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Chikungunya virus infection in a patient with *Myasthenia gravis*: A case report of lethal meningoencephalitis associated with high viral load.

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ABSTRACT

Background: Chikungunya virus (CHIKV) is a reemerging arbovirus. Besides its classical acute symptoms, rare complications such as myocarditis, hepatitis, Guillain-Barré syndrome, encephalitis and meningoencephalitis are being increasingly reported worldwide

Case presentation: In the present study, we report a case of lethal encephalitis caused by CHIKV associated with high viral load in an immunosuppressed patient

Case report: A 45-year-old woman with medical history of *Myasthenia gravis* had onset of fever (Day 1), followed by skin rash and polyarthralgia of large joints. Headache and lethargy started on Day 4. On Day 7, she was hospitalized, and four days later she developed neurological deterioration, being transferred to the Intensive Care Unit. Analysis of cerebrospinal fluid (CSF) suggested viral meningoencephalitis. The first CT-scan showed no significant findings, but real time quantitative PCR was positive for CHIKV in CSF with high viral load. About 24 h after the first CT-scan, brain edema was evident on the second CT-scan. On Day 26, the patient presented progressive deterioration of brain activity and died. Few other cases of patients presenting neurological complications associated with CHIKV were reported in Brazil already, including a patient with *Myasthenia gravis* and myelitis due to CHIKV

Conclusions: These cases suggest such autoimmune disorder may favor CHIKV invasion of nervous system. The present case points out the potential relation of immunosuppressive conditions and severe neurological disease caused by CHIKV infection.

Case report

Chikungunya virus (CHIKV) is a reemerging arbovirus (family *Togaviridae*, genus *Alphavirus)* transmitted by *Aedes* mosquitoes (Burt et al., 2017). In Brazil, an epidemic situation was declared in 2015–2016, and at present, CHIKV still co-circulates with Zika virus (ZIKV) and Dengue virus (DENV) (Silva et al., 2019). The clinical presentation of CHIKV infection is usually an acute febrile illness which begins with high fever, arthralgia, myalgia, headache, nausea, fatigue and skin rash (Burt et al., 2017; Silva et al., 2019). Complications such as myocarditis, hepatitis, Guillain-Barré syndrome (GBS), encephalitis and meningoencephalitis were rarely reported. However, neurological complications of CHIKV are being increasingly reported worldwide (Mehta et al., 2018b, a).

In the present study, we report a case of lethal encephalitis caused by CHIKV infection in a patient with *Myasthenia gravis*. The study was approved by the INCA's Ethics Committee (CAAE 60,385,416.1.0000.5274). A 45-year-old woman with medical history of *Myasthenia gravis* in treatment with prednisone and azathioprine had onset of fever as first symptom on 04/06/2018 (Day 1) followed by skin rash and polyarthralgia of large joints. Headache and lethargy started on 04/10/2018 (Day 4). On 04/13/2018 (Day 7), she was hospitalized because of progressive worsening of clinical status. Physical examination revealed skin rash with petechiae in the trunk and edges of the upper limbs, subconjunctival petechiae, and edema in wrist and knee

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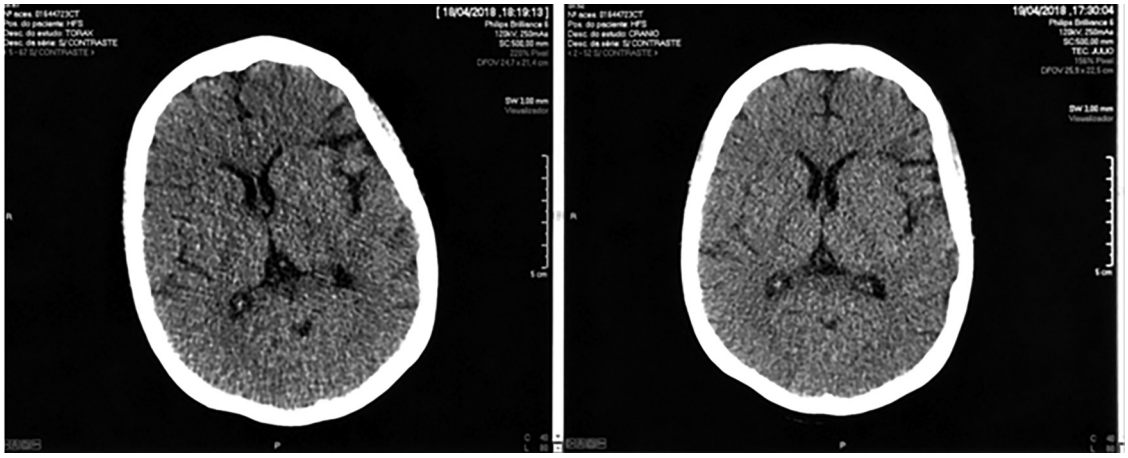

