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LETTER TO THE EDITOR

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Guillain-Barré syndrome and dengue-like disease in 2015: temporal relationship in *Piauí* state and implications on Zika virus surveillance

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Dear editor

Neurological symptoms of approximately two thirds of patients with *Guillain-Barré* syndrome (GBS) begin a few weeks after an apparently benign febrile infection with respiratory or gastrointestinal manifestations[1]. Using serological methods, several studies identified as major infectious agents involved in GBS: *Campylobacter jejuni*, *Mycoplasma pneumoniae*, Cytomegalovirus, Epstein-Barr virus and *Haemophilus influenzae*[2-5], but some flaviviruses with a documented circulation in Brazil were identified as triggers of GBS in the last two decades, especially dengue virus (DENV), West Nile virus (WNV) and Saint Louis encephalitis virus (SLEV)[4,6-9].

The introduction of the Zika virus (ZIKV) in Brazil was laboratory confirmed in May 2015 in the midst of an epidemic of a mild and sub-febrile exanthematic disease that affected especially inhabitants of the Northeast region of the country[10]. The disease was considered by some, at that time, as a mild form of infection by DENV. Thus, many symptomatic human infections by ZIKV may have been reported as dengue cases to health authorities. A few months later, the benign character attributed to ZIKV infection was questioned in face of its association with an increased number of GBS cases, microcephaly and other congenital malformations[11]. The first cases of Zika virus infection in *Piauí* State were laboratory confirmed in July 2015, but medical records point to its significant occurrence in that State up to five months before[12]. Phylogenetic analysis and molecular clock showed that the introduction of ZIKV in Brazil occurred between May and December 2013[13].

The local State Division of Epidemiology was already carrying out a surveillance program of neurological cases since the laboratory confirmation of the first West Nile human case in the country in August 2014, in Aroeiras do Itaim municipality – *Piauí* State – Brazil[9]. Since then, cases of aseptic meningitis, viral encephalitis, transverse myelitis and GBS have been submitted to epidemiological and laboratory investigation, which allowed monitoring the occurrence of these disorders[12].

Considering the State records on the occurrence of neurological diseases and data from the National System of Notifiable Diseases - *Piauí* section (SINAN-PI, in Portuguese), the existence of a temporal correlation between GBS time series and notifications of suspected cases of dengue in 2015 were verified. The cross-correlation analysis of the time series was chosen instead of a simple linear correction because: (i) a gap was expected between the previous infectious syndrome and the onset of neurologic manifestations, and (ii) the record of suspected dengue is more dynamic than the occurrence of GBS due to factors related to the natural history of each disease and the patient's access to a medical notifier service. Correlation calculations were performed using the software Bioestat 5.0® and Free Statistic Software v1.1.23-r7®[14].

In 2015, in *Piauí* State, 7,659 suspected dengue cases were reported in parallel with 42 cases of GBS. Serological tests (ELISA-IgM) were positive for dengue in 23.8% of GBS cases. There were no positive results for WNV. Testing for ZIKV had not yet been included in the GBS case investigation panel in 2015. Distributions

(1) Secretaria de Estado da Saúde do Piauí, Instituto de Doenças Tropicais Natan Portella, Teresina, Piauí, Brasil

(2) Fundação Municipal de Saúde de Teresina, Diretoria de Vigilância em Saúde, Teresina, Piauí, Brasil

(3) Instituto Evandro Chagas, Seção de Arbovirologia e Febres Hemorrágicas, Ananindeua, Pará, Brasil

(4) Secretaria de Estado da Saúde do Piauí, Gerência de Vigilância em Saúde, Teresina, Piauí, Brasil.

(5) Universidade Federal do Piauí, Departamento de Medicina Especializada, Teresina, Piauí, Brasil

Correspondence to: Marcelo Adriano da Cunha e Silva Vieira

Secretaria de Estado da Saúde do Piauí, Instituto de Doenças Tropicais Natan Portella, Departamento de Neurologia, Rua Governador Artur de Vasconcelos, 151, CEP 64001-450, Teresina, Piauí, Brazil

E-mail: macsvieira@superig.com.br

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of monthly notifications of suspected dengue and GBS cases in 2015 obeyed a monophasic up and down pattern, with the maximum occurrence reported for April and June, on an annualized rate of 5.5 GBS cases per 1,000 dengue notifications (Figure 1). The cross-correlation analysis (Figure 2) showed the maximum parallelism upon assigning a delay from one (rho = +0.78, CI 95% = 0.36 to 0.93; p = 0.003) to two (rho = +0.86, CI 95% = 0.59 to 0.96; p = 0.0003) months between time series. The maximum correlation between the time series of GBS cases and suspected dengue notifications recorded in *Piauí* State (1-2 months) is consistent with the description of the syndrome as a post-infectious phenomenon, characterized by an autoimmune attack on the myelin sheath triggered by an antigenic stimulation a few weeks before[1,4].

