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CASE REPORT

Alice in Wonderland syndrome: a novel neurological presentation of Zika virus infection

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Abstract

Zika virus (ZIKV) is a flavivirus endemic in Africa and Southern Asian countries, which has recently emerged in unprecedented epidemic proportions around the world. Although ZIKV infection is often asymptomatic or distinguished by non-specific influenza-like symptoms, an increase in its pathogenicity and biological behavior has been the hallmark of the current pandemic. Increasing evidence suggests that neurotropic strains of ZIKV have evolved from less pathogenic strains of the virus. Neurological manifestations of ZIKV infection include a spectrum of congenital and non-congenital clinical entities, however visual somatosensory perceptual disorders have not been recorded to date. Herein, we report a case of a 15-year-old female who presented with a constellation of perceptual symptoms (metamorphopsia, telopsia, and pelopsia) following acute ZIKV infection. Although such symptoms may have originated from direct viral injury, a post-ZIKV autoimmune reaction to previously unexposed neuronal surface antigens or through molecular mimicry cannot be excluded. The development of Alice in Wonderland syndrome in our patient highlights the ever-increasing expanding spectrum of neurological symptoms associated to ZIKV infection.

Keywords Zika virus · Alice in Woderland syndrome · Viral · Metamorphopsia

Case report

A 15-year-old adolescent female with no significant past medical history presented to our clinic complaining of visual distortion of her body shape, confusion, and increased anxiety. 10 days prior she had developed a pruritic maculopapular-rash, fever (38.5 °C), malaise, and distal small joint arthralgia, which resolved uneventfully after 3 days. At that time a

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complete blood-count was notable for total leukocytes of 8.700/mm^3, 54.6% lymphocytes, 2.5% monocytes, and an elevated erythrocyte sedimentation rate (95 mm). Immunofluorescence testing for Zika virus (ZIKV), chikungunya virus (CHIKV), and dengue virus types 1–4 (DENV) was performed using the IIFT Arboviral Fever Mosaic 2 Euroimmun AG® IgG, IgM Test System (Euroimmun AG® Luebeck, Germany) revealing a positive IgM and negative IgG antibodies against ZIKV, as well as no detectable antibodies to CHIKV nor DENV serotypes. Additional serologic testing for EBV, CMV, rubella, and parvovirus were negative. A urine sample was sent to a reference laboratory for nucleic acid amplification tests returning positive for ZIKV genomic RNA (vRNA) by real-time PCR.

According to her parents she had remained asymptomatic for 7 days after resolution of her ZIKV symptoms, after which she started experiencing multi-daily episodes of visual aberrations including a distorted perception (in size and shape) of her body, as well as those of her close relatives. She perceived her head and hands as exceptionally large with a small trunk and distorted limbs, and occasionally, she also perceived objects as being closer or further away in relation to herself, along with a feeling of being "haunted" (Fig. 1). Her past medical history was unremarkable, with no history of migraines, seizures, neurological impairment, medication or recreational drug consumption, exposure to pets/animals, sick contacts, or recent travel history.

Her physical examination was unremarkable except for slight residual joint pain. Neurologic examination yielded normal sensory, motor, and cerebellar function. Ophthalmologic, including fundoscopic examination was normal. A computed tomography (CT) scan of brain was normal, and an electroencephalogram revealed a normal base wave pattern with no evidence of high voltage slow waves or bursts suggestive of epileptiform activity nor evidence of encephalopathy. Subsequent scans of chest, abdomen, and pelvis were also unremarkable.

A complete blood count, chemistry, metabolic panel, and urine toxic screen were normal. Additional screening for herpes simplex virus types 1 and 2, varicella zoster, enterovirus, HIV, syphilis, and Toxoplasma returned negative as well. Results from a paraneoplastic autoantibody (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) yielded negative results. Because de diagnosis of NMDR encephalitis was entertained, anti-N-methyl-D-aspartate receptor (anti-NMDA-R) IgG both in serum and CSF was sent for testing and were also negative. A lumbar puncture revealed a normal opening pressure with cerebrospinal fluid studies revealing absence of pleocytosis, elevated protein, or presence of oligoclonal bands.

