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Outcomes of lupus and rheumatoid arthritis patients with primary dengue infection: A seven-year report from Brazil

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ABSTRACT

Objective: We described the clinical profile and outcomes of patients with SLE and RA diseases reported to the Brazilian Health Information System with primary dengue infection.
Methods: Databases from the Brazilian Public Health Informatics System (SUS) were linked as the source of information. Three databases comprising different longitudinal information of lupus or rheumatoid arthritis (RA) patients under treatment and care through the Brazilian Health System were linked. Patients who had lupus ICD-9 code or RA ICD-9 code and their treatment approved by SUS were included in the study. In Study 1, we described the clinical characteristics of RA/lupus patients who had dengue infection. In Study 2, we compared RA/lupus patients with or without dengue for hospitalization rates after index dengue diagnosis for dengue-exposed or matching date for dengue-unexposed.
Results: We included 69 SLE and 301 RA patients with dengue. In the RA/lupus with dengue case series, hospitalization was found in 24.6% of lupus subjects and of 11.2% of RA subjects. It differed by geographic region ($p = 0.03$), gender ($p = 0.05$) and the use of azathioprine ($p = 0.02$). Dengue was the most frequent reason for hospitalization reported (43.0%). Hospitalization due to dengue was noted in 12 (42.9%) dengue-exposed patients ($p = 0.02$), while rheumatoid arthritis was reported as the cause of hospitalization in 22.2% of dengue-unexposed ($p = 0.005$). Five deaths were reported among the dengue-exposed and none among dengue-unexposed. Bacterial infection was the most frequent cause of death. We found that the dengue exposure was associated with an increased risk of hospitalization outcome in RA and lupus patients (RR = 6.2; 95% CI: 2.99–12.94).
Summary: We found that when comparing RA/lupus patients with or without dengue, dengue-exposed patients had an increased rates of hospitalization and death.

Introduction

Dengue is an arbovirus that presents clinical symptoms similar to those in rheumatic diseases. Myalgia, arthralgia, and thrombocytopenia are found in this mosquito-borne illness, with increasing prevalence [1]. Along with other arboviruses transmitted by *Aedes aegypti*, dengue is currently one of the most important emerging infectious diseases in the world. It has increased fourfold over the past 3 decades and has been reported in more than 100 countries across Latin America, Africa, Asia and continues to spread in many developed countries [2]. An estimated 390-million dengue cases occur globally each year. However, its precise burden is still difficult to determine because of under-reporting in many mild-to-moderate dengue cases [3].

The typical incubation period for dengue is 3–7 days, followed by a disease period of 7–10 days [4]. In 2009, the World Health Organization (WHO) reclassified the case definition of dengue clinical syndromes into classical dengue and severe dengue, with hospitalization due to dengue defined as an indicator of severity [5].

In Brazilian general population, according to the Annual Bulletin of Ministry of Health, there were 1,587,680 new dengue cases

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in 2015. The majority of them were found in the Southeast region (62%). Severe dengue (hospitalization) was reported in 1529 of these dengue cases (0.09%); among them, death was found in 839 dengue cases. Similar distribution was found in 2014 and previous years [6].

The occurrence of hospitalization due to dengue is a concern in adult patients with comorbidities, even in primary dengue that is less severe when compared to repeated infections [7,8]. Rheumatic diseases may contribute to severe outcome of dengue, although their contribution has not been previously characterized. Therefore, we described the clinical profile and outcomes of patients with SLE and RA diseases reported to the Brazilian Health Information System with primary dengue infection [9].

Methods

Data sources

This study was based on the national administrative databases of Brazilian Health Information System. A linkage between two databases from DATASUS, the outpatient and inpatient databases, with the surveillance database, called SINAN was constructed [10]. These databases comprise different longitudinal information of SLE and RA patients treated at the Brazilian Public Health System (Sistema Único de Saúde, SUS). We received anonymized information from 2008 to 2014 for this analysis. Details on each database are described in the Supplementary Web Appendix.

In order to collect clinical and treatment information, we used the outpatient database where high cost medications are described. This database is built based on written information provided by the doctor to the patient, aiming to get the medication approved in the context of SUS. Hospitalization information came from the inpatient database. Length of hospitalization, resources used, such as dialysis, antibiotics are also described in this database. Reasons for hospitalization and, in case of death, its cause are contemplated using the ICD-9 codes. For this, we also used the primary, secondary, or additional ICDs codes informed. For dengue description, we used the dengue SINAN database. In this file, there is a variable called 'observations.'. Its content consists of written descriptions from the patient provided to the health professional that include the notification.