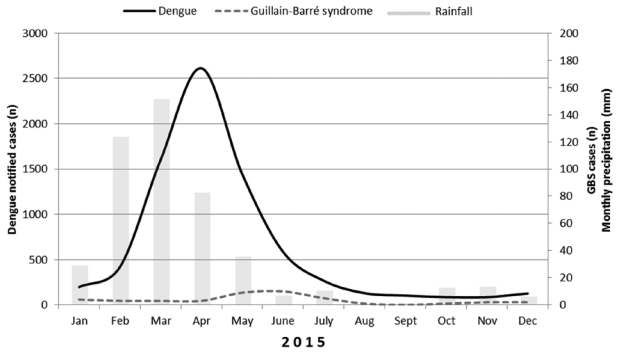

Figure 1 - Reported cases of dengue fever, *Guillain-Barré* syndrome and monthly rainfall in the State of *Piauí* in 2015. (*Piauí* State Secretary for Health, Brazilian National Institute of Meteorology)

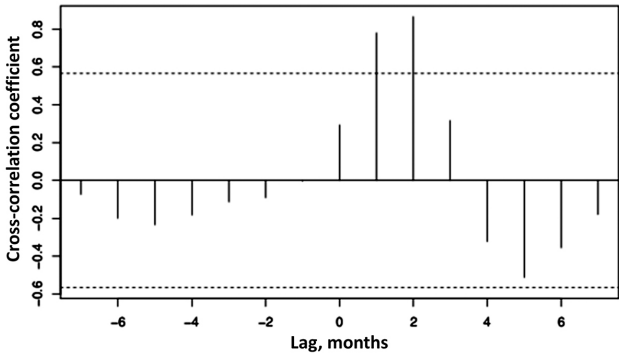

Figure 2 - Cross-correlation between the time series of dengue-suspected cases reported monthly and hospitalizations due to *Guillain-Barré* syndrome in the state of *Piauí*, Brazil, 2015. The dashed lines indicate a 95% confidence interval.

It is possible that a significant proportion of notifications of suspected dengue cases have corresponded to the infection caused by ZIKV because there is great similarity between the clinical manifestations of these viral diseases. In addition, the availability of laboratory tests in *Piauí* municipalities is limited. Until the first laboratory confirmation of the infection caused by ZIKV in the country by the Ministry of Health in May 2015, the disease was little known by most health-care medical services and epidemiological surveillance teams in *Piauí* State. The first five months of 2015 concentrated 82% of dengue-suspected notifications in *Piauí*. In the same year, 22% of the 7,659 reported cases were serologically negative for dengue, and only 19% of the cases were confirmed by laboratory testing. The remaining cases were classified by clinical and epidemiological criteria. All the confirmatory laboratory tests were carried out by ELISA-IgM on serum samples[12]. A temporal relationship has been observed between the occurrence of peaks in rash Zika-simile and GBS outbreaks in several other regions[15-18].

It is difficult to quantify accurately the occurrence of Zika virus disease in Brazil in 2015. The universal notification of disease suspicion has only been established by health authorities in March 2016. So far, only laboratory-confirmed cases were reported, except for sentinel units deployed in some cities in the second half of 2015, when the epidemic had already decreased in Northeastern Brazil. The Ministry of Health estimates that up to 1.5 million Brazilians were affected by the Zika disease in 2015[19]. There is a likelihood of cross-reactivity in serological tests used to confirm dengue cases before non-recognized ZIKV infections - especially in patients with a previous history for that disease[20]. Therefore, even dengue cases classified as confirmed are subject to questioning due to the lack of a molecular biology diagnostic method and a simultaneous serological testing for ZIKV.

The inferences to be drawn from this study are limited. The proportion of dengue cases reported as suspicious in 2015, which corresponded to infections by Zika, remains in fact speculative. The similarities between the clinical presentations of the two diseases and the possibility of cross-reactions to serological examinations make the confirmation of cases by clinical, epidemiological and laboratory criteria are unpredictable when a diagnostic by molecular biology is dismissed. Until recently, there were no commercial kits for diagnosing ZIKV infection in the country, and detection of the viral genome by large-scale molecular biology is still impracticable. The magnitude of the occurrence of GBS is much lower than that of dengue - this did not allow the comparison of data in the temporal unit of an epidemiological week. This fact, combined with differences between the speed of recognition, the reporting of dengue and GBS and the ease of access to adequate diagnostic services to perform them, makes the delay calculated at the maximum cross-correlation subject to rough approximations. The time of higher occurrence

of dengue in *Piauí* State coincides with the rainy season, which is also associated with more respiratory and diarrheal diseases, which are potentially involved in the pathogenesis of GBS.

There was a correspondence between GBS time series and notifications of suspected dengue in *Piauí* State in 2015. The delay of up to eight weeks between the correlated time series is compatible with the natural history of the syndrome and its post-infectious nature. In the face of evidence that ZIKV may act as an important GBS set-off and the unavailability (at that time) of notification and confirmation instruments of prior infection with Zika virus, the results of this study reinforce the need for clinical, laboratory and epidemiological study to differentiate DENV and ZIKV infections, encouraging systematic studies on the etiology of neurological infectious diseases in different regions of the country.