Because autoimmune encephalitis was favored in our differential diagnostic workup, she was subsequently treated with intravenous immunoglobulin (IVIG), steroids, and acyclovir with gradual slight improvement, thus deciding to install adjunctive treatment with therapeutic plasma exchange (TPE) for a total of four sessions (1.2 plasma volume, alternate day) with 2.5 L of 5% albumin solution used as replacement fluid after which the patient completely recovered in 2 weeks.

Discussion

Alice in Wonderland syndrome (AWS) is a perplexing neurological condition with a wide array of symptoms that include alterations in perception on the size of objects and/or body parts (metamorphopsias), illusions of expansion, reduction or distortion of body image, hallucinations—which may

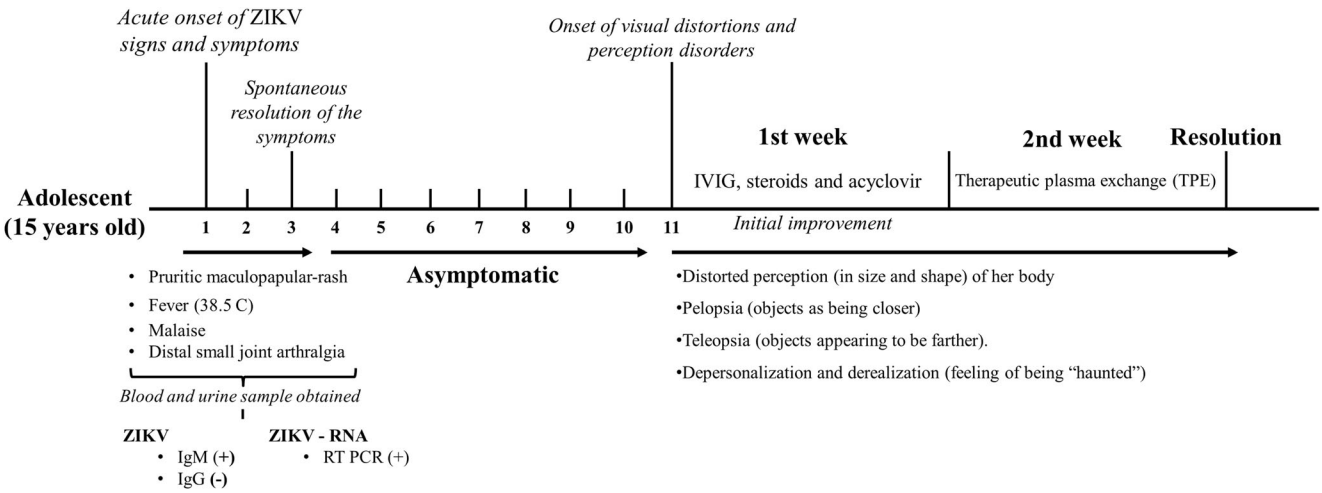

Fig. 1 Clinical timeline of patient depicting testing results (serology and nucleic acid amplification test –RT-PCR) as well as main clinical events and therapeutic interventions. ZIKV denotes Zika virus, IVIG intravenous immunoglobulin

involve animals (zoonopsia)—, as well as a distorted sense of time and space perspective (Farooq and Fine 2017).

To date, the underlying mechanisms responsible for the somesthetic distortions in AWS remain poorly understood. Nevertheless, several theories examining functional and structural correlates have been proposed (Mastria et al. 2016).

Migraines, medications, infections (Weidenfeld and Borusiak 2011; O'Toole and Modestino 2017), epilepsy, schizophrenia (Weidenfeld and Borusiak 2011; O'Toole and Modestino 2017), cerebral lesions, and intoxications with psychoactive drugs have all been linked with the development of AWS clinical symptoms along its spectrum (Fine 2013; O'Toole and Modestino 2017). In particular relation to its infectious etiology, inflammation and edema, as well as blood flow disturbances to areas of the sensory cortex and visual network appear to influence the development of altered visual and sensory perceptions (O'Toole and Modestino 2017). Infectious agents associated with the development of AWS to date include Epstein-Barr (EBV), cytomegalovirus, varicella zoster (VZV), herpes simplex (HSV) Coxsackie, and influenza virus, as well as bacterial agents such as *Streptococcus pyogenes*, *Borrelia* sp. (Mastria et al. 2016), and *Mycoplasma pneumoniae* (Omata et al. 2016).

