Clinical Case Report

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Guillain-Barré-like axonal polyneuropathy associated with Toscana virus infection

A case report

Eugenia Rota, MD[a,b,*], Nicola Morelli, MD[a], Paolo Immovilli, MD[a], Paola De Mitri, MD[a], Donata Guidetti, MD[a]

Abstract

Rationale: Numerous cases of post-infectious Guillain-Barré syndrome (GBS) have been reported in the literature. Toscana virus (TOSV) is an arthropod-borne emerging pathogen in the Mediterranean area.

Patient concerns: A 40-year-old male patient was admitted to hospital for acute facial weakness, associated to numbness paraesthesias at lower and upper limbs. The neurological examination revealed facial diplegia and reduced tendon reflexes. The nerve conduction studies documented an acute motor and sensory axonal neuropathy (AMSAN); the lumbar puncture detected albuminocytologic dissociation. Serology for human immunodeficiency virus (HIV), Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), mumps, and Borrelia was negative, as was cerebrospinal fluid (CSF) polymerase chain reaction assay for Herpes virus, Borrelia, Mycoplasma pneumoniae, Cryptococcus, and Mycobacterium tubercolosis. Positivity for TOSV IgG antibodies was found on both CSF and serum; the patient remembered being recently exposed to mosquitoes.

Diagnoses: The AMSAN subtype of GBS, subsequent to a TOSV infection, was diagnosed.

Interventions: The patient was treated with plasma-exchange with complete clinical recovery, but a relapse occurred 9 months later, when the nerve conduction studies confirmed the presence of an AMSAN, which benefited from oral steroids.

Outcomes: A good clinical recovery was achieved after treatments.

Lessons: This is the first case, to the best of our knowledge, of a TOSV infection associated to a peripheral neuropathy mimicking a GBS syndrome, both clinically and electrophysiologically. The clinical spectrum of TOSV neurological complications seems to be wider than previously known: this should be taken into account by the scientific community and public health institutions.

Abbreviations: AIDP = acute inflammatory polyneuropathy, AMAN = acute motor axonal neuropathy, AMSAN = acute motor and sensory axonal neuropathy, CMV = Cytomegalovirus, CSF = cerebrospinal fluid, EBV = Epstein-Barr Virus, GBS = Guillain-Barré syndrome, HIV= human immunodeficiency virus, PCR = polymerase chain reaction assay, TOSV = Toscana virus.

Keywords: acute motor and sensory axonal neuropathy, Bunyaviridae, Guillain-Barré syndrome, post-infectious polyneuropathy, Toscana virus

1. Introduction

Guillain-Barré syndrome (GBS) and its major subtypes, that is, acute inflammatory polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy (AMSAN), is a prototype of post-infectious autoimmune diseases, where the pathophysiological role of bacterial infection by Campylobacter jejuni has been well established, mostly in relation to the axonal variants.[1] Molecular mimicry and cross-reactive antibody response to gangliosides have been hypothesised as the main pathophysiological mechanisms. Other antecedent infections, both viral and bacterial, have been reported in relation to GBS, among which Mycoplasma pneumoniae, Haemophilus influenzae, Cytomegalovirus, Epstein-Barr, Varicella-Zoster virus,[1] Influenza, Hepatitis E,[2] West Nile viruses, human immunodeficiency virus (HIV),[3] Norovirus,[4] Chikungunya,[5] and Zika[6] viruses.

Toscana virus (TOSV) is an arthropod-borne emerging pathogen in the Mediterranean area.[7] Despite the increasing evidence of a role played by TOSV in central nervous system infections, it remains a neglected agent and, to the best of our knowledge, no cases of polyneuropathy associated to TOSV infection have been reported to date.

2. Case presentation

A 40-year-old male white patient, with unremarkable family history and no antecedent disease, was admitted to hospital in September for acute facial weakness, associated to headache and numbness paraesthesias in the lower and upper limbs. The neurological examination revealed facial diplegia and reduced tendon reflexes. In the suspicion of a GBS syndrome, the patient was given a lumbar puncture, which detected raised protein levels (242 mg/dL; normal range <50), in the presence of 8 lymphocytes/microl (normal range <5). The nerve conduction studies

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[a] Neurology Unit, Guglielmo da Saliceto Hospital, Piacenza, [b] Neurology Unit, San Giacomo Hospital, Novi Ligure, Alessandria, Italy.

[*] Correspondence: Eugenia Rota, Neurology Unit, San Giacomo Hospital, Via E. Raggio 12, 15067, Novi Ligure, Alessandria, Italy (e-mail: eugenia.rota.md@gmail.com).

