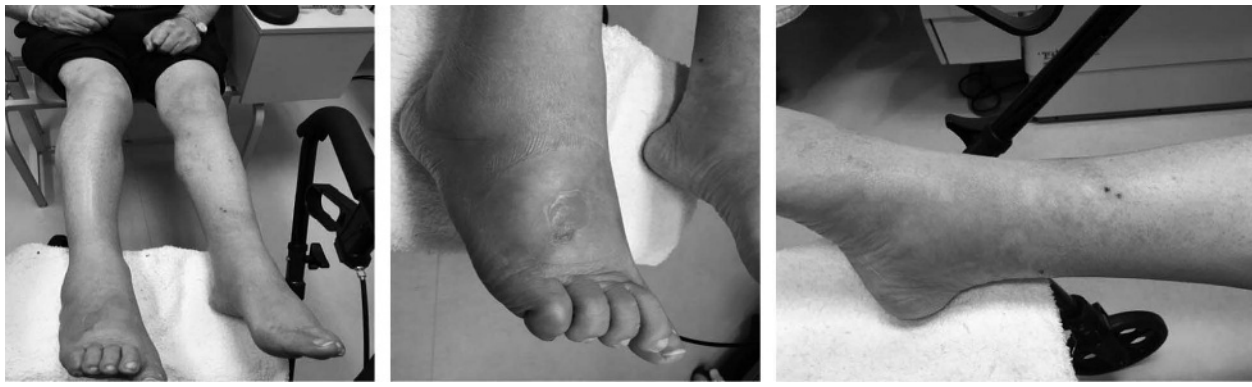

FIGURE 1. Bullous pemphigoid in a geriatric patient with PD and amantadine treatment. The patient provided written consent for use of these photographs for publication.

of the Naranjo adverse drug reaction probability scale indicated a probable relationship between the patient's development of skin lesions and amantadine therapy.[6]

Commonly reported adverse effects of amantadine include gastrointestinal complaints, mood symptoms, and sleep disturbance.[7] More adverse events, such as delusions, paranoia, corneal edema, hypertension, and urinary retention, have also been reported. A link between amantadine and BP has not been identified previously. To clarify whether amantadine contributes to the increased incidence of BP in PD patients, further exploration of the medication profiles of PD patients who develop BP is merited.

Given that amantadine is used off-label for several psychiatric indications, for example, for cognition in traumatic brain injury patients, antipsychotic-associated extrapyramidal symptoms, and fatigue in multiple sclerosis, an awareness of amantadine-associated BP is important for the psychiatrist who prescribes this medication.[8–10] History of PD and the use of immunomodulation therapies need to be considered in cases of apparent amantadine-associated BP.

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Manic Episode After a Chikungunya Virus Infection in a Bipolar Patient Previously Stabilized With Valproic Acid

To the Editors:

Chikungunya virus (CHIKV) is a re-emerging alphavirus transmitted by mosquitoes from the genus *Aedes* and is responsible for causing chikungunya. The clinical presentation of chikungunya involves fever that is typically high grade with a sudden onset and usually lasts approximately 1 week (nearly 10% of patients may not present it) and involves polyarthralgia, polyarthritis, or both, which can last weeks to months.[1] The CHIKV-associated central nervous system disease is not a common feature of the clinical picture of CHIKV infection. However, some reports showed elevated incidences of encephalitis, Guillain-Barré syndrome, and meningoencephalitis in patients with CHIKV infection.[2,3]

Bipolar disorder (BD) is a highly disabling disorder, with a global prevalence of 1.9%.[4] Patients with BD often show recurrent affective symptoms, switching from depression to mania/hypomania and vice versa. The pathophysiology of BD remains unclear. However, some recent findings suggest that immune dysfunction and high levels of proinflammatory cytokines may be associated with BD's pathophysiology.[5] Bipolar treatment guidelines from Canada

and the United States recommend valproate as a first-line strategy in the acute treatment and maintenance treatment of BD.[6]

The antiinflammatory properties of valproic acid (VPA) treatment have been described in several disorders, such as sepsis, hemorrhage, and traumatic brain injury.[7,8] In 2016, Bambakidis et al[9] showed that VPA modulates genes related to inflammation, cell signaling, cell adhesion, and endothelial growth.

We report a case of recurrence of a manic episode after an infection by CHIKV in a patient already diagnosed with BD who has been asymptomatic for the last 11 years with VPA treatment.

