



The association of Guillain-Barré syndrome with dengue fever was first described in Cuba

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ABSTRACT

Introduction: Dengue fever is endemic in almost all tropical and subtropical countries. Guillain-Barré syndrome is one of the neurological complications that have been described. **Objective:** To establish the first published articles associating dengue virus infection with the occurrence of Guillain-Barré syndrome. **Development:** they were searched PubMed/Medline, Scielo and Google Scholar for articles relative to this association, published between 1950-2000. The search revealed that the first two articles were published in Cuba in 1981 and 1983 by professor Jose Rafael Estrada González in Revista Cubana de Higiene y Epidemiología. It was reported an increased incidence of Guillain-Barré syndrome during the first two large dengue outbreaks in Cuba (1977-1978 and 1981 respectively). The articles that immediately followed were case reports published in 1990 and 1993 from French Polynesia and French Guiana respectively. **Conclusions:** The first documented evidence of the association between Guillain-Barré syndrome and dengue fever in the international scientific literature was published in Cuba by professor Estrada Gonzalez in 1981 and 1983.

Keywords: dengue; Guillain-Barré syndrome; Cuba, outbreaks; viral diseases

La asociación del Síndrome de Guillain-Barré con la fiebre por dengue se describió por primera vez en Cuba

RESUMEN

Introducción: El dengue es endémico en casi todos los países tropicales y subtropicales, siendo el síndrome de Guillain-Barré una de las complicaciones neurológicas descritas. **Objetivo:** Establecer los primeros artículos publicados que describieron la asociación entre Síndrome Guillain-Barré y dengue. Se buscaron artículos relacionados con esta asociación en

las bases de datos PubMed/Medline, Scielo y Google Scholar y publicados entre 1950-2000.

Desarrollo: La búsqueda reveló que los primeros 2 artículos fueron publicados en Cuba en 1981 y 1983 por el profesor José Rafael Estrada González en la Revista Cubana de Higiene y Epidemiología. Se describió un aumento de la incidencia de Síndrome Guillain-Barré durante las 2 primeras grandes epidemias de dengue en Cuba (1977-1978 y 1981 respectivamente). Los artículos que siguieron fueron reportes de casos publicados en 1990 y 1993 de la Polinesia francesa y Guyana francesa respectivamente. **Conclusiones:** La primera evidencia documentada en la literatura científica internacional acerca de la asociación de Síndrome Guillain-Barré y fiebre por dengue fue publicada en Cuba por el profesor Estrada Gonzalez en 1981 and 1983.

Palabras clave: dengue; Síndrome de Guillain-Barré; Cuba; epidemias; enfermedades virales

INTRODUCTION

Dengue fever, subsequent to infection by dengue virus (DENV)-an arbovirus transmitted by mosquitoes-is endemic in almost all tropical and subtropical countries. ⁽¹⁻³⁾ In the region of the Americas, the number of cases has increased almost 11 times from the 1980s to 2019, ⁽³⁾ allegedly due to a failed public health policy since the late 1970s. ⁽⁴⁾ The year 2019 yielded the highest number of infections since the Pan American Health Organization (PAHO) started collecting data in 1980. Until August 15th, 2022 a cumulative incidence of 226.6 cases/per 100,000 population had been reported. This region has evolved from a non-endemic or hypoendemic status to hyperendemicity, with major outbreaks occurring every 3-5 years. Dengue fever is considered a significant public health problem due to the high incidence of the disease. ⁽³⁾ Although most cases are asymptomatic or exhibit only mild symptoms, some patients develop a potentially lethal complication coined severe dengue, with a mortality rate varying from 1% to 10%, depending on the quality of medical care. ⁽¹⁾

DENV infection is also known to elicit neurological complications, which have been reported in 0.5%-20% of classic dengue patients admitted to hospitals. The frequency of encephalopathy and encephalitis, the most common among these, have been estimated to occur in 0.5%-6.2% of the patients. ^(1,5-8) Neurological involvement includes: central nervous system (CNS) and eyes (encephalitis, meningitis, encephalopathy, stroke, vasculitis, myelitis, retinochoroiditis, retinal vasculopathy); peripheral nervous system syndromes (Guillain-Barré syndrome, mononeuritis multiplex, brachial plexitis, hypokalemic quadriplegia, myositis), and post-dengue immune-mediated syndromes (acute disseminated encephalomyelitis, transverse myelitis, neuromyelitis optica, cranial neuropathies, and Miller-Fisher variant of the Guillain-Barré syndrome (GBS)). ⁽⁶⁾

