteria, 61% occupied level 1, 33% level 2, and 6% level 4 of diagnostic certainty.

Two thirds of patients with GBS refer upper airway or gastrointestinal infections, generally associated with *Campylobacter jejuni* infection, although there are other microorganisms such as *Cytomegalovirus*, *Epstein-Barr virus*, *Mycoplasma pneumoniae*, *human immunodeficiency virus*, and *influenza virus* with a causal relationship [15]. Other flaviviruses have been linked to this rare complication, including Zika and chikungunya, whose incidence in countries like Mexico is increasing [17-19]. It is necessary to point out that cross-reactivity leads to false positive results in tests for dengue virus and other flaviviruses such as Zika. In this case, the positivity of NS1 antigen with a specificity of 98%, led to confirmation of infection with dengue virus. Even though GBS is an uncommon complication of dengue, the high incidence of dengue in countries like Mexico could increase the prevalence of this presentation. The presence of GBS should be suspected with a previous exposure to dengue virus, especially when an etiology is not clear even in the absence of classical symptoms suggesting a viral infection since 90.2% of infected individuals are asymptomatic [20].

4. CONCLUSION

GBS caused by dengue fever should be considered as a diagnostic possibility in countries with a high incidence of dengue infection, such as Mexico. It is also important to remember that even in the absence of classical dengue symptoms, GBS secondary to dengue fever can be possible. Early recognition and prompt treatment is crucial since patients can die from complications or suffer severe motor sequelae.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this paper.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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