Am. J. Trop. Med. Hyg., 94(6), 2016, pp. 1380–1384
doi:10.4269/ajtmh.15-0070

Epidemiology of Guillain–Barré Syndrome in Aruba

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Abstract. The epidemiology of Guillain–Barré syndrome (GBS) in tropical areas is different compared with developed countries. We investigated the epidemiology of GBS on the Caribbean island of Aruba. Data were collected retrospectively from all 36 patients hospitalized with GBS between 2003 and 2011 in Aruba. We observed a seasonal distribution of GBS cases with a peak in February. The incidence rate (IR) fluctuated heavily between individual years. The overall IR was 3.93/100,000, which is higher than that observed in developed countries. Serological studies indicated a possible relation of GBS cases with dengue virus infections. We also observed a relation between the annual number of dengue cases in Aruba and the number of GBS cases in the same year. We conclude that the epidemiology of GBS in tropical areas can be different from temperate climate regions and that dengue may be a trigger for developing GBS.

INTRODUCTION

Guillain–Barré syndrome (GBS) is an acute immune-mediated disorder of the peripheral nerves which is characterized by progressive, symmetrical weakness of the limbs accompanied by absent or depressed deep tendon reflexes. GBS is the most frequent cause of acute flaccid paralysis, the worldwide incidence ranges from one to two cases per 100,000.[1–3] Males and older people are more likely to be affected.[4] GBS is often triggered by a preceding infection.[5,6] The most frequently described preceding infections are *Campylobacter jejuni*, cytomegalovirus (CMV), Epstein–Barr virus (EBV), and *Mycoplasma pneumonia*.[7–11] Flavivirus outbreaks regularly occur in the Caribbean. The incidence of dengue virus infections has increased over the past few years.[12] West Nile fever and dengue virus have been associated with neurological diseases, including GBS, but little has been published about this relationship.[13–15]

On Curaçao, one of the Netherlands Antilles in the Caribbean, an increased incidence rate (IR) of GBS was observed several years ago.[16] Remarkable features were a seasonal preponderance, almost exclusively related to *C. jejuni*, and a more severe clinical course of the disease. In the first decade of the twenty-first century an increase in the number of GBS cases was observed in Aruba, also a part of the Netherlands Antilles. This prompted us to investigate the characteristics and triggering infections of the Aruban GBS patients. In this study, we describe the epidemiological, clinical, and microbiological features of the GBS cases in Aruba from 2003 to 2011.

PATIENTS AND METHODS

We performed a retrospective study over a period of 9 years from January 2003 to December 2011 on the island of Aruba, the Lesser Antilles. This island is located 25 km from Venezuela, has a population of approximately 100,000 inhabitants and an area of 180 km.^{2} The Aruban population is of mixed descent and origin, descending from Europe, Latin America, and Africa. Nowadays, 80% of the inhabitants of the island are Aruban, 10% are Dutch, and the rest are from different parts of the world.

We collected data from all patients who were discharged with a diagnosis of GBS admitted to the Dr Horacio E. Oduber Hospital, which is the only hospital on the island. We identified cases using the International Classification of Disease code for GBS (ICD-9, 357.0). Records were retrieved from the hospital data management system (Cognos Impromptu database). Chart review was performed of all patients diagnosed with GBS. Two investigators re-evaluated all cases using the "National Institute of Neurological and Communicative Disorders and Stroke" (NINCDS) criteria for GBS[17] based on the first two features required for diagnosis: progressive motor weakness of more than one limb or areflexia. If this was not well documented, features that strongly support the diagnosis were taken into account. Two cases were excluded after this re-evaluation. This method was also used by Van Koningsveld and others.[16] In this study, the authors reviewed all patients discharged under ICD codes 357.8 and 357.9 to exclude false-negatives. No patients under these codes met the NINCDS criteria; therefore, we omitted the ICD codes 357.8 and 357.9.

Data were acquired regarding age, sex, antecedent events, detailed neurological signs/symptoms, electromyography characteristics, cerebrospinal fluid (CSF) results, treatment, days to nadir, complications, and GBS disability scale[18] at time of diagnosis and at approximately 2 weeks, 4 weeks, and 6 months after the onset of symptoms from hospital and rehabilitation records. Based on the available information the GBS disability scale was inferred to evaluate severe maximum weakness. To assess the severity of the disease, we used the following parameters: mechanical ventilation, rapid progression, severe maximum weakness (GBS disability score ≥ 3), and mortality. The rapidity of progression was defined as inability to walk within 4 days after the onset of weakness.