Síndrome de Guillain-Barré is an acute monophasic immune-mediated disorder of the peripheral nervous system and the most frequent cause of acute flaccid paralysis. Well-established associations have been reported with recent respiratory and gastrointestinal infections involving *Campylobacter jejuni*, Cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae*, and Human immunodeficiency virus (HIV). ⁽⁹⁾ Moreover, dengue virus has been one of the infectious agents which has been consistently associated with antecedent infections in endemic regions. ^(10,11)

A recent review article concerning neurological complications of dengue fever called our attention since the oldest citation they referred to describing the association of DENV infection and GBS dated back to 2004. ⁽¹²⁾ Having investigated GBS in Cuba at the Instituto de Neurología y Neurocirugía (INN) since the 1970s, the authors were aware that the association between the large dengue outbreaks which occurred in the country in 1977-78 and 1981 and the occurrence of GBS had been timely communicated by professor José Rafael Estrada González (1921-1991). Estrada González was a prominent neurologist in Cuba, with postgraduate training at Massachusetts General Hospital and Harvard Medical School under the mentorship of Dr. Charles Kubik (1891-1982). He was founder of the INN in 1962, and director of this institution until his demise in 1991 (figure 1). The purpose of the present work was to search the scientific literature to establish when the possible association of dengue fever with GBS had been reported for the first time.

DEVELOPMENT

Methods

Search strategy: PubMed database of the US Library of Science at the US National Institutes of Health, Scielo database and Google Scholar search engine were searched for articles published between 1950 and 2000 in English, Spanish, or French, containing information relative to the association

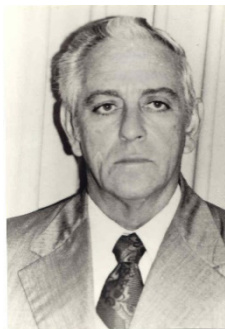


Fig. 1. Professor José Rafael Estrada González (1921-1991)

of dengue virus infection with the occurrence of GBS. ^(13,14) They were identified relevant publications using the following search terms: Guillain-Barré Syndrome and dengue. Additionally, they were also considered citations from reviews and other articles. They were included only articles corresponding with case reports and case series.

Overall, Pubmed search revealed 310 entries; but from 1950 to 2000, they were identified only two reports, ^(13,14) Google Scholar produced 189 entries from 1950-2000 (including citations), but only eight articles complied with the inclusion criteria. ⁽¹⁵⁻²²⁾ The remaining articles were reviews and other topics not related with the inclusion criteria. Scielo search revealed 11 entries (none during the study period).

They were thoroughly read the 8 articles included and it was registered all the information regarding the country of origin, date of publication, type of study, number of cases, clinical presentation of GBS, reference to antecedent infections, serotyping and outcome. It was extracted detailed information from the 3 articles published by Estrada González in order to summarize the study designs and authors main findings, considering that these results are not easily available to the scientific community.

Results

Documented evidence of the association between dengue virus infection and the occurrence of Guillian-Barré syndrome from 1950-2000

They are presented the eight articles identified during the study period in the table 1. The article of Estrada González *et al.* published in *Revista Cubana de Higiene y Epidemiología* in 1981 was the first report of the possible association between dengue fever and the occurrence of GBS (figure 2). ⁽¹⁷⁾ Based on the analysis of the national and institutional (INN) incidence of GBS, Estrada González perceived an increased occurrence of GBS concurring with the first widespread dengue outbreak in Cuba (1977-1978). Two years later, Estrada González reported the association between GBS and dengue fever during the second dengue outbreak in Cuba. ⁽¹⁸⁾

