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CASE REPORT

# Meningitis determined by oligosymptomatic dengue virus type 3 infection: Report of a case

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## KEYWORDS

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**Summary** Dengue infection is a mosquito-borne disease caused by a flavivirus, and is recognized in over 100 countries with 2.5 billion people living in areas of risk. Neurological manifestations such as encephalitis, myelitis, Guillain–Barré syndrome, cranial nerve palsies, neuromyelitis optica, and encephalomyelitis have been recognized as clinical consequences of dengue infection. Meningitis is a rare complication. We report the case of a 24-year-old woman who presented with fever, headache, and nuchal rigidity without the typical symptoms of dengue infection. Cerebrospinal fluid analysis showed lymphocytic pleocytosis with a normal glucose value and negative bacterial and fungal cultures. The etiology of meningitis was confirmed by positive dengue PCR in the serum. This case report highlights dengue infection as a potential cause of meningitis in endemic areas. Also, meningitis can be the first manifestation of the infection. Dengue should be investigated even in the absence of a typical picture of the infection.

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## Introduction

Dengue infection is caused by a flavivirus, and is recognized as one of the most important mosquito-borne human infections of the 21<sup>st</sup> century.<sup>1</sup> The number of cases has increased enormously, arising from more than 100 tropical and sub-

tropical countries of the world, with 2.5 billion people living in areas of risk.<sup>2</sup> Dengue virus type 3 (DENV-3) was isolated in Brazil for the first time in December 2000. During the DENV-3 epidemic of 2002, the number of dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS) cases and deaths exceeded the number of these cases caused by other serotypes of dengue virus in other epidemics.<sup>3</sup> This virus type is also more related to neurovirulence.<sup>4</sup>

Several neurological manifestations have been described each year, however the prevalence of neurological manifestations is unknown. Atypical neurological complications have

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been reported as acute disseminated encephalomyelitis,<sup>5</sup> neuromyelitis optica,<sup>6</sup> and Guillain–Barré syndrome, the last one with poor or without dengue infection signs before the neurological picture.<sup>7</sup> Encephalitis is the most common neurological manifestation associated with dengue infection. Unlike other viral infections, meningitis determined by dengue infection is a rare complication.<sup>8</sup>

We describe a case of meningitis caused by an oligosymptomatic dengue infection that occurred during the dengue epidemic of 2007–2008, in the city of Rio de Janeiro, Brazil.