During hospitalization for GBS, several microbiological studies were performed, including culture for *C. jejuni* and dengue serology, but this was not done according to a specific protocol and therefore information on preceding infections is limited. Hence, we performed additional serological tests, including testing for anti-glycolipid antibodies, on two

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available acute phase serum samples. In addition, we took follow-up samples from 14 patients who had been admitted with GBS 1–2 years ago. Thirty-two control serum samples were obtained from hospital employees (male and female) from Aruban descent with no history of GBS. Antibodies to *C. jejuni*, dengue virus, West Nile virus (WNV), CMV, EBV, and *Mycoplasma pneumoniae* in serum were detected using enzyme-linked immunosorbent assay (ELISA). The levels of antibodies are expressed in ratio. Data on dengue diagnosis in Aruba were obtained from the laboratory information system of Landslaboratorium Aruba. We performed the statistical analysis using IBM SPSS version 20 (IBM, Armonk, NY).

RESULTS

From January 2003 to December 2011, 39 GBS cases were identified. Two patients were excluded because they were diagnosed with transverse myelitis and one patient was excluded because the file was lost. The group of cases did not include any tourists or Dutch citizens.

Clinical features. Baseline characteristics are shown in Table 1. The age of the GBS patients varied from 14 to 77 years, with a peak around the age of 50. Age was not related to the IR ($P = 0.563$, Pearson correlation test). The patients were predominantly male (69%). The patients reported clinical symptoms suggestive of infection in the 4 weeks before the onset of GBS symptoms in 65.7%. Seven patients (19.4%) needed mechanical ventilation. Fourteen patients (38.9%) were bedridden within 4 days after the onset of weakness, 19 patients (52.8%) were bedridden when admitted to the hospital. The majority of patients (77.8%) suffered from severe maximum weakness (GBS disability score ≥ 3) and two patients (5.6%) died. Eleven patients (32.4%) had cranial nerve involvement. Fifty percent of the patients required a long-term follow-up, which is defined as rehabilitation for more than 6 months. Ten patients (27.8%) had a GBS disability score ≥ 3 after 6 months.

TABLE 1

Demographic and clinical characteristics of 36 patients with GBS in Aruba from 2003 to 2011

	N (%)
Characteristics	
Age > 50	22 (61)
Men	25 (69)
Preceding symptoms (≤ 4 weeks before GBS signs)	23 (66)
Cranial nerve involvement	11 (32)
Rapid onset of disease (bedridden within 4 days after onset of weakness)	14 (39)
Severe maximum weakness	28 (78)
Mechanical ventilation	7 (19)
Mortality	2 (6)
Long-term follow-up (> 6 months)	18 (50)
Poor outcome (GBS disability score ≥ 3 after 6 months)	10 (28)
Infections (not all patients tested)	
Campylobacter jejuni	1/2 (50)
Dengue virus	7/15 (47)
West Nile virus	0/2
Cytomegalovirus	0/2
Epstein–Barr virus	0/2
Mycoplasma pneumoniae	0/2

GBS = Guillain–Barré syndrome.

In 30 cases, electromyographic (EMG) studies were performed and we could retrieve the data of 22 patients. In general, data were available for conduction velocity and amplitude in one or more limbs. All patients had evidence for any type of electrophysiological dysfunction in one or more limbs (slowing of conduction velocity or decreased motor amplitude). The EMG data were not sufficient to allow a distinction between several EMG types (acute motor axonal neuropathy, acute inflammatory demyelinating neuropathy) of GBS.

In 30 cases, data from clinical chemistry studies on CSF were retrieved. Cell count ranged from 0 to 17 cells/μL. The albumin level ranged from 0.1 to 1.2 g/L. Of the 30 cases, 24 had classical cytoalbuminologic dissociation.

Incidence and seasonality. The number of inhabitants in Aruba increased from 93,700 in 2003 to 106,100 in 2011. We found an overall IR of 3.93/100,000 inhabitants.

We found a seasonal distribution in frequency of GBS cases in Aruba, with a peak in February (Figure 1). When analyzed by month of onset or season, we found a significant variation in the number of cases (χ^2 goodness to fit test, $P = 0.007$ month/$P < 0.001$ season).

Figure 2 shows a very clear fluctuation of IR over the last few years, with a major peak in 2011.