The next documented report in the scientific literature appeared in 1990, describing a 46-year-old man who seemingly acquired the disease during a trip to French Polynesia. GBS onset occurred approximately five weeks after the first manifestations of dengue. ⁽¹⁹⁾ In a study published in 1991 concerning the epidemiology of GBS during a 12 year period, Estrada González engaged more profoundly in the association of GBS with concurrent viral epidemics in the province of Havana (measles, chicken pox, mumps, dengue fever, mononucleosis, rubella). ⁽²⁰⁾ In 1993, Sainte Foie *et al.* reported the case of a young woman from the French Guiana serologically positive to DENV, who developed GBS that coursed to tetraplegia one week after the onset of dengue, recovering without sequels. ⁽¹⁹⁾ Two case reports followed from Malaysia and the West Indies (Caribbean) respectively. ^(15,22) The first article described a 43-year-old woman with acute flaccid paralysis, requiring assisted ventilation and a 51-year-old man with bilateral facial nerve palsy and areflexia without motor weakness from Malaysia, with serologically confirmed DENV infection. ⁽²²⁾ The second

Table 1. Publications associating Guillian-Barré syndrome with infection by dengue virus infection from 1950-2000

Country	Year	Authors	Study design	N
Cuba	1981	Estrada González <i>et al.</i> ⁽¹⁵⁾	Case series and national incidence	38
Cuba	1983	Estrada González, JR ⁽¹⁶⁾	Case series and institutional incidence	15
French Polynesia	1990	Paul <i>et al.</i> ⁽¹⁷⁾	Case report	1
Cuba	1991	Estrada González, JR ⁽¹⁸⁾	Epidemiological study	
French Guiana	1993	Sainte Foie <i>et al.</i> ⁽¹⁹⁾	Case report	1
Malaysia	1998	Chew <i>et al.</i> ⁽²⁰⁾	Case report	2
West Indies	1999	Esack <i>et al.</i> ⁽¹³⁾	Case report	1
Not mentioned	2000	Gaultier <i>et al.</i> ⁽¹⁴⁾	Case report	1

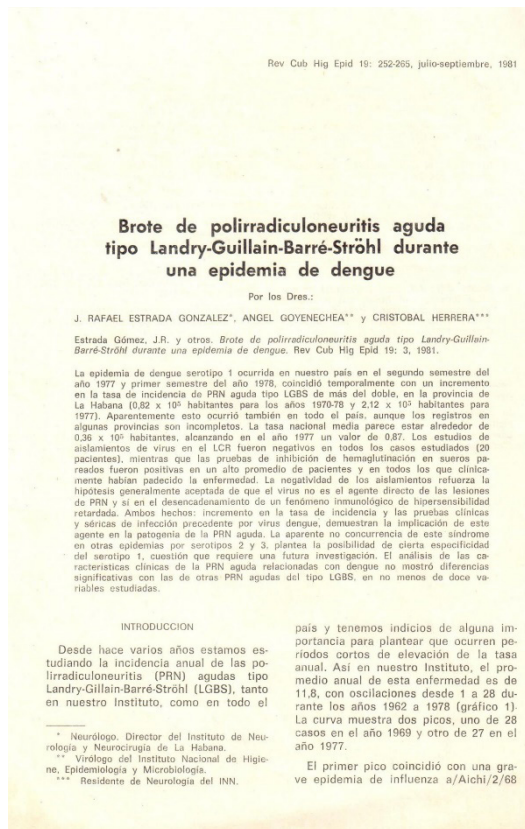


Fig. 2. First page of the article published in 1981 by Estrada González *et al.*: Acute polirradiculoneuritis outbreak type Landry-Guillain-Barré-Strohl during a dengue epidemic ⁽¹⁵⁾

article reported a 44-year-old Caribbean woman who referred numbness and weakness of both legs and arms, two weeks after having suffered from classical dengue fever, that quickly evolved to a disabling paraparesis. ⁽¹⁵⁾ All patients had a complete recovery. In the year 2000 it was first described a putative association of dengue fever with Miller Fisher syndrome in a 57 year-old-man who developed a left ophthalmoplegia with ataxia and areflexia, concomitant with DENV Immunoglobulin M (IgM) seroconversion and positive Polymerase chain reaction (PCR) for serum and Colony stimulating factor (CSF). ⁽¹⁶⁾

