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A comprehensive analysis and immunobiology of autoimmune neurological syndromes during the Zika virus outbreak in Cúcuta, Colombia

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ABSTRACT

We have focused on the epidemiology and immunobiology of Zika virus (ZIKV) infection and factors associated with the development of Guillain-Barré syndrome (GBS) and other neurological syndromes in Cúcuta, the capital of North Santander department, Colombia. Data of patients with ZIKV disease reported to the national population-based surveillance system were used to calculate the basic reproduction number (R_0) and the attack rates (ARs) as well as to develop epidemiological maps. Patients with neurological syndromes were contacted and their diagnoses were confirmed. A case-control study in which 29 patients with GBS associated with ZIKV compared with 74-matched control patients with ZIKV infection alone was undertaken. Antibodies against arboviruses and other infections that may trigger GBS were evaluated. The estimated value of R_0 ranged between 2.68 (95% CI 2.54—2.67) to 4.57 (95% CI 4.18 —5.01). The sex-specific ARs were 1306 per 100,000 females, and 552 per 100,000 males. A non-linear interaction between age and gender on the ARs was observed. The incidence of GBS in Cúcuta increased 4.41 times secondary to ZIKV infection. The lag time between ZIKV infection and neurological symptoms was 7 days (interquartile range 2—14.5). Patients with GBS appeared to represent a lower socioeconomic status and were living near to environmentally contaminated areas. All GBS patients were positive for IgG antibodies against both ZIKV and Dengue virus, and 69% were positive for Chikungunya virus. Noteworthy, GBS was associated with a previous infection with *M. pneumoniae* (OR: 3.95; 95% CI 1.44—13.01; p = 0.006). No differences in antibody levels against *C. jejuni,* Epstein-Barr virus and cytomegalovirus were observed. High rates of cranial nerves involvement and dysautonomia were present in 82% and 75.9%, respectively. Intensive care unit (ICU) admission was necessary in 69% of the GBS patients. Most of the patients disclosed a high disability condition (Hughes grade 4). Dysautonomia was the main risk factor of poor GBS prognosis (i.e., ICU admission and disability). Thirteen patients were diagnosed with other neurological syndromes different to GBS (6 with transverse myelitis, 3 with encephalitis, 3 with peripheral facial palsy and one with thoraco-lumbosacral myelopathy). Our data confirm an

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increased transmission of ZIKV in Cúcuta, and provide support to the view that severe neurological syndromes are related to ZIKV disease. The complex ways by which previous infections and socioeconomic status interact to increase the risk of GBS in people infected by ZIKV should be further investigated.

1. Introduction

Infection by Zika virus (ZIKV), an arbovirus of the *Flaviviridae* family, is transmitted by the female *Aedes* mosquito genus. The response to infection normally varies between completely asymptomatic individuals to those with mild and self-limiting disease [1]. In such individuals, the typical symptoms include rash, fever, arthralgia, and conjunctivitis. However, in Latin America and in the South Pacific, from where it is believed the spread originated, there have been increasing reports of neurological complications attributable to ZIKV. The sudden increase in microcephaly and Guillain-Barré syndrome (GBS) [2–4] prompted the World Health Organization (WHO) to declare a "public health emergency of international concern" [4]. According to the Colombian National System of Public Health Surveillance (SIVIGILA for "Sistema Nacional de Vigilancia en Salud Pública"), between epidemiological week (EW) 32 of 2015 to week 28 of 2016, the date on which the closure of the epidemic phase of the disease was declared, 99,721 cases of ZIKV disease were registered, of which 8826 (8.9%) were serologically defined and confirmed by reverse transcription polymerase chain reaction (RT-PCR) [5].

Cúcuta, the capital of North Santander department of Colombia, is located in the northeast of the country at the border between Colombia and Venezuela and is the most affected Colombian city for arboviruses [6]. It also has one of the largest proportions of registered cases of neurological syndromes related to ZIKV disease [5]. This finding prompted us to evaluate the factors associated with the development of these neurological syndromes in Cúcuta.

