Optic Neuritis in a Traveler Returning From Dominican Republic to Spain With Dengue Virus Infection

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A search of medical literature will show that dengue infection is rarely linked to optic neuritis. Here we report the development of loss of vision in a female traveler who returned to Spain from the Caribbean after acquiring a dengue infection.

Dengue virus infection is caused by a flavivirus which in 4% to 5% of cases involves neurological manifestations.1 It has four virus serotypes (types 1–4), with serotypes 2 and 3 being the principal agents related to the involvement of the nervous system.1 The major mechanisms of the disease may be related to direct viral infection or a postinfectious autoimmune process.1 Its main neurological manifestations are: myelitis, encephalitis, encephalomyelitis, optic neuritis, or Guillain–Barré syndrome.1 Although dengue virus infection is a major health threat for travelers, medical literature makes very few references to it in relation to cases with neurological involvement.2 In this article, we report a case of a female with loss of vision after acquiring dengue virus infection in the Dominican Republic.

Case Report

A 60-year-old Spanish woman was referred to our clinic in April 2013 with a history of bilateral visual loss. In February 2013, she had been working as a missionary in the Dominican Republic and on February 17, 2013, she arrived at the local hospital in the Dominican Republic with a 3-day history of fever, headache, myalgia, and vomiting. Physical examination revealed 38.5°C temperature and dehydration, and laboratory examination revealed leukopenia [white blood cell (WBC) count 2.0×10³ per μL), thrombocytopenia (platelet count, 36×10⁶ per μL), and an increased level of aspartate transaminase (AST, 385 U/L) and alanine transaminase (ALT, 226 UI/L). The most likely diagnosis for this patient was considered to be dengue infection; the dengue virus serology test by enzyme-linked immunosorbent assay (ELISA) showed immunoglobulin M (IgM) positive (4.9 index value) and IgG negative (0.9 index value). There was no clinical evidence of hypovolemic shock having occurred, and the patient was treated conservatively with intravenous fluid, electrolytes, and glucose. She had been living in the Dominican Republic until March 14, 2013, at which time the laboratory examination was normal, and she returned to Spain with her family. In April 2013, the patient started experiencing a gradual loss of vision in her left eye and consequently, on April 20, 2013, she came to our clinic. Physical examination at our hospital revealed a generally fit woman with no signs of dengue virus infection. She had reduced visual acuity of 0.8. In the left eye, pupil diameter was 3 mm under illumination and reacted normally to light, and extraocular motility was normal without pain. The optical coherence tomography revealed left papillary edema with serous nasal macular (Figure 1). Computerized perimetry showed the right optic disc to be normal and examination of the left optic disc showed cecocentral scotoma with media deviation of ~3.30 dB. The serology by ELISA (Panbio® Dengue Duo IgM and IgG Capture ELISA, Alere Healthcare, Barcelona, © 2014 International Society of Travel Medicine, 1195-1982
Spain) showed IgM [index value: 1.3 (positive >1.1)] and IgG [index value: 2.6 (positive >1.1)] antibodies for dengue virus. Viral sub-typing was not performed, and neither was a cerebrospinal fluid test for dengue infection. We considered other optical nerve afflictions, but medical history, symptoms, clinical examination, and complementary examinations allowed us to rule out other causes of optic neuritis, including: inflammatory diseases (multiple sclerosis, lupus, sarcoidosis, and Horton disease), hereditary conditions, infectious diseases, vascular etiologies, and those linked to general illness or nutritional deficiencies.

The patient was treated with methyl-prednisolone 250 mg four times a day for 3 days, followed by 60 mg/day of prednisolone, which was slowly reduced over 4 weeks, and diclofenac eyewash. At 6 months, visual acuity was 0.7 in the left eye; the optical coherence tomography revealed a widespread loss of fibers from the lower sector and computerized perimetry revealed inferior altitudinal scotoma with mean deviation of $-9.24 \text{dB}$.

**Discussion**

The Dominican Republic has experienced a tremendous increase in the number of cases of dengue virus reported in the past few years. All serotypes (1–4) are currently circulating in the Dominican Republic, but the Department of Epidemiology of the Dominican Republic has only been able to isolate serotype-2 and serotype-4.