Main findings described by professor José Rafael Estrada González relative to the association of Guillain-Barré syndrome and dengue fever

Concurring with the 1977-1978 dengue outbreak in Cuba Estrada Gonzalez conducted an investigation to explore the possible association of dengue fever and GBS. It was evident from October 1977 on, that there was a considerable increase in the monthly incidence of GBS at the INN. They were evaluated thirty eight GBS patients between July 1977 and December 1978, and they were reported antecedent infections in 27 (71%): 19 referred clinical dengue, 4 had flu, and 4 exhibited symptoms

of common cold. Serotyping for DENV1 in 31 patients revealed a positivity rate of 64.5%. Nevertheless, the positivity rate during the peak of the epidemic (July-December 1977) was much higher (94%), while during the year following (January-December 1978), only 28.6% were positive for DENV1. ⁽¹⁷⁾

The authors highlighted some aspects based on these results: during the outbreak of dengue fever, there was an increased incidence of GBS in the institution, with DENV infection as an antecedent factor 8 d-9 d previous to GBS onset in most cases. Serotyping revealed a high percentage of DENV1 positivity. Although these results supported a relationship between these two conditions, the authors argued that the presence of DENV antibodies in GBS patients could reflect the elevated dengue morbidity in the population during the epidemic. Thus, they evaluated the incidence of GBS over time, because an increase during the outbreak could sustain their hypothesis. It was encountered a higher national incidence of GBS during the 1977-1978 epidemic of dengue fever in Cuba, from an average of 0.36/100 000 inhabitants (registered from 1970-1978, excluding the year 1977) to 0.87 per 100,000 in 1977. In the province of Havana, the incidence increased from 1.02/100 000 to 2.39 per 100,000 inhabitants. The authors considered that the incidence reported from provinces outside of Havana most probably exhibited an under-registration. ⁽¹⁷⁾

Subsequently Estrada González investigated the occurrence of GBS during the 1981 dengue outbreak in Cuba, which peaked from June to September 1981. Taking into account that national data were unavailable at the moment, he compared the monthly incidence of GBS at the INN from 1976 to 1981 in relation to the incidence of dengue cases in the population. It was found that the number of GBS patients at the INN increased during the peaks of the 1977 and 1981 dengue outbreaks (figure 3). Nevertheless, the proportion of clinically positive dengue as antecedent infection in this group, was lower than in 1977 but there was no reference to seropositivity. ⁽¹⁸⁾

Estrada González emphasized that according to the thorough bibliographic search conducted, no reference had been previously made relative to the association of GBS with dengue epidemics, despite the fact that in the preceding 15 years, eight dengue outbreaks had been registered in Caribbean countries. He also highlighted the importance of being alert for an increase in the incidence of GBS during the course of dengue outbreaks in countries where DENV was endemic.

In 1991 Estrada González *et al.* published an epidemiological investigation based on the medical records of hospitalized GBS patients from the province of Havana during a 12-year period (1970-1981). The average annual incidence rate was 0.9/100,000 inhabitants, and the analysis of the relationship between the incidence of GBS with viral outbreaks

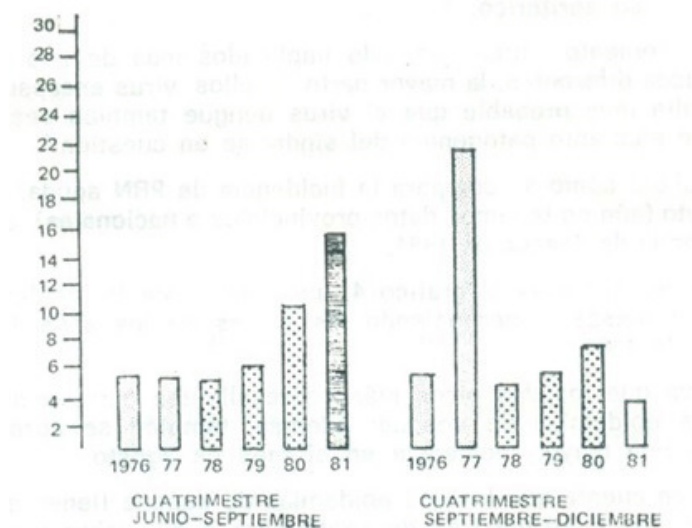


Fig. 3. Incidence of GBS patients at the INN from 1976 to 1981 during the quartermonths when the 1977 and 1981 dengue outbreaks peaked (September-December and June-September respectively) ⁽¹⁶⁾

in the city revealed fluctuations of the incidence ratios in relation to the different viral epidemics. They reported that during this 12 year period in Havana, the outbreaks that were most closely related to the annual increase in the GBS incidence rate were the ones of dengue fever in 1977 and 1981; measles, chickenpox and mumps outbreaks also exhibited an association in time. ⁽²⁰⁾

