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CASE REPORT

Ocular flutter following Zika virus infection

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Abstract Zika virus (ZIKV) is an emerging flavivirus which has been linked to a number of neurologic manifestations such as Guillain-Barré syndrome (GBS), transverse myelitis, and meningo-encephalitis. Ophthalmologic manifestations are increasingly being reported; however, ocular dyskinesias have not been described in this context to date. Herein, we report a case of a 22-year-old female who presented with ocular flutter and associated Guillain-Barré syndrome following acute ZIKV infection. We speculate that although such symptoms may have originated from a direct viral insult, a post-infectious autoimmune mechanism may not be excluded. Physicians should include ZIKV as well as other flaviviruses in their diagnostic workup for all patients with ocular flutter/opsoclonus, after excluding other non-infectious causes of central nervous system pathology. To the best of our knowledge, this is the first report on the association of ocular flutter, GBS, and ZIKV infection.

Keywords *Zika virus* · Ocular flutter · Viral · Guillain-Barré syndrome

A 22-year-old woman developed fever, malaise, arthralgia, cough, and generalized maculopapular rash lasting 6 days. Past medical history was significant for Hashimoto's thyroiditis with no exposure to sick contacts, pets/animals, or recent travel. A week after the acute onset of symptoms, she developed symmetrical weakness and numbness of the upper limbs which progressed to all four extremities associated with generalized lymphadenopathy, anorexia, diaphoresis, and myalgias. Her condition worsened developing seizures and hypotension 2 weeks after; followed by subacute onset of dizziness, dysarthria, photophobia, and episodes of blurred vision with abnormal ocular movements.

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On physical examination, she presented flaccid tetraparesis, severe truncal ataxia, and areflexia. Extraocular movements showed frequent bursts of rapid conjugated, and periodic horizontal back-to-back saccades, in a chaotic series of vectors. Pursuit was saccadic and ductions were full with comitant versions. (Supplementary material: Video 1, brief low-amplitude back-to-back horizontal saccades lasting < 1 s). Funduscopic examination was normal.

A complete blood count was notable for total leukocytes of 3400/mm^3, 70.2% neutrophils, 2.7% monocytes, and decreased hemoglobin (8.6 g/dl) and hematocrit (26.3%), with an elevated erythrocyte sedimentation rate (95 mm) and a lactate dehydrogenase of 433 U/L. Blood urea nitrogen, serum creatinine, and glucose were within reference ranges. Serum testing for syphilis, toxoplasma, cytomegalovirus, Epstein-Barr, varicella zoster, herpes simplex virus types 1 and 2, enterovirus, Hepatitis B and C, West Nile virus (WNV), HIV, and fungal agents following established methods were all negative. Autoimmune profile and para-neoplastic autoantibody panel including anti-Ri (ANNA-2), anti-Hu (ANNA-1), anti-Yo (PCA-1), anti-Ma1, anti-Ma2, Lambert-Eaton myasthenic syndrome (LEMS), CAR, anti-CV2 (collapsing response mediator protein 5), Zic4, and VGKC were also unremarkable. Lumbar puncture revealed (normal opening pressure and cerebrospinal fluid analysis revealed pleocytosis (93 mg/dL), a positive Pandy's reaction test, glucose 41 mg/dL, and lactate dehydrogenase of 33 U/L.

Immunofluorescence testing was performed using the IIFT Arboviral Fever Mosaic 2 Euroimmun AG® IgG, IgM Test System (Euroimmun AG® Luebeck, Germany) revealing that the patient had positive IgM and negative IgG antibodies against ZIKV, and no detectable antibodies to *Chikungunya virus* (CHIKV) nor *Dengue virus* (DENV) serotypes 1–4. Samples were submitted to a regional reference laboratory for plaque reduction neutralization test (PRNT) confirmation, returning positive (≥ 1:10). Evaluation of convalescent sample collected 8 months later demonstrated a seven-fold increase in neutralizing antibody titers to ZIKV in the absence of a titer increase to DENV or other endemic flaviviruses in the region.

Brain magnetic resonance imaging and CT scan performed at that time were unremarkable. The patient was hemodynamically stabilized and initially treated empirically covering for bacterial meningitis and viral encephalitis (ceftriaxone and acyclovir) without improvement of neurologic symptoms. Subsequently, treatment with intravenous immunoglobulin (IVIG) 400 mg/kg/day for 5 days was initiated obtaining a progressive improvement.