Marcelo Adriano da Cunha e Silva Vieira[1,2]
Ana Cecília Ribeiro Cruz[3]
Ananda Naya Mesquita Barros[4]
Dorcas Lamounier Costa[5]
Eliana Vieira Pinto da Silva[3]
Francisca Miriane de Araújo Batista[4]
Raimunda do Socorro da Silva Azevedo[3]
Sueli Guerreiro Rodrigues[3]
Rui Cipriano Araújo-Júnior[2]
Pedro Fernando da Costa Vasconcelos[3]

REFERENCES

1. van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome. Lancet Neurol. 2008;7:939-50.
2. Hadden RD, Karch H, Hartung HP, Zielasek J, Weissbrich B, Schubert J, et al. Preceding infections, immune factors, and outcome in Guillain-Barré syndrome. Neurology. 2001;56:758-65.
3. Jacobs BC, Rothbarth PH, van der Meché FG, Herbrink P, Schmitz PI, de Klerk MA, et al. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. Neurology. 1998;51:1110-5.
4. Solomon T, Willison H. Infectious causes of acute flaccid paralysis. Curr Opin Infect Dis. 2003;16:375-81.
5. Winer JB, Hughes RA, Anderson MJ, Jones DM, Kangro H, Watkins RP. A prospective study of acute idiopathic neuropathy. II. Antecedent events. J Neurol Neurosurg Psychiatry. 1988;51:613-8.
6. Carod-Artal FJ, Wichmann O, Farrar J, Gascon J. Neurological complications of dengue virus infection. Lancet Neurol. 2013;12:906-19.
7. Figueiredo LT. Emergent arboviruses in Brazil. Rev Soc Bras Med Trop. 2007;40:224-9.
8. Sejvar JJ, Bode AV, Marfin AA, Campbell GL, Ewing D, Mazowiecki M, et al. West Nile virus-associated flaccid paralysis outcome. Emerg Infect Dis. 2006;12:514-6.
9. Vieira MA, Romano AP, Borba AS, Silva EV, Chiang JO, Eulalio KD, et al. West Nile virus encephalitis: the first human case recorded in Brazil. Am J Trop Med Hyg. 2015;93:377-9.
10. Campos GS, Bandeira AC, Sardi SI. Zika virus outbreak, Bahia, Brazil. Emerg Infect Dis. 2015;21:1885-6.
11. Pan American Health Organization. Epidemiological alert: neurological syndrome, congenital malformations, and Zika virus infection: implications for public health in the Americas: 1 December 2015. [cited 2017 Jan 11]. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=32405&lang=em
12. Piauí. Secretaria de Estado da Saúde. Arboviroses e síndromes neurológicas no Piauí. Bol Epidemiol Semanal. 2016 Nov 12; ed esp. [cited 2017 Jan 11]. http://www.saude.pi.gov.br/uploads/document/file/129/Boletim_agravos_neurol_gicos_nov_2016_WORD__2_.pdf
13. Faria NR, Azevedo RS, Kraemer MU, Souza R, Cunha MS, Hill SC, et al. Zika virus in the Americas: early epidemiological and genetic findings. Science. 2016;352:345-9.
14. Wessa P. Cross Correlation Function (v1.0.8) in Free Statistics Software (v1.1.23-r7). [s.l.]: Office for Research Development and Education; 2012. [cited 2017 Jan 12]. Available from: http://www.wessa.net/rwasp_cross.wasp
15. Broutet N, Krauer F, Riesen M, Khalakdina A, Almiron M, Aldighieri S, et al. Zika virus as a cause of neurologic disorders. N Engl J Med. 2016;374:1506-9.
16. Dirlikov E, Major CG, Mayshack M, Medina N, Matos D, Ryff KR, et al. Guillain-Barré syndrome during ongoing Zika virus transmission - Puerto Rico, January 1-July 31, 2016. MMWR Morb Mortal Wkly Rep. 2016;65:910-4.
17. Santos T, Rodriguez A, Almiron M, Sanhueza A, Ramon P, de Oliveira WK, et al. Zika virus and the Guillain-Barré syndrome - case series from seven countries. N Engl J Med. 2016;375:1598-601.
18. Paploski IA, Prates AP, Cardoso CW, Kikuti M, Silva MM, Waller LA, et al. Time lags between exanthematous illness attributed to Zika virus, Guillain-Barré syndrome, and microcephaly, Salvador, Brazil. Emerg Infect Dis. 2016;22:1438-44.
19. World Health Organization. Zika situation report: 19 February 2016. [cited 2017 Jan 12]. Available from: http://www.who.int/emergencies/zika-virus/situation-report/19-february-2016/en/
20. Rabe IB, Staples JE, Villanueva J, Hummel KB, Johnson JA, Rose L, et al. Interim guidance for interpretation of Zika virus antibody test results. MMWR Morb Mortal Wkly Rep. 2016;65:543-6.