Discussion

Dengue fever was recognized in the region of the Americas since the XVIIIth century; although they were reported outbreaks of a dengue-like disease as early as 1699 in Panama. In 1780 it was described dengue for the first time during an epidemic that occurred in Philadelphia; during the XIXth century and first half of the XXth century they were reported outbreaks arising mainly in the Caribbean and South of the United States of America. From 1960 to 1980 they were recognized three great outbreaks affecting the Caribbean, Central America and some South American countries: DENV3 in 1963-1964, DENV2/DENV3 in 1968-1969 and DENV1 in 1977-1978. ⁽²³⁾

In 1945 it was reported a dengue fever epidemic in Havana, but further notification of clinical disease did not occur until the DENV1 outbreak in 1977. They were recorded almost half a million patients throughout the country, all with the benign form of the disease. ⁽¹²⁾ A second dengue outbreak occurred in 1981, this time caused by DENV2, associated with cases of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). They were notified 344,203 cases, 10,312 of them corresponded with DHF and they were reported 158 deaths. ^(23,24)

It is necessary to highlight the profound analytical thinking of Estrada González, based not merely on case reports (as in the papers that followed until 2000) but on case series and epidemiological data. To our best knowledge, the first case series after he published the 1981 and 1983 articles were not published until 2008 by Soares *et al.* in Brazil. ⁽²⁵⁾ Unfortunately, his article was only cited by Chew *et al.*, ⁽²²⁾ possibly because it was published in Spanish in a Cuban journal, which at the time was not indexed in any of the major scientific databases.

Estrada González *et al.* were not only the first to describe the possible association between GBS and dengue fever in the scientific literature, but also put forward the proposal that dengue virus serotype 1 should be added to the list of viruses then recognized as antecedent factors for the development of GBS. Based on this they indicated the necessity of being vigilant for an increase in the incidence of GBS during dengue outbreaks in countries where DENV was endemic. ⁽¹⁷⁾

It is crucial to recognize the pioneering contribution of professor Estrada González regarding the association of GBS and DENV infection. His achievements in the field of Neurology and specifically in the investigation of GBS, were recently published in Spanish. ⁽²⁶⁾ Based on his results and inspiration, this research area has continued to grow in our institution. ^(27,28) Eventually the investigation employing nonlinear analysis of a Guillain Barré time series to elucidate its epidemiology, originated from his groundbreaking hypothesis. ⁽²⁸⁾

Four decades after the release of his articles, the association between DENV infections and GBS has still not been confirmed. The low incidence of GBS renders it very difficult

to arrive at decisive conclusions, and much larger and specifically designed studies are necessary. Nevertheless, in regions where dengue is hyperendemic, screening for dengue illness must be a priority in patients with acute flaccid paralysis.

This study has some limitations due to the fact that the search had to be conducted since 1950, to be sure that at least 30 years prior to the articles published by Estrada González were screened. During that period, articles could have been published in journals not appearing in the data bases of the time. Nevertheless, a very detailed search of the references in all the articles (including review articles), and especially from large countries like Brazil and India, where dengue has been endemic for some decades, did not reveal any reference to any other studies published previous to Estrada Gonzalez's.

Conclusions

Professor Estrada Gonzalez's articles published in Cuba in 1981 and 1983 were the first communications in the scientific literature relative to the possible association between GBS and DENV infections.

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Interests Conflicts

The authors declare that there are not conflicts of interest among them or with the research presented

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Data curation: Alina González-Quevedo

Formal analysis: Alina González-Quevedo, Rosaralis Santiesteban Freixas

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