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RESEARCH ARTICLE

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HUMAN PARVOVIRUS IN DENGUE VIRUS NEGATIVE PATIENT SAMPLES IN SANTARÉM, WEST REGION OF PARÁ STATE

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ABSTRACT

The human parvovirus B19 (B19V) is an infectious viral agent associated with mild clinical conditions, such as the benign self-limiting exanthematous disease, but possibly fatal for fetuses. In this study, we observed positive cases of B19V in samples investigated due to suspicious dengue virus infection. The serum samples (n=17) were obtained in 2018 from patients attended by the public health system in Santarém municipality, located in the Amazon region of Brazil. Samples were submitted to ELISA (IgM) and also nested-PCR, presenting negative results to dengue virus in all tested samples. However, nested PCR detected five positive samples for B19V. The patients had fever, headache, and myalgia as the most frequent symptoms. To our knowledge, this is the first molecular detection of human parvovirus circulation in the west Pará region of Brazil, suggesting that the infection by this virus should be considered in all dengue-like cases, especially for risk groups like pregnant women.

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INTRODUCTION

The human parvovirus B19 (B19V) is a non-enveloped virus with an icosahedron capsid and a single-stranded DNA genome classified in the *Erythrovirus* genus, *Parvoviridae* family. It is the only member of the *Parvoviridae* family considered pathogenic for human beings (Siegl et al. 1985). Currently, there are three B19V genotypes described which display similar biological, pathogenic and antigenic properties, establishing a single serotype, being genotype 1 predominantly found worldwide (Servant et al. 2002). B19V is an infectious agent of global occurrence that can be transmitted through the respiratory route, hematogenic, and transplacental (Ornoy and Ergaz 2017), causing diverse clinical manifestations such as benign self-limiting exanthematous disease, similar to other human pathologies, but in some cases this virus may be associated with fetal

death (Bonvicini, Bua, and Gallinella 2017). The B19 virus infection frequently happens during childhood and remains in lower rates throughout adult life, in such a way that 15% of preschool children, 40% of young adults and 85% of adults display serologic evidence of past infections (Mage et al. 2014). The infection caused by B19V is characterized for two phases. The first is associated to clinical manifestations common in other nonspecific prodromal infections that may present fever, myalgia, headache, and chills (Anderson et al. 1985; Waza, Inoue, and Matsumura 2007), similar to dengue virus infection. However, the second phase of the disease may include striking manifestations of infectious erythema, rashes, and arthralgia (Anderson et al. 1985). Therefore, the clinical diagnosis of B19 parvovirus is usually associated with the second phase of the disease. In Brazil, the first records of B19 occurred in Rio de Janeiro in 1983, being observed in blood donors and in pregnant women with suspected rubella infection (da Silva Cruz et al. 1989; de Miranda,

Linhares, and Shirley 1989). In the same period, the association of B19V with exanthematic disease and infectious erythema was observed (de Miranda, Linhares, and Shirley 1989). In Belém, the biggest city of Pará, situated in the east region of the state, about a quarter of the exanthemas not caused by measles, rubella or arbovirus was positive to B19V infection (de Freitas *et al.* 1990). Epidemiological surveillance of B19 infection is limited. To our knowledge, B19V is rarely tested or even diagnosed in health care, and therefore the prevalence of this infectious agent is ignored in populations from endemic areas for arboviruses of related clinical manifestations (Di Paola *et al.* 2019). In the Amazon region, there is the circulation of acute febrile diseases, such as dengue, malaria and Mayaro fever (Figueiredo *et al.* 2008; Travassos da Rosa 2016; Saatkamp *et al.* 2020). Due to the large similarity of the clinical manifestations of these diseases with B19-related symptoms, there is a high probability of underestimating the prevalence of this virus, especially when the diagnosis is based on merely clinical evaluations in endemic areas (De Figueiredo *et al.* 2019). Furthermore, because of its widespread around the world, it is likely that the underestimation of its diagnosis contributes for inflating of the estimate of other endemic viral diseases with similar clinical symptoms, such as dengue, affecting the global understanding of the circulation dynamics of both viruses. In this study, we show evidence of this underestimation and discuss the importance of laboratory diagnoses in endemic areas.

CASE REPORT

The city of Santarém is located on the right bank of the Tapajós River near the confluence with the Amazonas River, in the west of Pará state, Brazil (02° 26'34" S, 54° 42'28" W). The city of Santarém is the third largest in the state and its population is estimated at 306,480 inhabitants (<https://cidades.ibge.gov.br/brasil/pa/santarem/panorama>). Human serum samples (n=17) were collected from patients treated at the public health service of Santarém and stored at -20°C in the Health Surveillance Division of the city.

