


First cases of DENV-3 circulation in the Casanare region of Colombia

Primeros casos de circulación DENV-3 en la región colombiana de Casanare

Primeiros casos de circulação de DENV-3 na região colombiana de Casanare

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Received: 22-05-2024 Accepted: 06-10-2024 Published: 11-10-2024

ABSTRACT

Dengue is a viral infection found in tropical and subtropical areas. It has four serotypes: DENV-1, DENV-2, DENV-3 and DENV-4. In the last 50 years the incidence of dengue has increased throughout the world. The first three cases with isolation of DENV-3 in the Casanare region, Colombia are presented: an adult woman and two children. Of the latter: a 6-year-old girl and a 7-month-old boy; which shared clinical characteristics, such as fever and abdominal pain. The first case presented rapid remission, with dengue with warning signs, and the children with severe dengue. The girl progressed adequately, but the 7-month-old boy with severe dengue died. The introduction of a new serotype into areas affected by preexisting serotypes constitutes a risk factor for dengue with warning signs and severe dengue.

Keywords: dengue virus; thrombocytopenia; leukopenia; severe dengue; serositis; pleural effusion

RESUMEN

El dengue es una infección viral propia de áreas tropicales y subtropicales. Posee cuatro serotipos: DENV-1, DENV-2, DENV-3 y DENV-4. En los últimos 50 años la incidencia de dengue ha aumentado en todo el mundo. Se presentan los tres primeros casos con aislamiento de DENV-3 en la región de Casanare, Colombia: una mujer adulta y dos niños. De estos últimos: una niña de 6 años y un niño de 7 meses; los cuales compartieron características clínicas, como fiebre y dolor abdominal. El primer caso presentó remisión rápida, con dengue con signos de alarma, y los niños con dengue grave. La niña logró adecuada evolución, pero el niño de 7 meses con dengue grave falleció. La introducción de un nuevo serotipo en áreas afectadas por serotipos preexistentes constituye un factor de riesgo para el dengue con signos de alarma y el dengue grave.

Palabras clave: virus del dengue; trombocitopenia; leucopenia; dengue grave; serositis; derrame pleural



RESUMO

A dengue é uma infecção viral encontrada em áreas tropicais e subtropicais. Possui quatro sorotipos: DENV-1, DENV-2, DENV-3 e DENV-4. Nos últimos 50 anos a incidência da dengue aumentou em todo o mundo. São apresentados os três primeiros casos com isolamento de DENV-3 na região de Casanare, Colômbia: uma mulher adulta e duas crianças. Destes últimos: uma menina de 6 anos e um menino de 7 meses; que compartilhavam características clínicas, como febre e dor abdominal. O primeiro caso apresentou remissão rápida, com dengue com

sinais de alerta, e as crianças com dengue grave. A menina evoluiu adequadamente, mas o menino de 7 meses com dengue grave faleceu. A introdução de um novo sorotipo em áreas afetadas por sorotipos preexistentes constitui fator de risco para dengue com sinais de alerta e dengue grave.

Palavras-chave: vírus da dengue; trombocitopenia; leucopenia; dengue grave; serosite; derrame pleural

Cómo citar este artículo:

García Agudelo L, Melo Mahecha Y, Medina Bernall MT. First cases of DENV-3 circulation in the Casanare region of Colombia RevInfCient [Internet]. 2024 [cited Access date]; 103:e4685. Available at: <http://www.revinfcientifica.sld.cu/index.php/ric/article/view/4685>

INTRODUCTION

Dengue is a disease caused by a virus transmitted by the bite of mosquitoes of the genus *Aedes* (*aegypti albopictus*) prevalent in tropical and subtropical regions of Africa, Southeast Asia, Pacific Ocean, Western Mediterranean and the Americas, mainly in urban and suburban areas,^(1,2) where the disease burden has increased in the last three decades and is expected to continue to increase due to population growth and rapid urbanization, inadequate sanitation and waste disposal, high geographic dispersion and increased vector competition in relation to climate change and virus evolution; It is therefore recognized as a global health threat by the World Health Organization (WHO) in 2019.⁽³⁾

Dengue virus is classified into four closely related serotypes named according to the chronology of discovery (DENV-1, DENV-2, DENV-3 and DENV-4). The simultaneous circulation of several serotypes in the same geographic region increases the likelihood that a person will be concurrently infected, i.e. infected with more than one serotype at the same time or sequentially infected by them, This leads to secondary infections that carry a risk of increasing the severity of the disease due to a complex immunological phenomenon of amplification dependent on the antibodies generated in the primary infection⁽⁴⁾, although it is not expected that all severe infections result from a secondary infection, taking into account the high risk of dengue complications in infants under one year of age.⁽⁵⁾

At the individual level, predictors of increased severity are age, sex, comorbidities, and infection with different serotypes.⁽⁵⁾ Approximately 80% of primary infections are asymptomatic, with less than 20% of infected persons manifesting symptoms. In persons with a secondary infection, 2 to 4% of cases progress to severe disease.⁽⁶⁾



