

EPIDEMIOLOGIC FEATURES OF GUILLAIN-BARRÉ SYNDROME IN SÃO PAULO, BRAZIL

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ABSTRACT - Introduction: There are few epidemiologic studies concerning Guillain-Barré syndrome (GBS). Due to difficulties with definition and lack of a standard diagnostic test of reference, GBS is not easy to study epidemiologically. We evaluate some epidemiological features of GBS in a sample of cases treated at a tertiary hospital in São Paulo, Brazil. **Method:** We retrospectively reviewed all cases of GBS with hospitalization in Santa Marcelina hospital, over the period of January 1995 through December 2002. **Results:** Ninety-five cases were included in this study. Fifty-five were men and forty women, with a proportion of 1.4 men to 1 woman. The age ranged from 1 to 83 years with a mean age at onset of 34 years. GBS was less frequently observed below 15 years (18.9%) and above 60 years (16.9%). The highest frequency was observed in patients aged 15 to 60 years old (66.2%). The annual incidence rate was 0.6 cases/100,000 people. There was a highest frequency of cases during the months of September through March (62.1%). **Conclusion:** Our data differs from that of other epidemiological studies in that we did not observe a bimodal distribution in age and found a seasonal pattern in hotter months.

KEY WORDS: Guillain Barré syndrome, epidemiology.

Aspectos epidemiológicos da síndrome de Guillain-Barré em São Paulo, Brasil

RESUMO - Introdução: Os estudos epidemiológicos da síndrome de Guillain-Barré são escassos, devido às dificuldades com a definição da doença e à ausência de marcador biológico diagnóstico. Avaliamos aspectos epidemiológicos de uma amostra de pacientes com a SGB internados em hospital terciário da zona leste de São Paulo. **Método:** Avaliamos retrospectivamente prontuários de internação de todos os pacientes com o diagnóstico de SGB internados no Hospital Santa Marcelina no período de janeiro de 1995 a dezembro de 2002. **Resultados e conclusão:** A amostra consta de 55 pacientes do gênero masculino e 40 pacientes do feminino, na proporção de 1.4 homens para 1 mulher. A idade variou de 1 a 83 anos (média: 34 anos). Observamos menor incidência da doença em pacientes com idade abaixo de 15 anos (18,9%) e acima de 60 anos (16,9%). A frequência maior foi observada no subgrupo com idade entre 15 e 60 anos (66,2%). A incidência anual foi de 0,6 casos/100,000 habitantes, sendo 62,1% dos casos observados nos meses de setembro a março e 37,9% nos meses de abril a agosto. A mortalidade observada foi de 3,1%. **Conclusão:** Nossos resultados diferem daqueles publicados na literatura médica pela ausência de distribuição bimodal na idade e pelo caráter sazonal apresentado.

PALAVRAS-CHAVE: síndrome de Guillain-Barré, epidemiologia.

Guillain-Barré syndrome (GBS) covers a set of clinical syndromes in which idiopathic peripheral neuropathy affecting motor, sensitive and autonomic nerves and spinal roots causes acute, or subacute, progressive motor weakness in more than one limb^{1,2}. The degree ranges from minimal weakness in the legs to total paralysis of the muscles of all four extremities and of the trunk. External ophthalmoplegia, bulbar and facial paralysis may occur with varied frequency. GBS has near complete, or complete, clinical recovery in

most cases³. It is mediated by humoral and cellular immune responses that result in the direct destruction of either the myelin sheath surrounding the peripheral nerves or the axon itself⁴. Immune reactions against target epitopes contained in Schwann cell surface membrane or myelin result in acute inflammatory demyelinating neuropathy, and reactions against epitopes in the axonal membrane cause the acute axonal form of the syndrome⁵. It may follow triggering events, most frequently nonspecific or "flu-like" upper respiratory

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infections, gastrointestinal illnesses and vaccinations^{6,7}. Nowadays Guillain-Barré syndrome has become the principal cause of acute flaccid paralysis in Western countries, after the control of poliomyelitis^{8,9}.

Epidemiological studies can provide a more complete picture of the natural history and clinical spectrum of a disease, mainly when the studies are based on all cases of the disease in a well defined population. Peripheral neuropathies are definitively not easy to study epidemiologically, due to the heterogeneity of the disorder and because many different clinical disorders have neuropathy as a component. Guillain-Barré syndrome is a subgroup of neuropathy and its diagnosis remains descriptive. We still have difficulties with its definition and there is not a standard diagnostic test of reference. Epidemiological studies of GBS are rare, with only ten series that include more than one hundred patients to date¹⁰⁻¹⁶. This occurs partially because the clinical, laboratory and electrodiagnostic criteria, although well defined, are difficult to apply retrospectively. Despite these caveats, GBS has been the subject of many epidemiological studies given that it is a striking neurologic condition and usually serious enough to require medical attention at a very early stage.