CASE REPORT

A 60-year-old white female patient was diagnosed as having BD when she was 28 years old. The diagnosis was made after her first episode of a nonpsychotic manic episode resulting in her first hospitalization. Insomnia, restlessness, uncontrolled expenses, grandiosity, pressured speech, and flight of ideas characterized her manic state presentation. At that time, she showed clinical improvement and optimal adherence to VPA therapy. She has been treated with 1 g/day of VPA (results of her serum dosage of VPA range from 65 to 82 μg/mL).

In March 2016, the patient presented to an emergency unit complaining of lower extremity edema, joint pain, and mild disseminated skin rash with no fever. There were no complaints suggesting neurological impairment. On examination, there was no focal neurological deficit, and no meningeal signs were observed. Psychiatric evaluation showed that she was euthymic with no symptoms, suggesting recurrence of a manic state. Routine blood investigation showed leukopenia with a total white blood cell count of 3.7×10^9 cells/L with neutrophils of 62%, lymphocytes of 18%, and monocytes at 13%. Her platelet count was in the normal range. C-reactive protein was measured and showed significant elevation (9.0 mg/L). After 2 weeks of the onset of the joint pain, the patient was investigated for arboviruses infection. Serologic testing showed a positive chikungunya IgM enzyme-linked immunoassay test.

Shortly after her first examination, the patient started on nonsteroidal antiinflammatory therapy and was warned to maintain her psychiatric treatment with VPA. One month after the onset of joint pain and skin rash, she presented a recurrence of manic symptoms characterized by insomnia, restlessness, pressured speech, irritability, and poor insight. As part of the psychiatric evaluation, we used the Young Mania Rating Scale - Portuguese Version to measure the severity of the manic syndrome.[10] At this time, she presented a total score of 30. A blood sample was collected to measure her serum level of VPA. The result showed maintenance of the serum therapeutic level of VPA (serum dosage: 74 μg/mL) compatible with the patient's previous results.

DISCUSSION

Meta-analyses published in 2013 showed that severe infection is considered a relevant risk factor for subsequent mood disorder diagnosis.[11] This association seems compatible with an immunologic hypothesis for the development or worsening of mood disorders in specific subgroups of patients.

The pathogenesis of chikungunya is not completely clear. A vast array of cytokines, chemokines, and growth factors were detected in the plasma of CHIKV-infected patients. The elevated profiles of inflammatory cytokines, pro-osteoclastic factors, chemokines, and Th17-associated cytokines play a crucial role in alphaviral arthritis.[12] Among them all, higher levels of interleukin (IL)-6 were correlated with worse severity and long persistence of articular symptoms.[13]

Psychiatric impairment due to CHIKV has been poorly investigated. One exception is the recent Indian report showing that CHIKV infection was associated mainly with the diagnostics of depressive and anxiety disorders. It is worth noting that none of the patients reported any symptoms of mania/hypomania and psychosis. However, we must consider that patients with a previous psychiatric morbidity history were not included.[14] Until now, there are no studies correlating CHIKV infection with the worsening or recurrence of symptoms of mania/hypomania.

Our hypothesis is that CHIKV infection is implicated in a severe systemic inflammatory response that may act as a trigger for the recurrence of mania symptoms. Inflammation is a condition characterized by cytokine cascades, cellular immune responses, increased levels of acute phase proteins, and complement factors.[15] There is a growing body of evidence suggesting the relevance of peripheral inflammatory mediators (cytokines, for example) in the pathophysiology of many psychiatric diseases.[16] More specifically, immune system dysregulation has been indicated in both in vitro studies and in clinical studies showing alterations of peripheral markers of inflammation. A recent study showed that serum TNF-α and IL-6 levels in manic, depressive, and mixed-state BD patients were significantly higher than those in controls. Serum IL-6 levels were significantly positively correlated with the Young Mania Rating Scale scores in manic episodes as well as in mixed episodes.[17]

Our study has some limitations. First, this is a single-case report. Therefore, even if we can set a hypothesis, we need more studies to confirm the hypothesis. Second, we have not measured the levels of cytokines or other specific inflammatory mediators. We only examined the C-reactive protein level in this patient. Although it may be relevant to strengthen the hypothesis of an immune-mediated mechanism underlying the recurrence of mania, the inflammatory response to CHIKV is already well established and exhaustively reported in the literature. Third, we have not performed a cerebrospinal fluid examination or a magnetic resonance imaging brain scan. This clinical decision was made considering the following: (1) the patient had no neurological findings in the clinical examination, and (2) during the psychiatric evaluation, the patient was extremely restless. Considering these 2 aspects of the case, we concluded that the risk-benefit was not reasonable for the patient.