Zika virus (ZIKV) is a mosquitoe-borne flavivirus (Slenczka 2016). Though initially linked to microcephaly and Guillain-Barré syndrome (GBS), the list of neurological manifestations continues to grow with newly associated conditions such as myelitis and meningo-encephalitis. (Araujo et al. 2016). Ocular manifestations of ZIKV have mostly been described in context of congenital ZIKV syndrome including a spectrum of findings such as coloboma, intraocular calcifications, glaucoma, microphtalmia, strabismus, and paresis of the oculomotor and abducens nerves, amongst other neuro-ophthalmic manifestations (Ventura et al. 2016; Slenczka 2016; Araujo et al. 2016). However, oculomotor dyskinetic syndromes in arboviral infections have rarely been reported in the literature to date (Mahale RR et al., 2016).

Though a rare phenomenon, ocular flutter has been reported to occur in context of the Miller-Fisher variant of GBS (Nakayasu et al., 2010). However, viral-associated ocular flutter is rare, and is seen mostly in the setting of non-flaviviral infection (Wiest et al. 1997). We evaluated a patient who developed a post-infectious ocular flutter in context of GBS short after ZIKV infection. The patient was diagnosed with probable ZIKV-associated GBS based on clinical and laboratory testing following current guidelines from the PAHO (2016) and the CDC (2017).

Considered a subform of opsoclonus (Leigh and Zee 1999), ocular flutter is a rare and distinct localizing sign characterized by bursts of sequential saccades limited to the horizontal plane in absence of inter-saccadic pauses (Bergenius 1986), as opposed to opsoclonus where rapid eye movements usually exhibit a multidirectional chaotic series of vectors with regular oscillations in both vertical and horizontal planes. (Leigh and Zee 1999).

Despite that, many of the physiopathological aspects of ocular flutter/opsoclonus remain unknown to date; the syndrome spectrum appears to have a common anatomic origin within the paramedian pontine reticular formation (Leigh and Zee 1999; Wong 2007). For ocular flutter, in specific, the functional origin appears to originate from a loss of omnipause cell inhibition over saccadic bursts neurons (Leigh and Zee 1999; Wong 2007; Ramat et al. 2005). Ocular flutter may occur in a number of clinical scenarios such as para-neoplastic (Furman et al. 1988; Pieret et al. 1996), toxic metabolic states (Vidarabine), autoimmune (Zaro-Weber et al. 2008), or as a result of para-infectious or post-infectious etiology. Yet, in many cases and obvious cause may not be apparent.

The first evidence to suggest a possible infectious cause in ocular flutter dates from the original observations of Hankey and Sadka (1987) on the association of CSF pleocytosis in affected patients. Para- and post-infectious causes are amongst the most common causes of ocular flutter/opsoclonus, including both bacterial and viral agents such as HIV, Lyme disease, EBV, CMV, enterovirus, and WNV. (Hébert et al. 2017).

Recent evidence suggests that post-infectious ocular flutter may be due to an autoimmune-mediated phenomenon (antiCQ) in which IgG antibodies against several gangliosides may target specific epitopes in selected neuroanatomical regions of the brainstem and cerebellum (antiCQ). This would explain the absence of evident anatomical lesions in imaging studies, as well as the clinical symptomatology seen in our

case. In addition, the fact that our patient failed to respond to antibiotics but did demonstrate an expedite improvement after the administration of intravenous high-dose immunoglobulin militates in favor of this association. In fact, a recent work carried out during the recent GBS outbreak associated to the Zika epidemic in the French Polynesia revealed that as much as 31% of ZIKV-positive patients, who developed GBS, exhibited anti-glicolipid antibody activity, notably against GA1 (Cao-Lormeau et al. 2016). Even though anti-glicolipid IgG antibody testing was not available and performed in our patient, we cannot fully exclude a possible role for molecular mimicry-mediated autoimmunity besides its association to direct viral neurotoxicity.

To the best of our knowledge, this is the first description on the occurrence of ocular flutter and truncal ataxia triggered by ZIKV infection. As the ZIKV pandemic continues to spread with an increasing number of patients presenting with ZIKV-associated neurological syndromes, physicians should include ZIKV as well as other flaviviruses in their diagnostic workup for all patients with ocular flutter/opsoclonus, after excluding other non-infectious causes of central nervous system pathology.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from the patient.

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