Microbiological studies. In the acute phase of the disease, 15/36 patients were tested for dengue virus, and 7/15 (47%) were IgM positive. Only two acute phase samples were available for detection of antibodies against *C. jejuni*. One of the samples was *C. jejuni* IgM positive, indicative of a recent infection. This patient also had detectable IgG antibodies against gangliosides GM1, GD1a, and asialo-GM1, which have been described in other *C. jejuni*–related GBS patients. Fourteen serum samples were collected from the GBS cases 1–2 years after the hospitalization for GBS. There was no significant difference in anti-*Campylobacter* IgG levels between the GBS cases and the control group (Figure 3). In contrast, the fraction of individuals with anti-dengue IgG antibodies differed significantly between GBS cases and healthy controls (Figure 3). Fourteen of the 16 (87.5%)

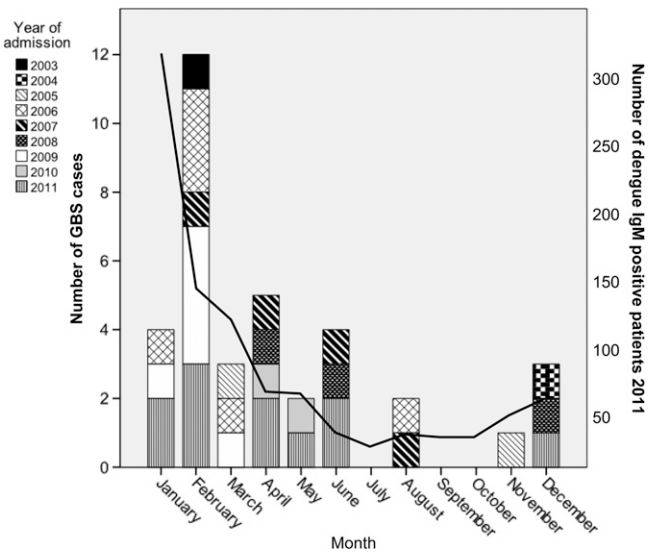

FIGURE 1. Seasonal distribution of Guillain–Barré syndrome and dengue cases in Aruba.

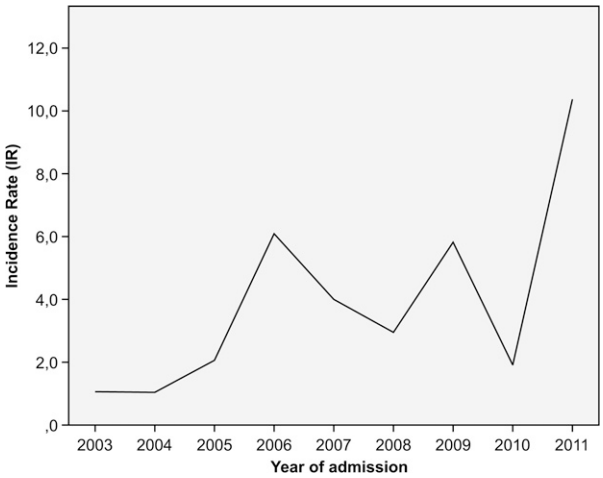

FIGURE 2. Incidence rate (IR) of Guillain–Barré syndrome in Aruba from 2003 to 2011.

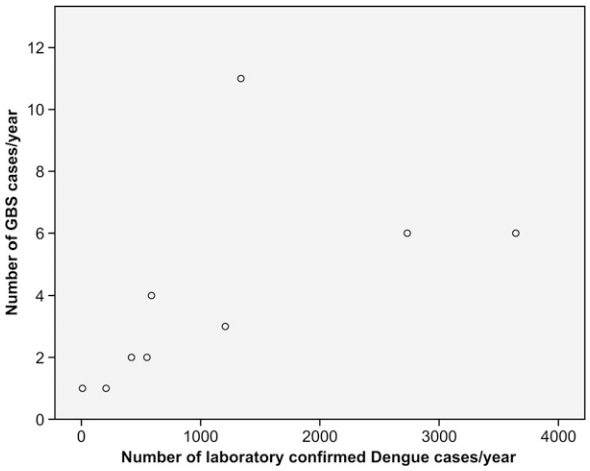

FIGURE 4. Scatterplot of absolute number of Guillain–Barré syndrome (GBS) cases/year versus absolute number of laboratory confirmed cases of dengue/year from 2003 to 2011.

samples of GBS patients were IgG positive for dengue, compared with 19 of the 32 (59.4%) healthy controls (χ^2, P = 0.05). In addition, anti-dengue IgG levels were significantly higher in GBS cases, compared with controls (Figure 3, t test, P = 0.004), whereas we did not observe a difference in anti-*Campylobacter* IgG levels. Interestingly, one of the two samples with a very low level of anti-dengue IgG is from the patient with anti-*Campylobacter* IgM antibodies.

