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Case Report

Opsoclonus-myoclonus-ataxia syndrome associated with chikungunya and dengue virus co-infection

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ABSTRACT

Opsoclonus-myoclonus-ataxia syndrome (OMAS) is a rare neurological disorder characterized by irregular multidirectional eye movements, myoclonus, cerebellar ataxia, sleep disturbances, and cognitive dysfunction. Although most commonly related to paraneoplastic syndrome, this condition has occasionally been described following infectious illnesses. This article reports the first case of OMAS in association with chikungunya and dengue virus co-infection. The genetic analysis identified chikungunya virus of East/Central/South African genotype and dengue serotype 4 virus of genotype II. This report represents an unusual clinical syndrome associated with viral co-infection and reinforces the need for clinical vigilance with regard to neurological syndromes in the context of emergent arboviruses.

Introduction

Opsoclonus-myoclonus-ataxia syndrome (OMAS), or dancing eyes syndrome, is a rare neurological disorder characterized by irregular multidirectional eye movements, myoclonus, and, less frequently, cerebellar ataxia, sleep disturbances, and cognitive dysfunction (Gorman, 2010). OMAS, first described in 1962, has classically been related to neuroblastoma in children as a paraneoplastic syndrome. Post-infectious OMAS, with benign recovery, has occasionally been described, including virus-associated OMAS following infection caused by dengue virus (DENV) (Tan et al., 2014) and other viruses (Gorman, 2010).

Co-infection with DENV and chikungunya virus (CHIKV) was first reported in 1962 in Thailand (Nimmannitya et al., 1969). Other studies later reported patients co-infected with CHIKV and DENV, in which the co-infection mostly resulted in an acute febrile syndrome with non-specific features (Furuya-Kanamori et al., 2016).

This article reports a case of encephalitis and OMAS associated with DENV–CHIKV co-infection, which occurred in June 2015 during the peak of a concurrent arbovirus outbreak in Salvador, the capital of the state of Bahia, located in northeastern Brazil.

Case report

In June 2015, a 38-year-old black woman reported generalized pruritus, skin rash, and arthralgia. Although these symptoms remitted 5 days later, her family members noted abnormal head movement and chaotic eye movement. These symptoms worsened, accompanied by confusion, dysarthria, dysphagia, and hypersomnolence. Eight days later, she was admitted to a neurological intensive care unit, at which time she was confused, lethargic, and uncooperative. The patient's orientation, language, calculation, praxis, gnosis, and memory were difficult to assess as she could not speak clearly due to confusion. She could not obey simple commands such as open and close the eyes or squeeze hands. The neurologist noted rapid, involuntary, multivectorial,

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unpredictable, conjugate rapid eye movements in the absence of intersaccadic intervals, characteristic of opsoclonus (**Supplementary material**, Video). Mild ataxia during the index–nose–finger test was noted bilaterally. There were no signs of meningismus.

Computed tomography (CT) of the cranium and contrast-enhanced magnetic resonance imaging (MRI) with thin cuts of the brainstem (FIESTA sequence) were normal. Cerebrospinal fluid (CSF) examination showed a white blood cell count of 3×10^6 cells/l (with lymphocyte predominance), glucose level of 111 mg/dl, and protein level of 33 mg/dl. GQ1b autoantibody tests were negative. Chest and abdomen CT, as well as gynecological and manual breast examinations were performed as standard cancer screening for the patient's age; all of these examinations were unremarkable.

Three days after admission, a course of human intravenous immunoglobulin (IVIG) was administered at 2 g/kg (total dose) for 5 days. She exhibited a mild improvement and 4 days later, a 5-day course of methylprednisolone pulse therapy (1 g/day) was started. No antibiotics or antiviral agents were given. One week after pulse therapy, she demonstrated further improvement: the opsoclonus symptoms had become milder and she was lucid and speaking clearly. Three weeks later, the patient exhibited normal cognitive function with no signs of ataxia or opsoclonus and was discharged.

One month after discharge the patient attended an outpatient appointment. She continued to have no signs of opsoclonus, ataxia, or cognitive impairment. Written informed consent was obtained from this patient to participate in the present case study.

Methods

Plasma, serum, and CSF were collected on admission, 8 days after the onset of viral symptoms. The detection of specific IgM antibodies for CHIKV and DENV was performed with CHIKV IgM ELISA (Euroimmun, Lübeck, Germany) and NovaLisa Dengue IgM ELISA (NovaTec Immundiagnostica GmbH, Dietzenbach, Germany), respectively, according to the manufacturer's recommendations.

Serological testing for HIV and hepatitis B and C viruses (HBV, HCV) was also performed, in addition to testing for cytomegalovirus (CMV), herpes simplex virus types 1 and 2 (HSV-1/2), and Zika virus (ZIKV) (NovaLisa ZIKV IgM μ-capture ELISA; NovaTec Immundiagnostica GmbH, Dietzenbach, Germany).