Most symptoms in AWS are attributed to affectation of the centrally located populations and cell columns responding to specific types of sensory input (cortical areas V1–V5), specifically those of the temporo-occipital regions which represent the crossroad where visual and somatosensory stimuli are processed and integrated to construct and translate the self-representation. (Mastria et al. 2016).

A possible explanation on how ZIKV infection triggers these symptoms would be by direct neuronal destruction inflicted by the virus on the above-mentioned areas. Support for this hypothesis comes from recent findings reporting on the presence of lysed cells and extensive areas of apoptosis affecting cortical and subcortical white matter (Mlakar et al. 2016; Driggers et al. 2016), occasionally comprising the whole cortical ribbon (Mlakar et al. 2016), and affecting also intermediately differentiated post-migratory neurons in the neocortex after ZIKV infection (Driggers et al. 2016). Nevertheless, the complete absence of imaging and electroencephalographic findings in this case militates partly against this hypothesis.

An alternate explanation for this case given the absence of evident anatomical lesions relies on the potential of the virus on triggering specific autoantibodies against specific neuropil epitopes in selected anatomical regions of the visual sensory cortex. A number of mechanisms have been proposed in an attempt to explain the possibility of parainfectious development of autoantibodies in relation to neurotropic viral agents. In this sense, two theories have gained relevance over time including the development of molecular mimicry or an over-aberrant antiviral immune response resulting in exposure of self-antigen(s) and consequent bystander T-cell activation (Getts et al. 2013).

The well-documented evidence in the relationship of ZIKV with the development of Guillain-Barre syndrome suggests that viral infection and antiviral immunity may play a potential role through which the virus can perhaps lead to neurological impairment via development of autoimmunity in a similar fashion to other neurotropic viruses such as HSV (Galli et al. 2017), EBV (Linnoila et al. 2016; Galli et al. 2017) CMV (Lucchese and Kanduc 2017) and HTLV-1 (Araujo and Silva 2006). In addition, a varying degree of viral induced neuronal tissue lysis and lympho-histiocytic inflammation may also lead to the development of autoimmunity against previously unexposed neuronal antigens through epitope spreading, thus triggering the release of self-antigens that lead to de novo activation of autoreactive responses (bystander activation of autoreactive cells) (Getts et al. 2013). Nevertheless, these non-mutually exclusive immunological mechanisms may also play a combined role in the breakdown of immune tolerance (Getts et al. 2013) as we speculate for this case.

Experimental evidence suggests that flaviviruses are capable of provoking MHC class I upregulation leading to transient T-cell autoimmunity (Lobigs et al. 1996) and at the same time downregulate both autoimmunity and virus-specific T cell memory (Lobigs et al. 1996). Other models studying Theiler's murine encephalomyelitis virus (TMEV), as well as the Semliki Forest virus (Togaviridae, alphavirus) provide further evidence on the development of antibodies reactive to myelin basic protein (*MBP*) and myelin oligodendrocyte glycoprotein (*MOG*) epitopes (Getts et al. 2013), unveiling a role for T-cell-mediated autoimmunity.

As in this case, antibody-associated encephalitis-like symptoms can, but not always, exhibit associated electroencephalographic (EEG) or neuroimaging (CT/MRI) changes as well as abnormal CSF alterations such as pleocytosis, increased protein levels or presence of oligoclonal bands as also seen in other types of limbic encephalitis. (Tüzün and Dalmau 2007). The slight improvement noticed after initiating steroid treatment and subsequent improvement and prevention of further development of symptoms in our patient after the therapeutic plasma exchange trial strongly argues in favor of a role for post-viral induced autoimmunity phenomena (Tunkel et al. 2008). To our knowledge, this is the first report on this novel clinical expression of ZIKV-related neurological disease.

Here, we provide further evidence on the potential role of ZIKV not only as an emerging neuropathogen but also, its likely involvement in the development autoimmunity and its possible mechanisms, while providing potential insights into therapeutic implications of this rare clinical presentation. Future studies should focus on exploring the immune and inflammatory microenvironment in ZIKV CNS infection.

Compliance with ethical standards

Conflict of interest No conflict of interest declared.

Informed consent Informed consent was obtained from all individual participants included in the study.

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