## Case report

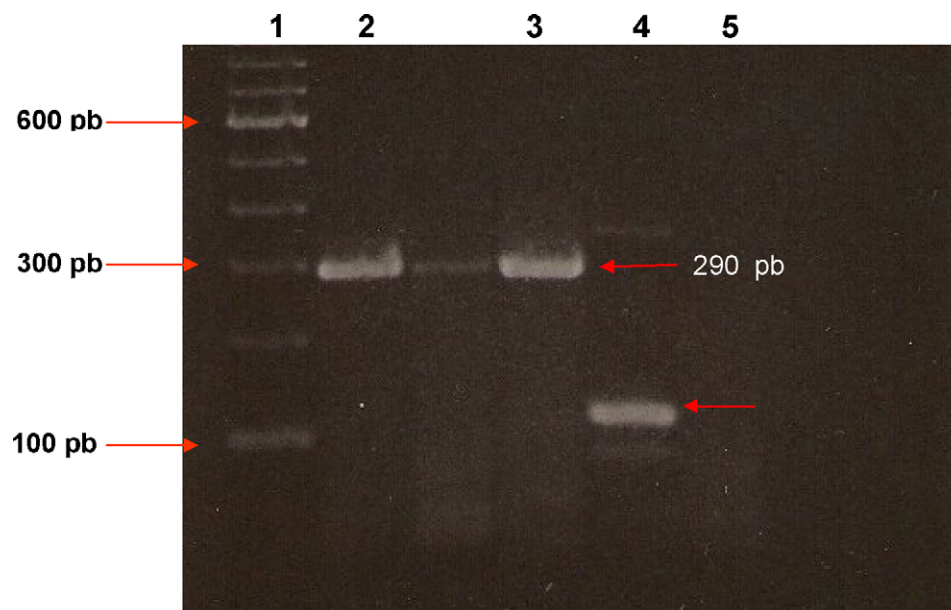
A 24-year-old woman complained of a frontal, throbbing headache, refractory to analgesic drugs. One day after the onset of pain, she developed fever and vomiting. The symptoms remained for four days. There was no myalgia, joint pain, bleeding, diarrhea, cutaneous rash, or past history of dengue. A neurological examination was normal, except for the presence of nuchal rigidity +/4 + . Hemogram/platelet count and biochemistry were normal. A brain computed tomography scan did not show any abnormalities. Cerebrospinal fluid (CSF) was collected by lumbar puncture on the fourth day of symptoms and showed  $362 \times 10^6$  cells/l (66% of lymphocytes), glucose of 86 mg/dl, and total protein of 144 mg/dl. On analysis of the CSF, bacterial/fungal cultures and immunological testing for syphilis (VDRL) were negative, as well as human T-lymphotropic virus I (HTLV-I), herpes simplex virus (HSV), varicella zoster virus, cytomegalovirus (CMV), and HIV1/2 antibodies (by ELISA). During hospitalization the serum and CSF were dengue IgM and IgG antibody negative (ELISA, Panbio, Australia). PCR for dengue was positive in the serum, for virus type 3. This was performed using a reverse transcriptase-PCR (RT-PCR) following the procedure described by Kumaria and Chakravarti<sup>9</sup> (Figure 1). PCR for HSV, CMV, and enterovirus were negative.

After analgesic treatment and venous hydration, the patient's symptoms disappeared completely.

## Discussion

Our case occurred during the dengue epidemic of 2007–2008 and did not have the typical infection symptoms of dengue. There was no history of muscle pain, diarrhea, joint or abdominal pain, petechiae or purpura, thrombocytopenia, rash, or bleeding. The main symptom was the severe headache, which was refractory to analgesics and throbbing, determining hospitalization. According to the literature,<sup>10</sup> headache is described as extremely severe in 51.8% of dengue cases and severe in 27.1%. However, CSF analysis is not used as a routine exam to differentiate a common dengue headache from meningitis. This fact makes dengue meningitis underestimated. Our case, besides the intense headache, also presented nuchal rigidity, suggesting a meningeal involvement.

To our knowledge, there have been no other descriptions of meningitis caused by dengue virus type 3 infection, since only dengue encephalitis has been reported. This is the first description of the disease in adults, confirmed by PCR. The hypothesis of meningismus was discarded, since the CSF sample showed active inflammation, characterized by pleocytosis and hyperproteinorachia. Although the virus was not found in the CSF, its presence in the serum confirms the diagnosis. Dengue PCR has a sensitivity of 98–99% and a specificity of 100% in serum during the first five days of symptoms.<sup>11</sup> The pathogenesis of dengue in the central nervous system is still unknown. As a hypothesis, the virus would invade the central nervous system. The breakdown of the blood–brain barrier during dengue infection in mice, determining virus invasion, was demonstrated by Chaturvedi et al.<sup>12</sup> However, the sensitivity and specificity of the PCR technique for the CSF have not been established. Hence, a



**Figure 1** Dengue type 3 detection by RT-PCR. Lane 1, molecular standard; lane 2, patient sample (dengue type 3); lane 3, positive dengue 3 control; lane 4, positive dengue 2 control; lane 5, negative control.

low concentration of the virus in the CSF may not be detected. The negativity of dengue IgM antibody was expected because the blood and CSF samples were collected before the seventh day after the onset of symptoms. Dengue IgM antibody can appear, in half of the patients, within 2–3 days of defervescence.<sup>13</sup>

Other causes of viral meningitis, mainly that as a result of enteroviruses, should be investigated in the differential diagnosis. Enteroviruses are responsible for 85% of viral meningitis cases, being usually benign and associated with a broad range of diseases, from an undifferentiated febrile illness to distinct clinical syndromes (herpangina, hand-foot-mouth syndrome, and pleurodynia).<sup>14</sup> Our case had non-specific clinical characteristics and the enterovirus diagnosis could only be discarded by the negative PCR test.