Reverse transcription real-time PCR (RT-qPCR) was performed for CHIKV, DENV, and ZIKV, as described previously (Johnson et al., 2005; Chiam et al., 2013). Partial viral genomes were recovered and nucleotide sequences were subtyped using the arbovirus subtyping tool (http://bioafrica2.mrc.ac.za/rega-genotype/typingtool/aedesviruses/). Phylogenetic reconstructions were performed using CHIKV and DENV reference strains obtained from the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). The datasets consisted of the novel CHIKV and DENV sequences obtained herein, in addition to publicly available complete genome sequences (CHIKV West African, East/Central/South African (ECSA), Indian Ocean Lineage (IOL), and Asian genotypes; DENV serotypes 1–4, genotypes I–III and sylvatic). Maximum likelihood phylogenetic trees were generated as described previously (Giovanetti et al., 2016).

Results

IgM ELISA yielded negative results for CHIKV, but was positive for DENV in the sample collected on admission. Serological testing was also negative for ZIKV IgM, CMV IgM, HSV-1/2 IgM, HIV, HBV, and HCV.

RT-qPCR for CHIKV was positive for plasma and CSF samples collected on admission. RT-qPCR for DENV was also positive for the same plasma sample, while RT-qPCR for ZIKV was negative for both samples. Partial genome sequences were recovered for two different regions of CHIKV, one at gene E2 (1885 nt; position 120–2008) and another at gene E1 (997nt; position 7639–8635), corresponding to 26% of the entire genome. Several regions of DENV were recovered, ranging from 160 nt to 1480 nt in length, covering approximately 64% of the entire genome.

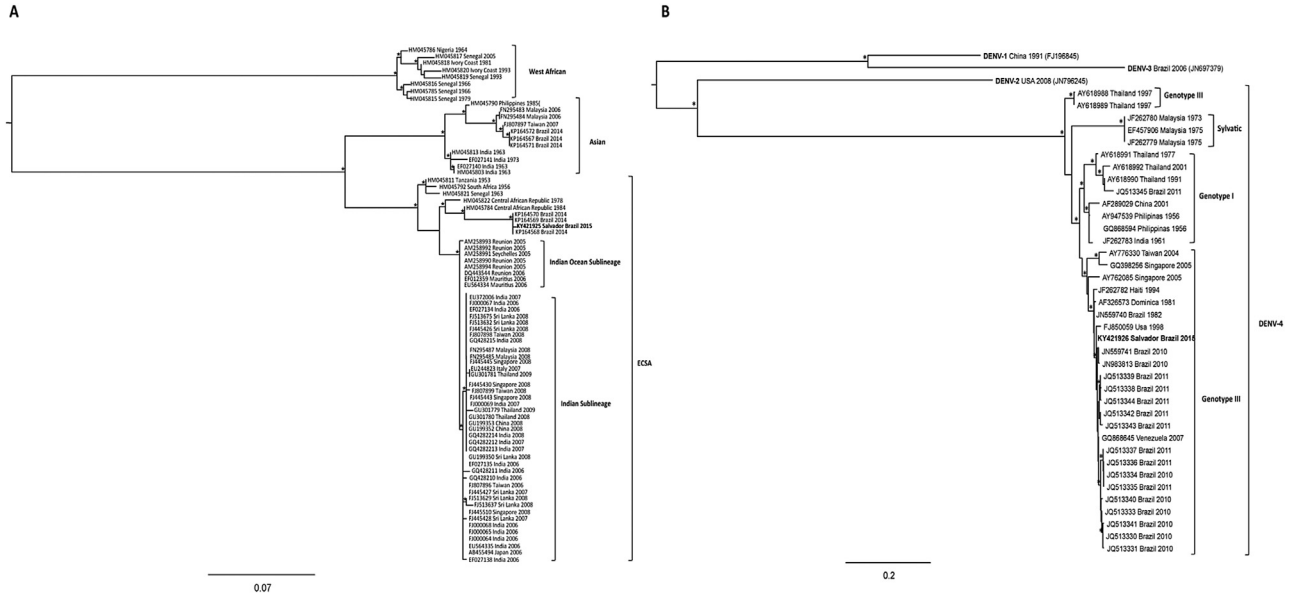

Figure 1. (A) Maximum likelihood tree, mid-point rooted, including the isolate of CHIKV from Brazil, in addition to 75 reference sequences. The GenBank accession number, year of isolation, and country of origin are indicated on the tips of the tree for all strains except for the newly obtained CHIKV isolate from Salvador, Bahia, Brazil (**KY421925**), which is highlighted in bold. (B) Maximum likelihood tree, mid-point rooted, including the newly isolated sequence of DENV from Brazil, in addition to 40 reference sequences. The GenBank accession number, year of isolation, and country of origin are indicated on the tips of the tree for all strains except for the newly obtained DENV isolate from Salvador, Bahia, Brazil (**KY421926**), which is highlighted in bold. The scale is expressed in units of nucleotide substitutions per site. Asterisks represent bootstrap values >90%.

