

# Miller Fisher–Guillain–Barré overlap syndrome during the Zika Virus outbreak

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## Abstract

Miller Fisher is a variant of Guillain–Barré syndrome, presented mainly with ataxia, areflexia and ophthalmoplegia. After the 2016 Zika virus (ZIKV) outbreak, an association between Guillain–Barré syndrome and ZIKV was established. ZIKV is a mosquito–borne–flavivirus, considered a mild disease with symptoms including fever, rash, conjunctivitis, and arthralgia. Most of cases with ZIKV infection are asymptomatic, however in neurologic complications including Guillain–Barré syndrome, symptoms could evolve leading to fatalities. A case of Miller Fisher–Guillain–Barré overlap syndrome during the 2016 ZIKV outbreak is presented.

**Keywords:** *Miller Fisher–Guillain–Barré overlap syndrome, Miller Fisher variant, Guillain–Barré syndrome, Zika Virus infection, Puerto Rico*

## Introduction

Zika virus (ZIKV) is a mosquito–borne–flavivirus transmitted primarily by *Aedes* mosquitoes, considered a mild disease with symptoms including fever, rash, conjunctivitis, and arthralgia [1]. Most of cases with ZIKV infection are asymptomatic; however an increase of congenital defects, neurologic complications, severe thrombocytopenia, and fatal cases has been reported [2, 3].

After the ZIKV outbreak in the French Polynesia in 2013, an increase in neurologic symptoms compatible with Guillain–Barré

syndrome (GBS) were reported [3]. Similarly, on 2015 an increase in the number of cases with congenital defects and neurologic complications secondary to ZIKV were reported in the Americas [4]. GBS is considered an immune–mediated condition characterized by different degrees of weakness, sensory abnormalities, and autonomic dysfunction associated to damage of peripheral nerve or nerve root [1, 5]. While a good prognosis has been reported, nearly 20% of patients with GBS remain disabled, including patients with overlap variants [5].

Miller Fisher (MF), a rare variant of GBS, was first described in 1956 due to its unique clinical symptoms, including ophthalmoplegia, areflexia, and ataxia [3]. Geographic differences in MF have been noted; in Western countries MF comprises 1–5% of GBS cases compared to 19% of GBS cases in Asian countries. Like GBS, MF cases are predominantly male, and incidence increases

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with age [5]. Most patients recover within several weeks or months, while < 5% are fatal cases [5, 6]. While MF has been described a unique triad of symptoms, other neurologic signs has been reported including overlapping with other variants of GBS [6].

This is the case of a 49-year-old man admitted to the Intensive Care Unit (ICU) with Miller Fisher–Guillain–Barré overlap syndrome (MF/GBS) during the 2016 ZIKV epidemic in Puerto Rico.

## Case Report

On early 2016, a 49-year-old man presented to the emergency room (ER) with double vision, bilateral facial paralysis, ataxic gait, ascending weakness, and difficulty walking properly. Past medical history includes diabetes mellitus, and hyperlipidemia; he denied toxic habits, vaccines, contact with a sick person, or recent travel.

On day 0 the patient described unquantified fever, redness of eyes, and arthralgia. On day 1 of symptoms, he visited an ER where he was diagnosed with a possible viral syndrome; an antibiotic was prescribed for 5 days and was discharge home. Illness symptoms resolved within the first 4 days; however on day 4 the patient started feeling swelling and tingling sensation in feet, arms and back. He visited another ER; a pain medication was prescribed, and was discharged home. From day 5 to 6, he developed headache, poor vision, numbness on bilateral upper and lower extremities, heaviness sensation in legs, and pain on the right side of the body. On day 6, a facial deviation (right side) was presented. On day 8, he went to another ER with the above symptoms; moreover he presented dysarthria. Laboratories, chest radiography, and a head computational tomography were done with normal findings; orphenadrine and opioids were ordered, and was discharge home. On day 14, he visited an outpatient clinic and was referred to a neurologist. On day 16 patient returns to an ER with double vision, mild slurred speech, bilateral facial paralysis, ataxia, areflexia, and ascending weakness. He was transferred to our institution to be evaluated by a neurologist.