Fig. 1. Computed tomography (CT) scan of the cranium, on 04/18/2018 (image in the left side) and 04/19/2018 (image in the right side), showing the development of evident brain edema along the period of 24 h.

joints; abnormal consciousness (lethargic but responsive to verbal commands), with voluntary movement of arms and legs capable of overcoming "some" resistance. No signs of focal findings and meningeal irritation were present. Initial white blood cell count of 13,630 (82% neutrophils, 9.6% lymphocytes) and 279,000 platelets/mm^3, which ensued with progressive thrombocytopenia. The diagnostics of arboviruses, encephalitis, sepsis and infective endocarditis (IE) associated with *Myasthenia gravis* decompensation were hypothesized. Empiric treatment with immunoglobulin and piperacillin-tazobactam was initiated. On 04/17/2018 (Day 11), she developed respiratory failure and neurological deterioration (deep stupor) with brainstem reflexes present, being transferred to the Intensive Care Unit. Analysis of cerebrospinal fluid (CSF) showed presence of pleocytosis with lymphocytic predominance (cell count 118 cells/mm^3; 117 lymphocytes/mm^3) plus mild elevation of protein and decrease of glucose concentrations (protein 143 mg/dL, glucose 70 mg/dL), suggesting viral meningoencephalitis. At this time, the antimicrobial therapy was changed with ceftriaxone, vancomycin and acyclovir being initiated. Findings of trans-thoracic echocardiography (04/18/2018) were not suggestive of IE. The first computer tomography (CT) scan (04/18/2018) showed no significant findings, while 24 h later brain edema was evident (Fig. 1). Blood and CSF cultures had no microbial growth. Differential diagnosis among CHIKV, DENV and ZIKV was performed by standardized RT-qPCR assays (Supplementary Fig. 1 and references therein). RT-qPCR was positive for CHIKV in CSF, serum, and urine (04/18/2018), and negative for all other virus investigated. Viral load of CHIKV was 61,711,049.75 copies/mL in serum; 27,305.74 copies/mL in urine and 300,861.75 copies/mL in the CSF. Between Day 11 and Day 13 of the disease, the patient had progressive deterioration of brain activity culminating with coma, median pupils' dilation without light reaction, bilateral reduction of corneal blink reflex response, oculo-cephalic response present in the right side only, cessation of the cough reflex, with respiratory drive still present. In 05/02/2018 (Day 26), despite life support measures, she developed clinical evidence of irreversible brain failure with dilated pupils, cessation of brainstem reflexes, refractory shock, and died.

Discussion

In this report, a fatal case of meningoencephalitis associated with high load of CHIKV in a patient receiving immunosuppressive therapy for *Myasthenia gravis* is described. In the present case, the inflammatory characteristics of CSF, progressive detection of brain activity, elevated load of CHIKV in CSF, and CT-scan showing brain edema support the diagnosis of encephalopathy due to meningoencephalitis caused by CHIKV. The clinical findings suggesting infection of central nervous system (CNS) occurred about four days after the fever onset (prodrome length), followed by progressive brain deterioration along three weeks until death. This poor outcome was associated with high viral load of CHIKV in CSF and serum. Encephalopathy is one of the most common neurological presentations in arbovirus infection. Although encephalitis is strictly a pathological diagnosis, it can be diagnosed in encephalopathic patients if there is evidence of brain inflammation (Mehta et al., 2018a), as happened in the present case.