The CHIKV maximum likelihood phylogenetic reconstruction indicated that the isolate belonged to the ECSA genotype. The DENV maximum likelihood reconstruction further indicated that the DENV genome belonged to serotype 4 DENV (DENV-4) of genotype II, with bootstrap support >90% (Figure 1). These new CHIKV and DENV-4 sequences have been deposited in the GenBank database under accession numbers **KY421925** and **KY421926**, respectively.

Discussion

Emergent and re-emerging arboviruses pose new and unforeseen challenges in regions affected by recent outbreaks. The identification of neurological complications arising from arboviruses has raised new public health concerns, mainly related to Guillain–Barré syndrome in association with ZIKV (do Rosario et al., 2016). Neurological complications associated with DENV or CHIKV are believed to be unusual. Relatively few cases of dengue-associated encephalitis have been reported; however reports of CHIKV-associated encephalitis increased during the 2005–2006 CHIKV outbreak on the island of La Réunion (Bintner et al., 2015).

The current medical literature contains few reports of arbovirus-associated OMAS. It appears that this is the first case report to describe OMAS related to CHKV–DENV infection. In fact, no cases of OMAS in association with CHKV have been reported to date, and a literature review identified just four cases of DENV-associated OMAS (Tan et al., 2014; Verma et al., 2014).

Empirical therapy for OMAS consists of immunosuppressive agents. Meanwhile, OMAS associated with viral infection seems to have a benign outcome, with prompt recovery observed in response to corticosteroids, or even full recovery without specific therapy (Gorman, 2010). While the case reported herein was initially treated with IVIG, resulting in a mild improvement, full recovery was only obtained after a course of methylprednisolone pulse therapy. Previously reported dengue-related OMAS cases were treated with low-dose clonazepam or prednisolone, with complete recovery occurring similarly to the present case (Tan et al., 2014).

While the pathogenesis of OMAS is not completely understood, autoimmune-mediated dysfunction has been suggested as the underlying mechanism (Blaes et al., 2008). It has been hypothesized that sequential arbovirus infections may cause immunological enhancement, which could be related to severe clinical forms of dengue (Solomon et al., 2000), or the triggering of neurological complications in ZIKV infection (Cao-Lormeau et al., 2016). Accordingly, it is possible that the co-infection by two distinct arboviruses seen in this case may have brought about the onset of OMAS.

Due to the similarity in transmission vector and geographical distribution of outbreaks, CHIKV–DENV co-infection could plausibly arise in endemic regions. However, as a result of similarity in clinical presentation, co-infection could well go undiagnosed. Many cases described previously as co-infections utilized serology as a diagnostic technique, which does not rule out the possibility of sequential infection, as opposed to concomitant infection. In the case presented here, CHIKV–DENV co-infection was diagnosed based on the RT-qPCR detection of both viruses in a single plasma sample, thereby confirming the concomitant nature of the reported co-infection. Furthermore, the presence of CHIKV RNA in the patient's CSF sample highlights the potential of this emergent arbovirus to present possible neurotropism.

Phylogenetic analysis indicated that this patient was co-infected with CHIKV ECSA and DENV-4 genotype II. The CHIKV ECSA genotype was introduced into Bahia, Brazil in mid-2014 (Nunes et al., 2015), and since the first detection of DENV-4 in Brazil in 1982, phylogeographic analyses have confirmed the co-circulation of two distinct DENV-4 genotypes (I and II) in Brazil (Nunes et al., 2012).

In summary, this report describes a case presenting CHIKV–DENV co-infection in association with OMAS, which reinforces the potential association between emergent arboviruses and neurological syndromes. This case should serve as an alert for clinicians to be vigilant with respect to neurological complications in regions affected by arbovirus outbreaks.

Author contributions

(1) Research project: A. conception; B. organization, C. execution; (2) Statistical analysis: A. design, B. execution, C. review and critique; (3) Manuscript: A. writing of the first draft, B. review and critique. MSR: 1A, 1B, 1C, 3A, 3B; MG: 2A, 2B, 3B; PAPJ: 1B, 1C, 3B; DSF: 1B, 1C; NRF: 2A, 2B, 2C, 3B; CPSL: 1B, 1C; SPS: 1B, 1C; MRN: 1B, 1C, 3B; LCJA: 1A, 2A, 2C, 3B; ICS: 1A, 1B, 2A, 3A, 3B.

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Ethical approval

Written informed consent was obtained from this patient for participation in the present case study.

Conflict of interest

The authors deny the existence of any potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.07.019.

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