

Saint Louis encephalitis virus and other arboviruses in the differential diagnosis for dengue

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Brazil is a tropical country with a wide variety of flora and fauna that includes many arthropods, especially mosquitoes and midges. This ecological diversity facilitates the maintenance of arboviral cycles and the emergence of novel arboviral pathogens. Indeed, many outbreaks attributable to zoonotic arboviruses such as Oropouche, Mayaro, Rocio virus (ROCV), Saint Louis encephalitis virus (SLEV) and yellow fever virus have been seen in the recent past. Furthermore, due to the increase in international travel, arboviruses present in other American countries, such as the emergent viruses West Nile and Chikungunya, have already been introduced, or could be introduced to this region in the future. The southeastern, northeastern, and southern regions of Brazil, which house the majority of the population (200 million inhabitants), are infested by the *Aedes aegypti*, *Aedes albopictus*, and *Culex* mosquitoes. *Aedes aegypti*, the vector for the dengue virus, is responsible for large epidemics with high morbidity and mortality. Cases of meningoencephalitis in Brazil have also been attributed to the dengue virus, and control of virus spread is a high priority topic for public health authorities; in addition to controlling the *Aedes aegypti* population, dengue control strategies also involve clinical and serological diagnosis of infection. However, testing only focuses on dengue, and other arboviruses that produce acute febrile illness and meningoencephalitis can remain undetected.

A recent study in *Revista da Sociedade Brasileira de Medicina Tropical*/Journal of the Brazilian Society of Tropical Medicine showed that horses can be infected by SLEV and ROCV¹. These are ribonucleic acid (RNA) viruses belonging to the Japanese encephalitis serocomplex in the Flavivirus genus of the Flaviviridae family. This serocomplex includes mostly the arboviruses that cause meningoencephalitis and have birds as reservoirs and mosquitoes of the Culicinae subfamily as vectors. SLEV is responsible for an increasing number of cases in Brazil, particularly in the State of São Paulo. In 2004, SLEV was isolated from a patient diagnosed with dengue fever in the City of São Pedro². In 2006, eight patients with acute febrile illness from the City of Ribeirão Preto were found to be

SLEV-seropositive by an immunoglobulin G-enzyme-linked immunosorbent assay (IgG-ELISA), and these findings were confirmed by a highly specific neutralization test. In the following year, during a widespread dengue type 3 epidemic, six patients tested positive for SLEV in the City of São José do Rio Preto^{3,4}. Recently, a patient from Ribeirão Preto who presented with acute febrile illness was also found to be SLEV-positive⁵.

In contrast to SLEV, ROCV has only been isolated in the southeastern region of Brazil in the 1970s during a large-scale outbreak of encephalitis that resulted in many fatalities. During this outbreak, ROCV was isolated from 3 sources, a patient, a *Psorophora ferox* mosquito, and a wild migratory bird, suggesting that birds are the hosts that spread this virus⁶.

Serologic surveys are important tools in the detection of arbovirus infections and are used to determine the anti-viral antibody titers. Serologic surveys to detect ROCV and SLEV were conducted in horses because these large domestic animals, which remain in close contact with humans, are constantly bitten by mosquitoes as they are frequently outdoors. Healthy horses from the West-Central, Northeast, and Southeast areas of Brazil were included in the survey. Serum samples from these animals were tested by ELISA using recombinant peptides from domain III of the envelope proteins of ROCV and of SLEV⁷. Of the 753 studied animals, over half (55%) were seropositive, suggesting that flavivirus infections are common among these animals. Monotypic reactions to SLEV were observed in 93 horses from Mato Grosso do Sul, Minas Gerais, Paraíba, Rio de Janeiro, and São Paulo. Monotypic reactions to ROCV were observed in 46 animals from the same states, with the exception of Minas Gerais. These results suggest that SLEV and ROCV have circulated in the horse population in the Northeast, West-central, and Southeast areas of Brazil. Unfortunately, the medical history of these animals is not available, making it impossible to correlate disease history and symptoms with ROCV and SLEV seropositivity.

Considering that dengue outbreaks have been reported in almost all parts of Brazil in the past 15 years and that infection with SLEV and ROCV or other closely related flaviviruses is common among horses, it is possible that many cases of acute febrile illness and meningoencephalitis that occurred during dengue epidemics have been incorrectly attributed to the dengue virus, as previously reported³. Moreover, patients infected by SLEV or other flaviviruses may test positive in serologic tests for dengue, including those that detect virus-specific IgM, due to a cross-reaction between viruses of the same genera, as previously observed in a study done in the City of Ribeirão Preto⁵. Thus,

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Received 20 August 2014
Accepted 10 September 2014

diagnostic laboratories should use more than one method to confirm the dengue diagnosis and it is also necessary to develop multipanel diagnostic tests to include several arboviruses that can cause disease in humans, and such multipanel tests should be routinely used during dengue epidemics. Additionally, to control SLEV, it is important to study the zoonotic cycle of the virus in urban areas by identifying the animal reservoirs (possibly avian) and the mosquito vectors (*Culex pipiens fatigans?*). The observation of ROCV infection in horses in the northeast, west-central, and southeast areas of Brazil is concerning because this virus could produce new outbreaks of meningoencephalitis. The lack of consideration for these pathogens in the differential diagnosis is concerning and should be addressed. Overall, public health authorities should increase surveillance for ROCV and other flaviviruses, and arboviruses other than dengue should be included in the differential diagnosis of acute febrile disease and meningoencephalitis during outbreaks in certain regions, especially the northeast, west-central, and southeast regions of Brazil due to the demonstrated prevalence of equine infection with these viruses in these areas.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Silva JR, Romeiro MF, Souza WM, Munhoz TD, Borges GP, Soares OAB, et al. A Saint Louis encephalitis and Rocio virus serosurvey in Brazilian horses. *Rev Soc Bras Med Trop* 2014; 47:414-417.
2. Rocco IM, Santos CL, Bisordi I, Petrella SM, Pereira LE, Souza RP, et al. St. Louis encephalitis virus: first isolation from a human in São Paulo State, Brazil. *Rev Inst Med Trop Sao Paulo* 2005; 47:281-285.
3. Mondini A, Cardeal ILS, Lázaro E, Nunes SH, Moreira CC, Rahal P, et al. Saint Louis encephalitis virus, Brazil. *Emerg Infect Dis* 2007; 13:176-178.
4. Bronzoni RVM, Baleotti FG, Nogueira RMR, Nunes M, Moraes LTM. Duplex reverse transcription-PCR followed by nested PCR assays for detection and identification of Brazilian alphaviruses and flaviviruses. *J Clin Microbiol* 2005; 43:696-702.
5. Maia FGM, Chávez JH, Souza WM, Romeiro MF, Castro-Jorge LA, Fonseca BAL, et al. Infection with Saint Louis encephalitis virus in the city of Ribeirão Preto, Brazil: report of one case. *Int J Infec Dis* 2014; 26:e96-97.
6. Figueiredo LTM. The Brazilian Flaviviruses. *Microbes Infect* 2000; 2:1643-1649.
7. Chávez JH, Reis VP, Silva JR, Laure HJ, Rosa JC, Fonseca BAL. Production and diagnostic application of recombinant domain III of West Nile envelope protein in Brazil. *Rev Soc Bras Med Trop* 2013; 46:97-99.