Study design

The report consists of two studies. Study 1 is a RA/SLE with dengue case series to describe the clinical characteristics of dengue infection among patients with pre-existing RA or SLE. Study 2 is a dengue-exposed/unexposed cohort study among RA/SLE patients who received dengue diagnosis (dengue-exposed) and calendar date-matched RA/SLE patients who did not receive dengue diagnosis (dengue-unexposed). The outcome of interest in Study 2 is the rate of hospitalization.

In Study 1 (RA/SLE with dengue case series), an index date was defined as the date of dengue diagnosis. From this date, baseline and disease period were defined. Baseline was any time the patient received SLE or RA care from SUS, prior to index date. The period from dengue diagnosis to 45 days later was the period when the outcomes were described. The disease time is in accordance to WHO experts panel recommendations. It includes 7 days after the initial symptoms and an extension to 45 days later, when complications due to dengue may occur. The period from dengue diagnosis to 45 days later was the period when the outcomes were described [11]. Sociodemographic data were supplied by both the outpatient and dengue databases. Information on clinical and treatment profiles of SLE and RA was found in the outpatient database. The dengue database also supplied clinical information on dengue infection. The inpatient database offered detailed information on hospitalization and death.

Study 2 (dengue exposed/unexposed cohort study) was designed to assess the impact of dengue exposure in RA or SLE, taking hospitalization as an outcome of interest. The dengue-exposed group was defined by RA or lupus patients with dengue. The dengue-unexposed group was defined by RA or lupus patients without a diagnosis of dengue. Data for this group was extracted according to the RA or SLE criteria definitions used above. The dengue-unexposed patients, who were matched to dengue-exposed patients on gender, age, geographic region, and calendar time, were followed for 45 days to simulate the follow-up period defined for the exposed group.

Participants—Dengue definition

Patients with dengue who met the following criteria were included:

(a) For SLE, patients with the following visit codes: ICD-10 M32 or L93 AND treatment procedure codes for azathioprine or cyclophosphamide or cyclosporine or methotrexate or chloroquine or hydroxychloroquine;
(b) For RA, patients with the following visit codes: ICD-10 M05 or M06 or M07 or M08 AND treatment procedure codes for sulfasalazine or leflunomide or adalimumab or etanercept or infliximab or certolizumab or golimumab or rituximab or tocilizumab or abatacept or cyclosporine or methotrexate or chloroquine or hydroxychloroquine.

Subjects identified using these algorithms were then linked to the outpatient, inpatient, and dengue databases. We excluded patients whose observations in the outpatient database had been identified only after the date of dengue diagnosis and patients with ICD-10 codes for rheumatic diseases other than SLE or RA.

As noted above in Study 2 (dengue exposed/unexposed cohort study), we compared patients with RA or SLE with dengue (dengue-exposed) to those without dengue (dengue-unexposed). Data for this group was extracted according to the RA or SLE criteria definitions used above. The dengue-unexposed patients who were matched to dengue-exposed patients were followed for 45 days to simulate the follow-up period defined for the exposed group.

Clinical data

Outpatient, inpatient and dengue databases observations were used for baseline description. From outpatient database, clinical and treatment profiles were described; from inpatient database, a detailed description of the hospitalization profile was performed, including reasons for hospitalization and causes of death. Dengue database observations were also used to build the baseline profile. Text statements of the course of dengue were categorized. These text statements describe a summary of the clinical status of each patient, including initial symptoms of the disease, clinical background, and the presence of any comorbidity. They were categorized as follows: 1—anemia, leukopenia, or thrombocytopenia; 2—arthralgia, fatigue, or myalgia; 3—diarrhea, nausea, vomiting, or abdominal pain; 4—fever; 5—headache; 6—hypotension; 7—neurological disorder; 8—rash; and 9—retro-orbital pain.

The protocol was approved by the Institutional Committee of Research at the Universidade Federal of Rio de Janeiro.

Statistical analysis

In Study 1 (RA/lupus with dengue case series), the statistical analysis consisted of descriptions of baseline characteristics,