To our knowledge, there have been just a few epidemiological studies of this syndrome in Latin American^{8,9,17,18}. The aim of this study is to demonstrate clinical and epidemiological aspects of GBS in a series of ninety-five Brazilian patients whose illness occurred over the years from 1995 to 2002.

METHOD

We included all patients with clinical diagnosis of GBS who had been hospitalized in Santa Marcelina Hospital, São Paulo, Brazil, from January 1995 to December 2002. Clinical data was collected from medical records of the patients whose hospitalization occurred during the period of 1995 to 1999, and from clinical registrations for cases occurring during the years of 2000 to 2002. We used a standard protocol that included demographic data and a questionnaire in order to disclose possible risk factors for GBS. We also applied clinical, electrophysiological and cerebrospinal fluid (CSF) criteria for GBS defined by Asbury and Cornblath³. Patients were included only if they fulfilled all criteria defined by Asbury and Cornblath: presence of roughly symmetrical motor weakness over a period ranging from days to four weeks and decrease or disappearance of deep tendon reflexes. All the patients were examined by the same neurological staff during all these years. They all underwent CSF biochemical analysis and

electrodiagnostic studies. Patients were excluded if they had Diabetes mellitus or acquired immunodeficiency syndrome, since these illnesses are related to acute inflammatory demyelinating polyneuropathy, and therefore present a high possibility of bias in an epidemiological study.

RESULTS

Ninety-five patients met diagnostic criteria of Asbury and Cornblath for GBS and were included in statistical analysis. (Figs 1 and 2) Fifty-seven percent of the patients were male and 43% were female, with a male/female ratio of 1.4/1.0. The mean age of the 95 patients at admission was 35 years (range 1 to 83). The female group was significantly younger than the male group. The female group had a mean age of 30 years (range 1 to 79) and the male group had a mean age of 39 years ($p < 0.05$). The analysis of subgroups of ages showed a higher proportion of patients aged 15 to 60 years (66.2% of all cases), and a small proportion of patients with age below fifteen (18.9%) and above sixty (16.9%). The analysis of the children subgroup showed an increased frequency among children aging 0-4 years (55.5%).

The annual mean coefficient of incidence of GBS was 0.4 per 100.000 persons considering both sexes and all ages of the population located at Santa Marcelina Hospital area (three million people). The mean annual frequency was 11.9 cases. Considering seasonal fluctuations, the highest incidence was observed from September to March with 62.1% of cases and 37.9% during the months of April to August ($p < 0.05$). Table 1 shows a higher incidence of GBS during the months of Spring and Summer in six out of eight years. Antecedent infections within one month before the onset of neurological symptoms were found in fifty-eight percent of the cases. Among them, respiratory infections were related in 46 percent of cases, and gastrointestinal infections in 12% of cases.

The initial symptoms were ascending in 86% of the cases. Respiratory failure with mechanical ventilatory support was observed in 19% of cases. Facial paralysis occurred in 40% of the patients and was bilateral in 70% of these cases. Oculomotor disturbance occurred in 35% of patients while urinary dysfunction was observed in only three patients. Sensory disturbances, including pain, were observed in 10% of all cases. Three patients died from respiratory failure and pneumonia or sepsis, with a mortality ratio of 3.1%.

DISCUSSION

Incidence - Forty large series of GBS patients from well-defined geographic areas were identified over the last 45 years¹⁹. Annual incidence has varied widely, from 0.4 to 4 cases/100,000 population with a median of 1.3 cases/100,000. Our series of GBS patients disclosed a mean annual incidence of 0.4 case /100.000. Although definitely not representative of the Brazilian population, as this was a hospital-based study, it showed an annual incidence similar to a recently published study, which analyzed the GBS in the whole Brazilian population under 15 years of age⁹. They found a mean coefficient of incidence of 0.46 for the whole country and 0.40 for the southeast region, where lies the city of São Paulo. These data, however, cannot be compared with that from the present study, since our survey included all age subgroups. In spite of that, our data showed an annual incidence that is not different from the overall incidence rates recorded in many other studies, ranging from 0.2 to 0.9 case/100.000^{10,19-22}. We did not consider the population of São Paulo's metropolitan area because all the patients in this series lived in the hospital referred area. The annual incidence of the cases (given in Table 1) showed no increasing incidence during these eight years, although we have observed a peak incidence in 1996 (Fig 1).