Stool culture for *C. jejuni* was performed in 10 patients. None of the cultures were positive. Serological tests for CMV, EBV, and *M. pneumoniae* on available samples did not identify any recently infected GBS patients.

Dengue is endemic in Aruba. Interestingly, the dengue IgM–positive cases in 2011 have a similar seasonal distribution as the GBS patients (Figure 1). The peak of dengue infections is in January, slightly earlier than the peak of GBS cases, which is compatible with the postinfectious nature of GBS.

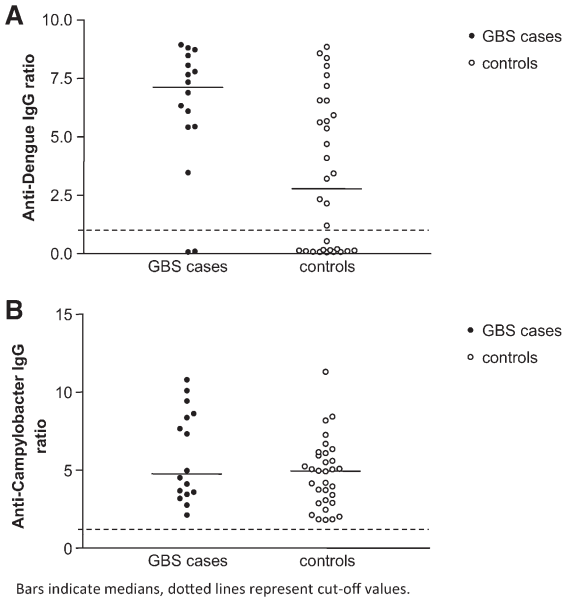

FIGURE 3. Anti-dengue and anti-*Campylobacter* IgG ratio in Guillain–Barré syndrome (GBS) cases versus controls.

Furthermore, we investigated whether the annual amount of GBS cases were related to the annual number of laboratory-confirmed dengue infections in Aruba during the period 2003–2011 and we found a significant correlation (Figure 4, P = 0.004, Kendall's tau-b).

Outcome and prognosis. Rehabilitation records or information of disability were available in 26 cases (72%) for at least 2 weeks or more. The outcome in Aruban GBS patients was comparable to that in western countries. We observed a poor outcome in 27.8% of the patients, defined as a GBS disability score ≥ 3 after 6 months of follow-up. The mean hospital stay was 47 days (range = 1–263).

Age and sex were no predictors of poor outcome (P = 0.394 and 0.929, respectively, Kruskal–Wallis and Mann–Whitney U tests, respectively). Although there was a trend between age and poor outcome, this was not significant (Jonckheere–Terpstra test, P = 0.229). Elderly patients had a more severe disease because age above 60 was a predictor of severe maximum weakness (χ^2, P = 0.018). A rapid onset of disease was a predictor of severe maximum weakness (Mann–Whitney U test, P = 0.009), but not of poor outcome (P = 0.069, Mann–Whitney U test). Severe maximum weakness, however, is a predictor of poor outcome (P = 0.004, Kruskal-Wallis). Season of admission was not a predictor of poor outcome or clinical severity.

DISCUSSION

In this study, we investigated the IR and seasonal fluctuation of GBS in Aruba and we observed an increased and strongly fluctuating incidence, with marked seasonality. Microbiological investigations suggest a triggering role of dengue virus.

We found an overall IR of 3.93/100,000 inhabitants. This number exceeds the IR reported in most other studies.[4,16] To our knowledge, only a few other studies reported an IR as high as this one during a longer time period[1,5] including the study performed in Curaçao.[16] An important question to ask is whether this number truly reflects the IR of GBS. There is a possibility of missing cases when performing a retrospective study, which means that the IR could be underestimated.

The use of hospital discharge data is allowed for epidemiological studies, if the appropriate diagnostic criteria are used and if the disease is likely to result in hospitalization. We consider the IR observed in this study as an acceptable representation of the IR of GBS in Aruba.