It is recognized that the co-circulation of several serotypes is related to the severity of dengue infection, as occurs in Latin America, where the presence of the four serotypes has been demonstrated with individual variation between countries and time periods, which has led to postulate that one of the reasons for the high epidemiological impact of some serotypes in this region corresponds to intraserotype antigenic variation, which in turn can generate a different immunological response.⁽⁷⁾

In the Americas, the presence of serotype 3 was first identified in 1960 and was reported in Colombia between 1975-1977; although all four serotypes have been involved in outbreaks in the country, serotypes 1 and 2 have had the highest circulation rate since 1971 and have been associated with greater disease severity. Since 2001, the reappearance of serotype 3 was detected and since 2006, the presence of the three serotypes has increased in endemic areas.⁽⁸⁾

In Casanare, circulation of serotype 3 was reported only until 2024. Considering the epidemiological implications of the co-circulation of several serotypes, the main objective is to describe the first three cases of dengue caused by serotype DENV-3 in the region.

PRESENTATION OF THE CASES

CASE 1

A 27-year-old female patient, with no history of interest, presented with four days of fever of 40°C, associated with retroocular pain, left hemicranial headache, myalgia, arthralgias, asthenia, hyporexia, watery stools with mucus without blood, chest pain and dyspnea, she received treatment with acetaminophen without improvement.

Physical examination showed heart rate 96 beats/min, respiratory rate 16 resp/min, temperature 39.7 °C, blood pressure 93/58 mmHg, weight 55 kg, height 1.54 m, congestive oropharynx, with no other positive findings.

Laboratory tests were ordered: the hemogram reported leukopenia 3.17 and thrombocytopenia 100 800 per microliter (mCL). A presumptive diagnosis of dengue was made and confirmatory tests were ordered. Intravenous fluid was administered. In a new evaluation, an ultrasound report was obtained which showed scarce fluid in the abdominal cavity, the transaminase report was slightly elevated; the platelet count decreased to 66,000, the hematocrit was 38.5%, with no other alterations. The result of IgG Dengue was positive.

During the hospital stay, the patient presented remission of symptoms, with an increase in platelet count and was discharged from the hospital. The report of the viral isolation RT PCR for Dengue virus typing was positive for DENV-3.



CASE 2

A 6-year-old female patient, due to the first gestation of 40 weeks, delivery by cesarean section for meconium grade II, spontaneous neonatal adaptation, complete immunization for age. She presented four days of fever of 38 °C, one episode of vomiting and abdominal pain. Physical examination revealed vital signs: heart rate 116 beats/min, respiratory rate 17 resp/min, blood pressure 101/60 mmHg, temperature 38.6 °C, weight 17.50 kg, and height 1.17 m, with dry oral mucosa, without other findings.

As part of the treatment, intravenous fluids, oral antipyretic and laboratory tests were ordered. The hemogram reported thrombocytopenia of 39900 per microliter (mCL), hematocrit 42.6%, lymphocytes 78%, with no other findings; the urinalysis was normal. He was ordered to increase intravenous fluids, ultrasound and liver function tests, which were found to be elevated: alanine aminotransferase: 127 U/L and aspartate aminotransferase: 204 U/L. Ultrasound showed gallbladder edema, right pleural effusion, serositis and free fluid in the abdominopelvic cavity.

He was diagnosed with dengue with alarm signs and confirmatory tests were requested. Test reports IgG Dengue: Positive, IgM Dengue: Positive. During the stay, an additional diagnosis of associated pneumonia was made and antibiotic treatment was given for 10 days. She presented an adequate recovery, with an increase in platelet count and was discharged from the hospital. Subsequently, they reported the results of viral isolation RT PCR for dengue virus typing with a positive result for DENV-3.

CASE 3

Male patient, 7 months old, product of second gestation of 39 weeks, vaginal delivery, spontaneous neonatal adaptation, mother's hemoclassification O negative, patient's hemoclassification O positive. With a total of eight prenatal controls, study to rule out TORCH group infections (toxoplasmosis, rubella, cytomegalovirus, herpes simplex and HIV): negative, with complete vaccination for age.

She presented with a three-day clinical picture of fever of 38°C, associated with multiple episodes of vomiting and diarrhea. Initially, a complete blood count was ordered, which showed thrombocytopenia and mild anemia, and intravenous fluids and acetaminophen were prescribed. In a new laboratory control, the platelet count was lower than the previous value and the transaminases were elevated: alanine aminotransferase: 521 U/L and aspartate aminotransferase: 289 U/L. In addition, he had a generalized exanthema.

He was referred to another institution, with a diagnosis of dengue with alarm signs. On physical examination on admission to the receiving institution, he was found in poor general condition, with signs of severe dehydration, heart rate 164 beats/min, respiratory rate 40 resp/min, blood pressure 80/48 mmHg, temperature 36.5 °C, weight 8.1 kg, height 61 cm, with decreased vesicular murmur in the right hemithorax and generalized skin rash, with no other findings.