Sex distribution - In almost all series studies,

males are more commonly affected by Guillain-Barré syndrome than are females, with a median rate of 1.25 men to one woman²². Considering the supposed autoimmune etiology of GBS, the male preponderance is somewhat unexplained. We also observed the same preponderance in our study with a male/female ratio of 1.4/1.0. Dias-Tosta and Huckelhaus found a slight preponderance of boys throughout the years of their study in the Brazilian population below fifteen⁹. Our study also showed that men were older than women at the onset of the disease. We do not have a reasonable explanation for that. Perhaps this represented only a statistical bias in consequence of the difference between the numbers of cases in both sexes.

Age distribution - The age distribution of GBS is usually bimodal, with peaks both in the young and the elderly²². The incidence is lower in children under fifteen, whereas the highest incidence is observed in the elderly. This increased incidence in the elderly is commonly attributed to an abnormal immune suppressor mechanism, leading to higher susceptibility to autoimmune disorders. Our study failed to demonstrate this bimodal age distribution. We saw an isolated peak in young adult, mainly in those between 15 to 40 years old, and lower incidences in children and in patients above 60 years old (Fig 2). Among children the greater prevalence was observed in tho-

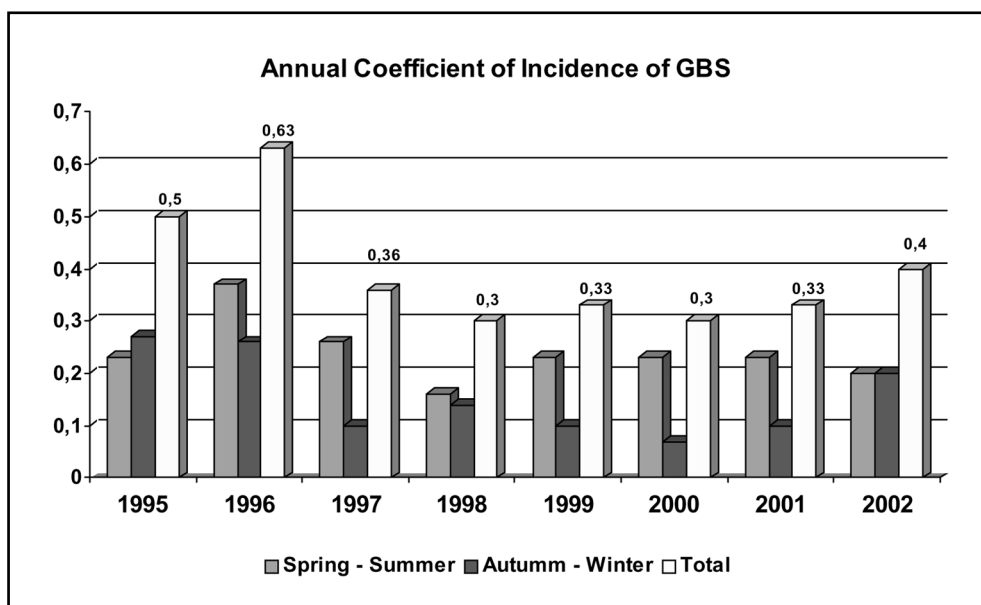


Fig 1. Annual coefficient of incidence of GBS and incidence in the Spring-Summer and Autumn-Winter months over the years 1995 to 2002.

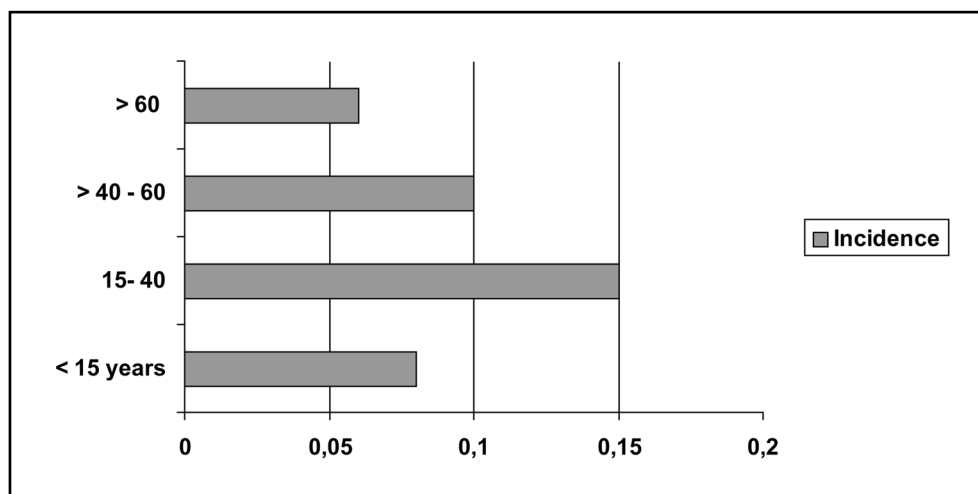


Fig 2. Age distribution of patients with GBS and their respective mean annual coefficients of incidence.