The ocular manifestations of dengue virus infection include photophobia, retrobulbar pain, conjunctival congestion, sub-conjunctival hemorrhage, retina engorgement, and accommodative weakness. To the best of our knowledge, the first case of optic neuritis was reported by Wen and colleagues in a Chinese article based on a series of 24 cases of ocular involvement in dengue virus infected patients. Another example is that of a series of 41 patients with dengue maculopathy who were reported to have shown signs of optic nerve involvement. Despite the prevalence of dengue virus infection in tropical and subtropical areas of the world, it is unusual for it to be associated with optic neuritis. The majority of cases have been reported in patients living in endemic areas, so the case of imported dengue, as reported here, is rare.

Ocular involvement after dengue infection can be unilateral or bilateral, and is described as occurring during the acute phase, which is a few days after the fever sets in. However, in other cases the loss of visual function appears several months after the fever has disappeared, as in our case. The pathological mechanisms responsible for the effects of dengue optic neuritis are not completely understood and may be related to direct viral infection (infectious neuritis) or a postinfectious
autoimmune process. The delay between the systemic manifestations of dengue fever and the onset of visual symptoms is consistent with the hypothesis that ocular manifestations could be an immune-mediated process rather than a direct viral infection. Direct viral infection of dendritic cells causes apoptosis and dysfunction. A transient aberrant immune response may occur, leading to cytokine overproduction and CD4/CD8 ratio inversion. Finally, overproduction of interleukin-6 may trigger production of autoantibodies against platelets and endothelial cells. Treatment with a course of intravenous boluses of methylprednisolone followed by oral prednisone, as described in the literature, is reported to work well. However, despite treatment with steroids, ocular involvement in dengue virus infected patients may occasionally result in profound permanent visual impairment (lost light perception). In our case, the patient had not recovered from visual impairment after 6 months. Steroid treatment may be associated with medical complications, such as secondary infections or avascular femoral necrosis. However, this has not been observed in patients with optic neuritis following dengue virus, nor has it been associated with changes in plasma cytokine levels in patients with dengue infection, so it does not attenuate the host immune response. The shortcomings of prednisolone for treating dengue infection can be related to its low effect in patients with optic neuritis associated with dengue. Other treatments are required, such as inhibitors of glycogen synthase kinase 3 (GSK3) like lithium, which are being explored as a therapy for experimental autoimmune encephalomyelitis, as in the mouse model of multiple sclerosis.

Cases of optical neuromyelitis after dengue virus infection are even more rare. The development of optic neuritis following dengue virus infection can be added to the huge list of late sequelae associated with dengue infection, such as persistent clinical manifestations associated with alterations in some immunological parameters and FcyRIIa gene polymorphism, large vein thrombotic events, or hemophagocytic lymphohistiocytosis. This is an uncommon manifestation of the dengue virus infection, and it is necessary to inform travel clinics in high-income countries about cases of dengue imported from endemic areas that travelers, aid workers, and visiting friends and relatives have visited. Ocular manifestations have been rarely described in association with arthropod vector-borne diseases, including rickettsioses, West Nile virus, Rift Valley fever, chikungunya and dengue fever, and common viruses such as influenza A (H1N1). The eyes can be the target for many infections, especially infections associated with travel and mobility; in which case ophthalmologists' and travel health specialists' patients may present conditions differing from other nontravel-related ocular infections.

Nadjam and colleagues summarized ocular symptoms and signs into three types: white eyes with vision loss, red eyes with no vision loss, and red eyes with vision loss and usually painful. Each type has its relevant causes; the eye could be affected by a parasitic, bacterial, viral, and/or fungal infection acquired during travel, such as malaria, toxoplasmosis, coccidioidomycosis, Leptospirosis, Rift Valley fever, West Nile virus infection, histoplasmosis, or coccidioidomycosis. In conclusion, according to Nadjam and colleagues, ophthalmologists and infectious disease physicians need to be aware of the potential for exotic and unusual infections in patients who present with eye problems after traveling.

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Declarations of Interests
The authors state that they have no conflicts of interest to declare

References