Laboratory and imaging tests were performed, due to high suspicion of severe dengue fever. The tests showed bilateral pleural effusion, free fluid in the abdominopelvic cavity, serositis, acalculous cholecystitis, low albumin, rising transaminases. He received management with intravenous fluids, antipyretic and was referred to the pediatric intensive care unit, where he died. Subsequently, the report of viral isolation RT-PCR for dengue virus typing was reviewed with a positive result for DENV-3.

DISCUSSION OF CASES

In a study conducted in Delhi, with a total of 440 acute phase samples, 4.77 % were positive for dengue NS1 Ag with a mean age of 35.1 years and a male to female ratio of 1.1:1. 38.09 % were positive by dengue RT-PCR and all belonged to serotype DENV-3. Analysis of the phylogenetic tree revealed that DENV-3 was grouped in genotype III, with 100 % homology with the 2008 Indian subcontinent strain.⁽⁹⁾ In this description, the first three cases to which the isolation of serotype DENV-3 was performed in the Casanare region were known, without having the possibility of performing intraserotype genetic analysis.

In 2022 in Nepal, RT-PCR analysis detected the circulation of three dengue serotypes: DENV-1, DENV-2 and DENV-3, with a predominance of serotypes 2 and 3, which in previous outbreaks had been less prevalent, so researchers propose that populations that have not been exposed to a specific serotype are at risk in future outbreaks,⁽¹⁰⁾ which can be considered in the population of Casanare, where previously there was no identification of serotype DENV-3.

Soe, et al.⁽¹¹⁾ analyzed DENV-1, DENV-2, DENV-3 and DENV-4 serotypes in 1235 serum samples collected between 2017 and 2019. They showed that most of the DENV-1-4 strains had been circulating in Myanmar for several years by whole genome sequencing. In addition, they identified the emergence of DENV-3 genotype I in 2017 samples, persistent during 2018 and 2019, which coincided with a period of increased DENV-3 cases and marked changes in serotype dynamics. However, no significant differences were detected between serum viral loads, disease severity, and infection status of individuals infected with different DENV serotypes during the 3 years of the study. Genotyping of the virus is not available in most regions in Colombia, so clinical follow-up and serological surveillance are the main tools to identify epidemiological dynamics in endemic regions.

In the department of Córdoba, in Colombia, they conducted a study between 2015 and 2016, where they obtained 294 samples from febrile patients; 33% of the samples were positive, 61.8% positive for dengue and 31% positive for Zika. The predominant serotype was DENV-2 (70.1%), followed by DENV-3 (8.9%), DENV-4 (6%) and DENV-1 (3%).⁽¹²⁾ In Casanare, serotypes 1 and 2 had been detected for many years and, currently, the first cases of DENV-3 were known in patients consulted for acute course fever and manifested alarm signs. No tests for co-infection between serotypes or with other arboviruses were performed.



On the other hand, in a study conducted in Bolivia 235 patients were identified between 2017 and 2020, 65 % were aged 19 to 45 years, 54 % were male and 56 % required hospitalization, 50 % presented symptomatology between the second and fifth day. Seventy-five percent had no alarm signs ($p < 0.01$). Fever ($p = 0.001$) was the most important symptom, associated with alarm signs such as abdominal pain, persistent vomiting and bleeding ($p < 0.05$). Leukopenia less than 5 000 mm³ was more common in women with alarm signs than in men. Thrombocytopenia was lower in men with alarm signs; hematocrit greater than 45% was more common in men, with more than 5 days of hospitalization ($p = 0.023$).⁽¹³⁾

In the present study, although no clinical comparisons were made with other cases caused by DENV-1 and DENV-2 serotypes, with respect to the clinical manifestations of the three cases in this description, fever was the main symptom, with the presence of other alarm signs, which led to hospital admission, treatment with intravenous fluids and strict follow-up.

With the advent of vaccines for the prevention of dengue in the region and the challenges faced in the development of an effective and safe vaccine, including a first vaccine licensed in Colombia for children over 9 years of age with seropositive status and a second vaccine licensed for children aged 4 to 16 years, whose efficacy against the four serotypes in seropositive patients is greater than in seronegative individuals, a low efficacy for serotype 3 and inconclusive data for serotype 4 were evidenced.⁽¹⁴⁾

FINAL CONSIDERATIONS

Constant surveillance of the circulating serotypes of DENV is important, since the introduction of a new serotype in areas affected by pre-existing serotypes constitutes a risk factor for requiring hospitalization and exhibiting more severe symptoms. Timely identification of warning signs and judicious clinical follow-up are essential to reduce the risk of complications. In addition, it is necessary to incorporate molecular analysis into local virological surveillance in order to better understand the behavior of the virus and its evolutionary process.

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Conflicts of interest:

The authors declare that there are no conflicts of interest.

Financing:

No funding was received for the development of this article.