se under four years old. We had a lower incidence in the age subgroup below fifteen than that found in Dias-Tosta and Huckelhaus series of patients⁹, although we had observed the same high prevalence in children below four as they had. Probably this reflected the influence of the lack of pediatric emergency reference to our hospital, known as a general one.

Seasonal distribution - Most studies have not identified a relationship between the incidence of GBS and season preponderance, despite the clear association with preceding upper respiratory infections, which are more frequent in the colder months of winter. Some epidemiological studies show a seasonality pattern, such as those studies that identify a higher frequency of the disease in autumn²³, or in the summer and autumn^{13,24} along with the study in Sardinia, Italy, which reported the most critical seasons to be Winter and Spring¹⁰. A study in northern China has found a markedly increased incidence of the acute motor axonal form of GBS in the Summer months. This form of the disease is clearly associated with enteric infections and *Campilobacter jejuni*, with higher incidence in hotter months²⁵. The lack of seasonal association observed in most studies may be due to the fact that the respiratory and enteric infections have opposite seasonality. We found a higher incidence of the illness in the months during Spring and Summer in Brazil, when sixty-two percent of the cases occurred (Table 1). This cannot be attributed to enteric infections like in China, since the most frequent trigger event in our series was respiratory tract infections. Dias-Tosta and Kuckelhaus' study, also in Brazil, shows

no clear peak distribution against months, although they had found a slight variation in January and May, which was not significant⁹.

Trigger events - GBS is the prototypic "post-infectious" disease, with about two-thirds of patients with an antecedent infection, but in many instances, the pathogen that caused the prodromal illness remains unidentified. Respiratory infections are the most frequently reported, followed by gastrointestinal infection, of which *Campilobacter jejuni* is the main identified agent²⁶. Many other identified pathogens have been reported, including human immunodeficiency virus, as being triggers for GBS, but these have been reported in small series and anecdotal reports, for which there is a lack of statistically valid evidence²⁷. The association with vaccinations has been reported in many studies as antecedent events¹⁴, but the only case with a satisfactorily explained mechanism is that of the rabies vaccines. Two separated case control studies failed to show a significant association between the occurrence of GBS and immunization, although they have found an increased risk likely to be four to five-fold²⁸. Other possible life event associations, such as pregnancy, surgery and trauma, have been reported as remote etiologic possibilities²². We found the respiratory infection to be the most frequently antecedent trigger event, being reported by 46% percent of our patients, followed by gastrointestinal infection, reported by 12% of patients. None of our ninety-five patients reported previous vaccination, trauma, surgery or pregnancy.

Mortality - The death rate of GBS ranges from 5 to 10% even in regions of high standard medi-

cal care quality and remains a significant cause of mortality and morbidity among persons aged over 40 years. Mortality rate increases among older age groups. The overall case-fatality ratio is about 4.4% in the United States, ranging from 0.7% among persons younger than fifteen years old to as high as 8.6% among persons older than 65 years old²⁹. In southeast England the mortality ratio was also about 8%, as it was demonstrated in a recent survey by Rees et al.³⁰. Dias-Tosta & Kuckelhaus found a death rate of 5.4% in a Brazilian series of pediatric GBS, with a regional variation from 2.7% in the southeastern part of Brazil to 7.6% in the northeast region⁹. We found a mortality ratio of 3.1%. The three patients who died were over 60. The mortality rate observed in our study was slightly lower than those discussed above, probably reflecting a constant concern over early critical care measures, and early use of plasmapheresis or high dose intravenous immunoglobulin, the standard treatment defined for all patients with certain diagnosis of GBS in our centre since 1995.

In conclusion, our study demonstrated incidence, sex distribution and trigger events of Guillain-Barré Syndrome similar to many other previous studies. However, our data differs from that of other epidemiological studies in that we did not observe the typical bimodal distribution in age, there was a slightly lower mortality than worldwide described and we have found a seasonal preponderance in hotter months.

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