Upon admission, body temperature was 36.1° C, blood pressure 143/104 mmHg, pulse 76 beats per minute, respiratory rate of 18 breaths per minute. On physical examination, patient was acutely ill, awake, alert, and oriented. System review was remarkable for diplopia, ataxic gait, poor coordination, and ascending weakness. On neurologic examination patient had bilateral facial weakness with a prominence in the left side as compared with right side, decreased sensation in left trigeminal nerve, including ophthalmic, maxillary, and mandibular nerves (V1–V3), and left cranial nerve VI paralysis. Motor strength was slightly diminished on upper extremities (5-/5), except triceps with slightly greater weakness (4+/5); in lower extremities mild weakness (4/5) was identified in both sides, more prominent in left side (4-/5). Furthermore, patient had diminished sensation to pinprick and soft touch involving right-sided extremities, bilateral diminished vibration, and adequate proprioception. On cerebellar evaluation patient had bilateral past pointing on finger to nose test more prominent on the right side. Areflexia was detected in biceps, patellar and Achillian deep tendon reflexes bilaterally and hypoactive in brachioradialis and triceps muscles; bilateral plantar flexor responses were observed. Due to neurologic findings including cranial nerve involvement and rapid progression of symptoms, an acute inflammatory demyelinating polyneuropathy was suspected, and supportive care in the ICU was recommended.

Upon admission to the ICU, laboratories and a complete spinal cord magnetic resonance were done without abnormal findings related to the symptoms. Serum samples were analyzed for ZIKV, dengue (DENV), chikungunya, and Influenza A & B viruses. Results were positive for ZIKV and subsequently to DENV antibodies by Zika IgM enzyme-linked immunosorbent array (ELISA). On day 16 patient was treated with a 5-days course of intravenous immunoglobulin (IVIg) (0.4 g/kg/day) infusion therapy.

On day 17, a lumbar puncture was performed; albuminocytologic dissociation was confirmed with total micro protein of 114.2 mg/dL; white blood cells 1 mg/microL, and glucose 67.3 mg/dL. From day 19 – 21, the patient develops severe headache, unresolved

with acetaminophen, opioids and gabapentin. On day 21, headache resolved and IVIg treatment was completed. By day 22, the bilateral facial weakness, reduce sensation at left mandibular nerves (V1–V3), left cranial nerve VI palsy, and diplopia persisted. Motor strength was equivocal with detectable weakness on bilateral upper extremities and left lower extremity, while definite strength with slight weakness on right lower extremity. The patient remained with diminished sensation in extremities, and absent reflexes in lower extremities; reflexes were normal in upper extremities. By day 25, the patient reported improvement of weakness, however bilateral facial paralysis, diplopia, and ptosis persisted; he was discharge home, with long-term follow up with neurology and physical therapy services.

One year after the onset of first symptoms limb weakness and ataxia resolved; reflexes were recovered, excluding biceps. On the other hand, bilateral facial paralysis and sensory changes including left V1–V3, diminished sensation to pinprick and soft touch (right side), and bilateral diminished vibration continued.

## Discussions

Recently, GBS has been associated with antecedent infection with ZIKV [1, 7]. The incidence of GBS cases during active ZIKV in Puerto Rico is estimated to be 3.2–5.1 times the incidence during non-active ZIKV, reported as 1.7 cases per 100,000 population [8, 9]. Likewise, an increase in the incidence of GBS in 7 countries of America has been reported, with 2.0–9.8 times higher as compared with non-active ZIKV transmission [10]. In Puerto Rico, a total of 56 cases of GBS were reported from January 1<sup>st</sup> – July 31<sup>st</sup>, 2016 of which 34 (61%) had evidence of ZIKV or flavivirus infection [7].

Laboratory findings suggested a flavivirus infection with positive results for ZIKV IgM ELISA; however a second test of the samples revealed DENV antibodies by IgM ELISA. In cases with evidence of recent flavivirus infection, clinical and epidemiological evidence should be considered to establish an association between neurologic symptoms and

ZIKV infection [11–13]. The present case was attributed to ZIKV infection due to location of exposure, clinical signs and symptoms, and epidemiologic data reported by health authorities. During November 1<sup>st</sup> – July 7<sup>th</sup>, 2016, most cases were attributed to ZIKV infection, as 5,582 cases were confirmed and presumptive with ZIKV infection, while 136 to DENV [7]. As in the present case, most of cases with GBS had an unspecified flavivirus test results; [7] however most of them were associated to ZIKV infection, as ZIKV was predominantly circulating compared with other flavivirus including DENV and chikungunya [12]. Due to cross reactivity of ZIKV IgM antibody with other related flaviviruses, the use of plaque reduction neutralization testing has been recommended for ZIKV identification; however is not recommended in Puerto Rico [13, 14].