To our knowledge, this is the first case reporting the psychiatric outcomes of CHIKV infection in a patient already diagnosed with BD who was psychiatrically stable for the last 11 years using VPA as a mood stabilizer. The findings presented in this case report are relevant for 2 main reasons: (1) first, we must consider that psychiatric patients may constitute an especially vulnerable population for more severe forms of CHIKV infection even if they are correctly treated for their psychiatric disorders; (2) second, the antimanic antiinflammatory properties of VPA are not sufficient to curb the inflammatory brain activity triggered by CHIKV in a patient with BD. This finding leads us to question whether this would occur with other mood stabilizers.

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Acute Anisocoria Related to Citalopram
A Case Report

To the Editors:

Anisocoria is a condition characterized by unequal pupil sizes. It is a common finding in eye clinics. The condition is often benign but can also represent a sign of a life-threatening disease.[1] Because pupil size depends on the effects of the autonomic nervous system, numerous conditions can cause anisocoria. Citalopram is a selective serotonin reuptake inhibitor (SSRI) used for depression with a generally accepted safety profile.[2] Here, we present a case of acute anisocoria related to citalopram.

A 48-year-old, right-handed woman was started on citalopram 20 mg to treat moderate symptoms of depression. A few days after starting citalopram she noticed that her pupils were uneven; her left pupil was larger than the right one. She did not complain of any other symptoms.

In her medical history, she had thyroid dysfunction, and she was on levothyroxine 100 μg. She did not smoke, and she was an occasional drinker.

On neurological examination, she had anisocoria (Fig. 1), in which the left pupil was larger than the right. Both pupils were, however, reactive to light and accommodation. The right pupil was 3.5 mm in diameter, whereas the left one was 5 mm in room light. There was no afferent defect, and both pupils presented direct and consensual light reflex and were reactive to accommodation. The ocular examination was completely normal, except for anisocoria: Best corrected visual acuity was 20/20 in both eyes, and the optic nerves appeared normal at the ophthalmoscopic examination. Intraocular pressure was 15 mm Hg in both eyes. No alterations of the visual field were found. The cranial nerves were otherwise intact; there was no ptosis or ocular movement abnormality. Tone and power were normal. Reflexes were normal. There was no ptosis or other signs that suggested a Horner syndrome, and therefore a cocaine test was not performed. Examination of previous photographs of the patient suggested no preexisting anisocoria.

An electrocardiogram and full routine blood tests were normal. A magnetic resonance imaging scan and magnetic resonance venogram of the brain were normal. A chest radiograph, performed to exclude Pancoast syndrome, was normal. At follow-up, 2 months after discontinuing citalopram, her pupils returned to normal size (Fig. 1), supporting the iatrogenic etiology. Using the Naranjo scale,[3] which evaluates the probability of a causal relationship, the score was 7, meaning that the causal relationship was "probable."

Anisocoria is characterized by unequal pupil sizes. Physiologic anisocoria is the most common cause of pupil asymmetry with a prevalence of 15% to 30% in the general population.[4] However, acute onset of anisocoria could be the sign of a severe disease such as brain lesion, lung and mediastinal tumor, or a posterior communicating artery aneurysm.[1]

Besides congenital or acquired structural defects, other known conditions

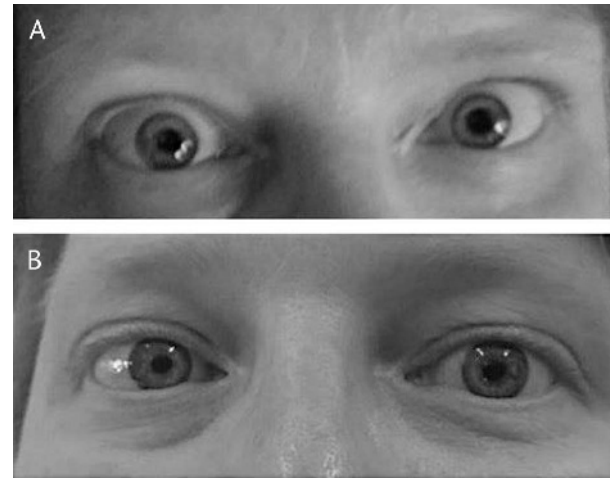

FIGURE 1. Selfies taken by the patient few days after starting citalopram (A) and after its withdrawal (B).