Table 1. Clinical and demographic characteristics from patients positive diagnosed for human B19 parvovirus in Santarém, Pará, Brazil

Sample	Age/Sex	d	Fever	Headache	Myalgia	Arthralgia	Leukopenia
27	20/F	6	No	Yes	Yes	No	Yes
29	18/M	3	Yes	Yes	Yes	No	No
32	32/M	7	Yes	Yes	Yes	Yes	No
36	15/M	8	Yes	Yes	Yes	No	No
1000	22/F	14	Yes	Yes	Yes	Yes	Yes

F= female; M= male; d= disease days

This study was approved by the Human Research Ethics Committee of Instituto Esperança de Ensino Superior – IESPES (Protocol N. 3.149.097). All patients were clinically screened for suspected dengue virus infection and the clinical data associated with each individual was collected from their previous medical record. Firstly, the samples were investigated for dengue virus using the serological method ELISA – IgM (Enzyme – Linked Immunosorbent Assay). In addition to serological tests, we follow the investigation at the Tropical Medicine Foundation – Heitor Vieira Dourado (FMT-HVD), using molecular diagnostics by PCR. For dengue virus testing, viral RNA was extracted using from QIAamp viral RNA Mini-Kit (Qiagen Inc., Hilden, Germany), according to the manufacturer's instructions, and used for the semi-nested multiplex PCR (Lanciotti 2003) testing. For the investigation of B19V, total nucleic acid was extracted using DNA PureLink viral RNA/DNA Mini-Kit (Invitrogen, Carlsbad, CA, USA) followed by viral genome detection through nested-PCR (de Mendonça *et al.* 2008). The product from the second PCR reaction was subjected to electrophoresis at 100 volts for 30 minutes on 2.5% agarose gel in 1X TBE buffer with ethidium bromide and visualized under UV light. All samples were tested negative for the presence of antibodies to dengue virus, as revealed by ELISA-IgM and negative for DENV RT-PCR. On the other hand, five individuals tested positive for B19V. The present study was motivated by the work developed by Figueiredo *et al.* (2019), which also identified the

circulation of B19V in children and adolescents with suspicious of dengue infection in Tefé, another mid-size city in the Brazilian Amazon region. Among the positive B19V cases, three were men and two were women, in ages between 15 to 32 years old. The most frequent symptoms in these individuals were fever, headache, and myalgia. Arthralgia and leukopenia, although being reported, were not predominant symptoms (Table 1). In this study, we identified the circulation of the human parvovirus B19 in people from Santarém, in the western region of Pará state, Brazil. The infection caused by B19V was relatively high, representing 29.4% of the samples tested (n = 17). In comparison, a study with 44 serum samples from children and adolescents aged 6 to 14 years in the municipality of Tefé, located in the Amazon region, detected 18.2% of B19 positive tests (De Figueiredo *et al.* 2019). Also in the Brazilian Amazon region, on both states of Tocantins and Amapá, a large study with 781 negative samples for IgM against dengue virus and other similar arboviruses had detected B19V in 17% of the plasma pools tested by PCR (Fahsbender *et al.* 2020). In Guarujá, in the southern region of Brazil, molecular tests showed that 63.2% of patients with dengue suspected during an outbreak that occurred between 2013 and 2014 had B19V infection, revealing the concomitant existence of an outbreak of the two viral diseases (Di Paola *et al.* 2019). The percentage difference of positive B19 samples observed in the study may be derived from different aspects, among them the difference of dynamics from urban displacements to the population related to local economic activity, the seasonality of viral circulation and its relationship with the local weather, as well as the age structure of the population, between others. Preschool children, for example, show infections more often, but throughout adult life, the frequency of infections depends on the existence of susceptible individuals (Mage *et al.* 2014). The positive results for B19 shown here, as well as in other regions of Brazil, highlight the importance of molecular diagnosis for viral diseases, especially during outbreaks, when other pathogens can be circulating, harming the efficiency of actions taken by public health agents and sanitary surveillance in the fight against these diseases. Blood samples from four B19-positive subjects were collected between 6 and 14 days after the beginning of symptoms.

A single positive patient had a sample collected 3 days before the first symptoms showed during the acute phase of the disease. The persistence of viral DNA has been documented after acute infection in immunocompetent and immunodeficient patients, caused by the failure to neutralize antibodies in the procedure for B19V infection (Lundqvist *et al.* 1999; Söderlund-Venermo *et al.* 2002). The most common symptoms reported in this study were fever, headache, and myalgia. In the study by Figueiredo *et al.* (2019) fever, headache, and eyeball pain were predominant between 6 and 14 years of age. Although with less frequency, this study also reported arthralgia and leukopenia, confirming the fact that the clinical symptoms presented by B19V illness are similar to those of dengue and other arboviruses, as has been reported in other studies (De Figueiredo *et al.* 2019). Thus, the clinical diagnosis of B19V infection is hard in medical routine and specific laboratorial tests should be used. In this sense, molecular-based epidemiological surveillance can have a strong application to improve public health services in Brazil and in other countries.

CONCLUSION

This study detected human Parvovirus B19 in clinical samples suspected of dengue infection. Fever, headache, and myalgia were the

most common symptoms, contributing to more recent studies that demonstrated the presence of B19V in patients with febrile syndrome and similar symptoms of dengue in other regions of Brazil. To our knowledge, this is the first molecular study showing the circulation of human parvoviruses in the western region of the State of Pará.

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