Among GBS cases, 5% of the cases are related to the MF variant [5]. The most common clinical signs reported in patients with MF include ataxia, areflexia, and ophthalmoplegia, yet incomplete and overlapping variants could be presented. Although a good prognosis has been reported in MF, the overlap with other variants of GBS represents a life-threatening risk requiring supportive care [15, 16]. In the present case, the patient had ophthalmoplegia, ataxia, and areflexia consistent with MF; however he had limb weakness, a common symptom presented in classic GBS [5, 16]. Due to the overlap of neurologic signs, the final diagnosis was MF/GBS. In Puerto Rico, the most common clinical symptoms documented in patients with GBS and ZIKV infection includes areflexia, leg weakness, leg paresthesia, arm weakness, facial weakness, arm numbness, and dysphagia. Among cases with neurologic signs due to GBS, nearly all of cases reported areflexia (97%), while 63% of patients had facial weakness. Most of them were admitted to ICU (63%), while 35% required mechanical ventilation [7].

GBS generally has favorable outcomes; however a poor prognosis has been associated with rapid onset and severity of weakness [17]. In the current case, severe headache was described as one of the initial neurologic signs, and 48 hours after the initial dose of IVIg treatment. Back and extremities

pain is frequent in GBS, however headache is a rare clinical manifestation barely reported but presented in some variants of GBS, mainly MF and MF/GBS overlap syndrome [18, 19]. The pathogenesis of headache has been attributed to inflammation of the trigeminovascular pathway and increased of cerebrospinal fluid protein leading to obstruction and intracranial pressure [19, 20]. IVIg is considered a safe treatment, yet adverse reactions could vary between 1-80% of cases [21]. As in the current case, adverse reaction after the first 48 hours of treatment are considered delayed reactions attributed to exacerbating factors, including previous episodes of headaches [21]. In this case, electrophysiological findings and anti-GQ1b antibodies results were not available; furthermore albuminocytologic dissociation and improvement upon IVIg treatment were consistent with the suspected diagnosis. Most of MFS cases confirmed with anti-GQ1b antibodies have ocular involvement with cranial nerves III, IV and VI; however in other cases with multiple cranial nerves as well as isolated ophthalmoplegia, anti-GQ1B antibodies has been identified [22]. As recorded, the patient requested medical care on multiples times. Healthcare resource needs during active ZIKV transmission on 2016 was 3–5 times greater as compared with non-active ZIKV transmission; [8] therefore, the quick response among healthcare providers is essential for the recovery process, to reduce long-term effects, and healthcare resources needed during the outbreak. Early treatment initiation, including plasma exchange or IVIg infusion therapy should be considered, particularly in patients presenting with a rapid progression of symptoms, including paralysis, weakness, and pain.

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## Conclusions

ZIKV infection should be considered in patients presenting with the most common clinical symptoms of MF syndrome associated to the ZIKV infection, including residents and travelers from endemic areas. Due to DENV being endemic in Puerto Rico, in cases where serologic testing indicates DENV and/or ZIKV patients should be managed for both infections due to possible infection of either viruses.

## Abbreviations

ZIKV: Zika Virus; GBS: Guillain–Barré syndrome; MF: Miller Fisher; ICU: Intensive Care Unit; MF/GBS: Miller Fisher–Guillain–Barré overlap syndrome; ER: Emergency room; DENV: Dengue virus; ELISA: enzyme–linked immunosorbent array; IVIg: Intravenous Immunoglobulin

## Conflict of interest

Gloria M. Rodríguez–Vega: Speaker Burial The Medicines Company–Cleviprex; Wilma González–Barreto, Patricia De Jesús–Umpierre, and José R. Rodríguez–Vázquez declare no conflict of interests.

## Contribution

All authors have contributed to this manuscript for: concept, design, drafting, and final revision.

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## Informed Consent

The Institutional Review Board of San Juan Bautista School of Medicine approved this study (EMSJB 9-2016). Consent was obtained from the patient for publication of this case report.

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