In conclusion, our report demonstrates that CSF analysis is necessary to differentiate headache due to systemic infection from that due to meningitis. In addition, meningitis can be the first manifestation of dengue infection. In endemic areas, dengue infection should be suggested and tested as a probable etiological agent of meningitis.

*Conflict of interest:* No conflict of interest to declare.

## References

1. Dash PK, Parida MM, Saxena P, Abhyankar A, Singh CP, Tewari KN, et al. Reemergence of dengue virus type-3 (subtype-III) in India: implications for increased incidence of DHF/DSS. *Viol J* 2006;3:55.
2. Guzman MG, Kouri G. Dengue and dengue hemorrhagic fever in the Americas: lessons and challenges. *J Clin Virol* 2003;27:1–13.
3. Nogueira RM, Shatzmayr HG, Filippis AM, Santos FB, Cunha RV, Coelho JO, et al. Dengue virus type 3, Brazil, 2002. *Emerg Infect Dis* 2005;11:1376–81.
4. Thisyakorn U, Thisyakorn C, Limpitikul W, Nisalak A. Dengue infection with central nervous system manifestations. *Southeast Asian J Trop Med Public Health* 1999;30:504–6.
5. Yamamoto Y, Takasaki T, Yamada K, Kimura M, Washizaki K, Yoshikawa K, et al. Acute disseminated encephalomyelitis following dengue fever. *J Infect Chemother* 2002;8:175–7.
6. Miranda de Sousa A, Puccioni-Sohler M, Dias Borges A, Fernandes Adorno L, Papais Alvarenga M, Papais Alvarenga RM. Post-dengue neuromyelitis optica: case report of a Japanese-descendent Brazilian child. *J Infect Chemother* 2006;12:396–8.
7. Soares CN, Faria LC, Castro-Cabral M, Oliveira C, Peralta JM, Freitas MR, et al. Oligosymptomatic dengue infection: a potential cause of Guillain–Barré syndrome. *Arq Neuropsiquiatria* 2008;66:234–7.
8. Soares CN, Faria LC, Puccioni-Sohler M, Peralta JM, De Freitas MR. Dengue infection: neurological manifestations and cerebrospinal fluid (CSF) analysis *J Neurol Sci* 2006;249:19–24.
9. Kumaria R, Chakravarti A. Molecular detection and serotypic characterization of dengue viruses by single-tube multiplex reverse transcriptase-polymerase chain reaction. *Diagn Microbiol Infect Dis* 2005;52:311–6.
10. Domingues RB, Kuster GW, Castro FL, Souza VA, Levi JE, Pannuti CS. Headache features in patients with dengue virus infection. *Cephalalgia* 2006;26:879–82.
11. Yong YK, Thayan R, Chong HT, Tan CT, Sekaran SD. Rapid detection and serotyping of dengue virus by multiplex RT-PCR and real-time SYBR green RT-PCR. *Singapore Med J* 2007;48:662–8.
12. Chaturvedi UC, Dhawan R, Khanna M, Mathur A. Breakdown of the blood–brain barrier during dengue infection of mice. *J Gen Virol* 1991;72:859–66.
13. World Health Organization. Dengue haemorrhagic fever: diagnosis, treatment, prevention and control. 2<sup>nd</sup> ed. Geneva: WHO; 1997, p.1-87.
14. Dedicat M, Muir D. Viral meningitis or encephalitis? *Practitioner* 1998;242:489–92.