The circulation of CHIKV in Brazil did not stop from 2015 up to now. In the first semester of 2021, there were 63,713 notifications of probable cases of CHIKV infection in our country (Saúde, 2021). In this period, some cases of encephalitis, meningoencephalitis, myelitis, and other complications associated to CHIKV infection were reported (Scott et al., 2017; de Azevedo et al., 2018; Mehta et al., 2018b; de Lima et al., 2020; de Almeida Oliveira Evangelista et al., 2021; Rueda-Lopes et al., 2021). However, the immune status and outcome of the patients were not declared, as well as RT-qPCR for CHIVK infection diagnosis was not routinely performed in most of them. In the present case, the association between high viral load of CHIVK in CSF and lethal outcome due to meningoencephalitis is firstly presented. Similarly to the present report, a female patient presenting *Myasthenia gravis* was previously described with neurological complication due to CHIKV infection, specifically myelitis (Rueda-Lopes et al., 2021). Thus, we may speculate that such autoimmune disorder may unbalance the neuromuscular junction and postsynaptic tissue, favoring the CHIKV entry in the CNS.

Data about group of patients with high risk of severe manifestations of CHIKV infection are limited. The present case points out the potential association between immunosuppressive conditions and severe neurological disease caused by CHIKV infection.

Contributions

All the authors made significant contributions to this study. Lorena Uruçu carried out patient assessments, follow-up and wrote the first draft, André de Albuquerque, Christian Naurath, Marcia Carreira and Marianne Garrido were involved in work management, Vanessa Emmel performed the arbovirus molecular diagnosis and prepared the manuscript, Bianca Gama performed the arbovirus molecular diagnosis, prepared the manuscript and discussed the final manuscript, Rocio Hassan and Ianick Martins conceived the idea of the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper. The authors declare that they have no conflicts of interest..

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nerep.2022.100099.

References

Burt, F.J., Chen, W., Miner, J.J., et al., 2017. Chikungunya virus: an update on the biology and pathogenesis of this emerging pathogen. Lancet Infect. Dis. 17, e107–e117.

de Almeida Oliveira Evangelista, G., Carvalho, R.H., menezes, G.S., et al., 2021. Meningoencephalitis associated with Zika virus and Chikungunya virus infection. Jpn. J. Infect. Dis..

de Azevedo, M.B., Coutinho, M.S.C., da Silva, M.A., et al., 2018. Neurologic manifestations in emerging arboviral diseases in Rio de Janeiro city, Brazil, 2015-2016. Rev Soc Bras Med Trop 51, 347–351. doi:10.1590/0037-8682-0327-2017.

de Lima, E.C.B., Januário, A.M.S., Fortuna, E.G., et al., 2020. Chikungunya encephalitis: report of a fatal case in northeastern Brazil. Rev. Inst. Med. Trop. 62, 1–5. doi:10.1590/S1678-9946202062040, Sao Paulo.

Mehta, R., Gerardin, P., de Brito, C.A.A., et al., 2018a. The neurological complications of chikungunya virus: a systematic review. Rev. Med. Virol. 28. doi:10.1002/rmv.1978.

Mehta, R., Soares, C.N., Medialdea-Carrera, R., et al., 2018b. The spectrum of neurological disease associated with Zika and chikungunya viruses in adults in Rio de Janeiro, Brazil: a case series. PLoS Negl. Trop. Dis. 12. doi:10.1371/journal.pntd.0006212.

Rueda-Lopes, F.C., da Cruz, L.C.H., Fontes, F.L., et al., 2021. Clinical and magnetic resonance imaging patterns of extensive Chikungunya virus–associated myelitis. J. Neurovirol. 27, 616–625. doi:10.1007/s13365-021-00962-4.

Saúde, 2021. Monitoramento dos casos de Arboviroses urbanas transmitidas pelo Aedes (dengue, chikungunya e Zika). Bol Epidemiológico Arboviroses 51, 1–13.

Scott SS de, O., Braga-Neto, P., Pereira, L.P., et al., 2017. Immunoglobulin-responsive chikungunya encephalitis: two case reports. J. Neurovirol. 23, 625–631. doi:10.1007/s13365-017-0535-y.

Silva, M.M.O., Tauro, L.B., Kikuti, M., et al., 2019. Concomitant transmission of Dengue, Chikungunya, and Zika Viruses in Brazil: clinical and epidemiological findings from surveillance for acute febrile illness. Clin. Infect. Dis. 69, 1353–1359. doi:10.1093/cid/ciy1083.