2. Methods

2.1. Setting

Cúcuta, located at latitude 07° 53 ′ 00 ″ N and longitude 72° 30′ 19″ W, is 320 m above sea level, and has a territorial area of 1176 km^2. In 2016, the Administrative National Department of Statistics (DANE for "Departamento Administrativo Nacional de Estadística"), estimated the total population as 656,380 habitants (sex ratio: 93%), distributed in 54,500 homes, in 600 neighborhoods with a population density of 592 people km^2; the urban area accounts for 96.62% of the population. The climate is warm and characterized by temperatures ranging between 59 and 104 °F (15–40 °C); in the months of April to June and September to November. There is an average annual rainfall of 655 mm. The annual average relative humidity is between 70 and 75% [7].

2.2. Public Health Surveillance system

In Colombia, the National Institute of Health (INS for "Instituto Nacional de Salud") maintains the SIVIGILA for notifiable clinical cases that include Dengue (DENV), Chikungunya (CHIKV), ZIKV, and birth defects, among others. The information gathered by the centers of health care is compiled and transmitted to the SIVIGILA, which updates the results weekly [8]. In addition, all cases of neurological syndromes (GBS, ascending polyneuropathy,

encephalitis, peripheral facial paralysis, among other similar neurological conditions), with suspicion of ZIKV disease are also provided to the SIVIGILA [9].

2.3. Patients and controls

In this restrospective case-control study, those patients with previous probable infection with ZIKV associated with a neurological syndrome registered in the SIVIGILA were considered as cases. The control group was defined as patients with previous probable infection with ZIKV, registered in the SIVIGILA that did not develop GBS or another neurological syndrome. These people were matched to GBS patients by age (±5 years), gender, neighborhood and date of ZIKV symptoms (±2 EW).

In order to evaluate the neurological conditions and to obtain samples from patients, a multidisciplinary team that included neurologists, immunologists, physicians and research assistants conducted 4 site visits to Cúcuta. Patients were diagnosed with GBS according to the Asbury [10,11] and Brighton criteria [12]. Transverse myelitis and encephalitis were diagnosed according to the transverse myelitis consortium working group [13], and the international encephalitis consortium [14], respectively. Data were collected in an electronic and secure database as reported elsewhere [15].

Medical examination and blood samples were done and withdrawal respectively, within a median of 108 days (IQR: 97.75–134) after the onset of the Zika symptoms and within a median of 100 days (IQR: 85–116) after the onset of the GBS.

2.4. Data collection

Data for the studies reported herein covered the time period from June 29, 2015 to July 30, 2016. In fact, retrospectively, a sentinel case was registered on June 29, 2015 [16]. The data monitoring system included all 65 health care centers within the city. Non-resident's cases in the city were excluded from analysis.

The date of GBS onset was defined as the first subjective experience of the symptom(s) and/or sign(s) as described in the classification criteria. Additional criteria included cranial nerve involvement, dysautonomia, intensive care unit (ICU) admission, respiratory failure, mechanical ventilation requirement, onset and type of treatment. Disability was assessed according to the Hughes' scale [17].

Other characteristics evaluated in this study included: level of education, socioeconomic status, smoking habits, coffee intake and exposure to toxic agents. The educational level was recorded as the number of years of education. This variable was divided into three groups (0 years, 1–9 years and more than 9 years of education) based on the Colombian General Law of Education [18]. The socioeconomic status was assigned based on criteria outlined by the Colombian legislature [19]. The smoking habits were assessed as no previous history of smoking, patients who consumed 1 to 5, 6 to 15, and more than 15 packs/year, or as an ex-smoker. Coffee intake was explored as a yes/no question, measured in cups intake per day (i.e., less than 1 and 2 to 4). Exposure to toxic agents such as organic