We found a significant seasonal variation in incidence toward the first few months of the year, with a peak in February. To our knowledge, a seasonal preponderance in incidence has not been reported with significant difference.[1,4–6,16,19–21] Some of these studies show more cases in colder months.[16,21] One of the largest epidemiological studies conducted in southwest Netherlands[4] shows more cases during the winter and June, in Brazil a cluster of cases in spring and summer was reported[22] and in Sweden autumn was the season with most GBS cases.[23] The seasonality prompted us to search for specific infectious triggers.

Several lines of evidence point to a role for dengue virus in the etiology of GBS in Aruba. First, almost half of the patients who were tested for dengue virus in the acute phase of GBS were tested positive for dengue IgM antibodies. Unfortunately, only two acute phase samples had been stored so we could not retest all patients for anti-dengue antibodies. Second, the seasonality of diagnosed cases of dengue has a similar shape as the seasonality of GBS cases. The time lag between the peak of the dengue cases and peak of GBS cases is compatible with the time lag that is observed for other infectious triggers of GBS.[5] Third, we observed significantly higher levels of anti-dengue IgG antibodies in former GBS cases than in the control group. This indicates that former GBS patients were more likely to have been exposed to dengue virus, which is in line with dengue as a trigger for their GBS episode. Cross-reactivity in serological tests between members of the flavivirus group occurs. However, one of the acute phase samples was tested for both dengue and WNV IgM and only dengue was found to be positive. We did not perform plaque reduction neutralization testing (PRNT) because earlier studies in the same region indicated that there was a very good correlation between ELISA and PRNT and dengue was the only identified flavivirus in the region during our study period.[24] The fourth line of evidence is that we observed a positive correlation between the number of dengue infections and the number of GBS cases in Aruba.

An association of dengue infections with GBS has been reported in a few cases. In one study, GBS was found in 4 of 13 patients with neurological manifestations after dengue infection.[25] The number of dengue-related GBS cases described in our study is therefore among the largest series of dengue-related GBS.

The most frequently identified triggering infectious agent of GBS is *C. jejuni*. There were two outbreaks of *C. jejuni* infections notified in Aruba, one in 2009 and other one at the start of 2011. Culture of stools in the acute phase did not result in positive cases but serological studies identified one *C. jejuni*–related case of GBS. Based on this observation, we think that multiple triggering infectious agents contribute to the large number of GBS cases in Aruba.

Another remarkable feature in our study is the strong fluctuation in incidence over the past 9 years, this fluctuation in incidence was also reported in Curaçao[16] and was not seen in the southwest Netherlands.[4] Although this may be caused by the relatively small number of patients, the association between the number of dengue infections in a particular year and the number of GBS cases indicates that the strong fluctuation of GBS cases may be caused by the fluctuations of triggering infections. We do not think that shifts in serotype prevalence of dengue virus are responsible for the fluctuations, because epidemiological data demonstrate the presence of multiple dengue serotypes throughout the study period.[26] Alternatively, these fluctuations may have occurred purely by chance.

As this was a retrospective study, case ascertainment was sometimes problematic. We selected patients based on ICD code and evaluated the available clinical data according to the NINCDS criteria.[17] Furthermore, EMG studies demonstrated nerve damage in all patients in whom data were available and the majority of the patients had classic cytoalbuminologic dissociation. Taken together, we think that our study population represented true GBS patients.

The GBS patients in our study do not have any special characteristics. We confirm earlier studies in which age and maximum weakness were found to be prognostic factors related of a poor outcome.[9,27] Because we inferred the data from patient records and these were not collected prospectively, a degree of uncertainty is added to the results, especially regarding the interpretation of clinical features.

In conclusion, we describe a cohort of GBS patients from the Caribbean island of Aruba. The incidence fluctuates strongly and is generally higher than in western countries. Microbiological evidence indicates that dengue virus may trigger a large proportion of GBS cases in Aruba. This requires more investigation. Prospective studies with standardized microbiological investigations could be of great value to our knowledge of the pathophysiological mechanisms and possible cofactors of this disease.

Received January 25, 2015. Accepted for publication January 5, 2016.

Published online March 28, 2016.

Acknowledgments: We thank P Herbrink, B.C. Jacobs, R van den Berg, and A. P. Tio-Gillen for their help with serological testing and Sekisui Virotech, Germany, for providing ELISA test kits.

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