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fulfilled the criteria for an AMSAN.[8] Serology for HIV, Epstein-Barr Virus, Citomegalovirus, mumps, and Borrelia was negative, as was cerebrospinal fluid (CSF) polymerase chain reaction assay (PCR) for Herpes virus, Borrelia, Mycoplasma pneumoniae, Cryptococcus, and Mycobacterium tuberculosis. He was treated with plasma-exchange (4 sessions) with good tolerability and complete clinical recovery, so that he was discharged home.

Nine months later, the patient returned complaining of relapsing numbness and tingling paraesthesias, along with episodic weakness in the lower limbs. The nerve conduction studies confirmed the presence of AMSAN. The lumbar puncture was repeated; the serology for Borrelia, Rickettsia Conorii, West Nile, Mosaico Sandy Fever was negative, but positivity for TOSV IgG antibodies was found on both cerebrospinal fluid and serum. Notably, the patient then remembered being exposed to mosquitoes and sand flies during the previous summer, mostly in the 2 weeks before the onset of symptoms. Steroid treatment (prednisone at the dosage of 0.75 mg/kg/d) was then started, with clinical recovery within 2 months and, subsequently, tapered within 4 months. (The patient gave his informed consent to the publication of these data).

3. Discussion

To the best of our knowledge, this is the first case of a TOSV infection associated to a peripheral neuropathy. Remarkably, at the onset, the TOSV-related polyneuropathy was able to both clinically and neurophysiologically mimic a GBS syndrome, in its AMSAN subtype. A recurrence of the sensory and motor symptoms occurred in our patient after 8 months. Such a clinical course would seem consistent with a recurrent GBS. Indeed, recurrent GBS has been reported in 1% to 6% of patients, after recovery and an asymptomatic period of several months to years.[9,10]

In the patient herein reported, the laboratory confirmation of the TOSV infection was obtained only during the recurrence, when TOSV IgG antibodies were detected by immunofluorescent assay on both CSF and serum. While, IgM antibodies against TOSV were not detected by the assay, due to the 8-month delay from the symptom onset and the acute infection. Therefore, we were unable to provide a serological confirmation of the relationship between the TOSV infection acute phase and the GBS onset. Nevertheless, the high specificity of the virologic assay for TOSV IgG antibodies and the fact that most of the other pathogens usually responsible for GBS had been accurately ruled out, may allow us to reasonably assume that TOSV was involved in the development of the GBS-like polyneuropathy. This hypothesis is also supported by the patient's intense exposure to mosquitoes/sand-flies in the 2 weeks preceding the first neurological onset of the symptoms. Although we cannot exclude that TOSV infection itself was the direct cause of the GBS-like polyneuropathy, the pathogenetic role of TOSV may be explained by the type of post-infectious immune-mediated complications. Indeed, the delay between the exposure to sand-flies, probably corresponding to the acute TOSV infection, and the onset of the GBS-like clinical picture, suggest that the immune system required a time interval to develop the seroconversion and, subsequently, the nerve damage.

The case herein reported firstly shows that TOSV infection may be the antecedent of GBS-like axonal polyneuropathy. Consequently, the clinical spectrum of TOSV neurological complications, to date only reported to affect the central nervous system (encephalitis and meningo-encephalitis),[7,11] is extended to the peripheral nerve. TOSV is an emerging pathogen in Italy, where it was first isolated from two species of sand-flies (*Phlebotomus perniciosus* and *Phlebotomus perfiliewi*).[7,11] This virus, which belongs to the Bunyaviridae family, usually has a short incubation period (3–15 days) and is influenced by the virus load.[11] In the province of Piacenza, where this case was observed, geographical and climatic conditions predispose to sand-fly and mosquito proliferation, increasing the risk for TOSV and also West-Nile neurological complications. Moreover, during the last 4 years, apart from this case, there was also a case of life-threatening encephalitis caused by TOSV infection, along with a small series of West-Nile-associated polyneuropathies (2 cases) and encephalitis (3 cases).

Three main considerations should be raised.

Firstly, an infection from TOSV and West-Nile Virus should be included in the diagnostic algorithm in all cases of acute polyneuropathy that resemble GBS during the warm season, even in the absence of an overt febrile antecedent illness, not only in rural, but also in urban areas in the Mediterranean countries.

Secondly, there is the potential for further geographical spread of these pathogens, particularly of TOSV,[11] favored by climatic changes and the fact that traveling is on the increase.

Thirdly, currently there are no specific vaccines or antiviral therapies available.

Therefore, we suggest that countermeasures against sand-flies and mosquitoes, including insecticides and other forms of prevention, should be carried out by the local administration and public health institutions.

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