Epidemiology and characteristics of Guillain-Barré syndrome in the northwest of Iran

Mohammad Ali Arami,* Mohammad Yazdchi,† Reza Khandaghi †

BACKGROUND: Little is known about the incidence of Guillain-Barré syndrome (GBS) in Iran. We determined the incidence and evaluated prognostic factors for GBS in a prospective, population-based study.

PATIENTS AND METHODS: We evaluated and followed all patients with a diagnosis of GBS admitted to three referral neurology centers in East Azerbaijan province over a 1-year period (2003). Clinical and electrophysiological characteristics of cases were reviewed and analyzed.

RESULTS: A total of 76 patients were found, corresponding to a crude annual incidence rate of 2.11/100 000 population. Six patients (7.9%) died acutely within 21 days from the onset of the disease. Acute mortality was due to respiratory involvement, sepsis and acute autonomic system dysfunction. The persistence of disability after the acute phase was related to axonal involvement (OR=3.19, 95%CI, 1.65 to 6.16). There was a significant correlation between a history of diarrhea and a further need for mechanical ventilation ($P<0.05$). Mechanically ventilated patients had a low GBS disability score on discharge compared with patients not mechanically ventilated ($P=0.05$).

CONCLUSIONS: The incidence rates of GBS in our province is similar to that in other countries. Acute mortality in GBS was mostly due to poor respiratory care of patients and infective complications, but disability and probably late mortality were due to axonal nerve injury.

*From the Departments of Neurology, *Kashan University of Medical Sciences, †Tabriz University of Medical Sciences*

Correspondence:
 Mohammad Ali Arami, MD
 Social Security Organization
 Milad General Hospital
 Shahid Hemat Avenue
 Tehran, Iran
 Tel: +98-9141149248
 arami_ma@yahoo.com

Accepted for publication
 July 2005

Ann Saudi Med 2006;26(1):22-27

Guillain-Barré syndrome (GBS) is an idiopathic acute inflammatory demyelinating polyneuropathy. Although the pathogenesis of GBS remains unclear, there are increasing indications that it is an autoimmune disease, usually triggered by an infection, especially diarrhea due to infection and upper respiratory tract infections.¹ Usually, hospitalization for early diagnosis and treatment is mandatory. There are numerous reports of incidence rates that range from 0.6 to 4.0/100,000 population.²⁻³ Data from the Mayo Clinic, based on National Institute of Neurological Disorders and Stroke diagnostic criteria, and thorough ascertainment methods gave a crude incidence of 1.7 per 100 000 per year.⁴

Despite effective therapies, such as IV immunoglobulins (IVIG) and plasma exchange (PE), acute mortality remains relatively high and about 20% of hospitalized patients may have a long-term disability.⁵ Prognostic factors for acute mortality and for residual disability are not yet completely understood. Also, mortality and morbidity rates are dependent on high-quality intensive care.

The aim of this study was evaluation of the incidence, clinical characteristics, and prognostic factors for GBS in one of the great provinces of Iran using a prospective design.

Patients and methods

Eastern Azerbaijan has a total area of 47 821 km² and had a population of 3 588 156 (2 324 200 urban and 1 293 656 rural) at the time of the study. Since 20 March 2003 all new cases of GBS admitted to three referral centers (Imam Khomeini General Hospital, Razi Hospital and Tabriz Pediatric Center) were prospectively recorded. The diagnoses were coded according to the International Classification of Diseases, 9th revision. Investigators used a standard questionnaire to collect the main demographic variables, clinical history, neurological and laboratory findings, and details of treatment and complications. Neurology residents carefully recorded antecedent events using a detailed checklist. One or more lumbar punctures were performed in each case, and the CSF was examined for cell count, protein, and glucose. For the analysis of prognostic factors, the clinical status of patients at admission and EMG examinations were considered. The Hughes or GBS disability scale was used to evaluate the clinical status of patients (grade 0=healthy; grade 1=minor signs or symptoms of neuropathy but capable of manual work; grade 2=able to walk without support of a stick but incapable of manual work; grade 3=able to walk with a stick, appliance, or support; grade 4=confined to bed or chair bound; grade 5=requiring assisted ventilation; grade 6=dead).⁶ Short-term prognosis was defined as mortality and morbidity in the acute phase of the disease (first 30 days). The most important variable in prognosis was the GBS scale.

Autonomic symptoms were recorded by neurology residents using a checklist (hypertension, hypotension, orthostatic hypotension, cardiac arrhythmias, bladder and gastrointestinal dysfunction). Serial EKG recordings and the R-R interval duration were also considered. The presence of resting dyspnea (defined as dyspnea in bed, with no exertion), arterial blood gas levels abnormalities, and the need to the intensive care unit (ICU) were registered for further evaluation. All patients with resting dyspnea, hypoxemia and other clinical clues of respiratory failure were admitted to an ICU unit, and depending on ABG results, mechanical ventilation was started. Patients with severe oropharyngeal weakness and swallowing disability were intubated to prevent aspiration.

The diagnosis of GBS was based on diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).⁷ Using specific criteria for demyelination and primary axonopathy, standard EMG examination with

EMG/NC study apparatus (Toenniss Neuroscreen-plus, Erich Jaeger GmbH, Hoechberg, Germany) was performed.⁸⁻⁹ Mixed neuropathy was diagnosed in patients with unexcitable or markedly reduced compound muscle action potentials (CMAP) in two or more nerves associated with the presence of at least two electrophysiological findings suggesting demyelination. According to the electrodiagnostic study (EDX), cases were classified in four groups: acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN) and mixed type. Follow-up visits were performed at regular intervals (every day during hospitalization, at discharge, at day 30 and at month 6). Incidence rates were adjusted to the 2003 area population of eastern Azerbaijan. Factors related to short-term prognosis were analyzed using GBS grade. Data were processed using the SPSS statistical package (version 11.05). Data were analyzed by the χ^2 or Fisher's exact test if frequencies were small, or McNemar's test for paired data. Continuous variables were analyzed using Student's test or ANOVA, with $P < 0.05$ considered significant.

Each center was free to decide about treatment plan. The three forms of treatment were plasma exchange, IVIG or both. The plasma exchange regimen used in all units was removal of a total of 200 to 250 mL/kg of plasma in eight to ten treatments on daily programs. The replacement fluid was saline combined with 5% albumin. In many patients treatment was instituted through the antecubital veins. The regimen was 0.4 g/kg per day for 5 consecutive days in all units.

Results

During the one-year study period, a total of 76 patients (45 men, 31 women) were diagnosed with GBS. A total of 33% of patients were the AIDP type, 9% patients the AMAN type and 5% were the AMSAN type EDX. The mean annual adjusted incidence rate was 2.11/100 000 populations, 2.5/100 000 for men and 1.73/100 000 for women. The incidence in the population under 15 years was 2.28/100 000 and the incidence for patients older than 15 years was 2.06/100 000. The incidence of the disorder between rural and urban regions was equivalent (2.05/100 000 versus 2.35/100 000). Most cases occurred in the winter (Figure 1).

The mean age of the patients was 34.43 years (SD 23.9) (range 6 years to 79 years) (Table 1). In contrast to developed countries, our population is

Figure 1. Seasonal occurrence of Guillain-Barré syndrome in northwest Iran.

Table 1. Characteristics of 76 patients with Guillain Barré syndrome.

Mean age	34.4 years
Sex	45 men, 31 women
Preceding infection	50 (68.5%)
GBS disability scale on admission	
Diarrhea	12 patients (15.8%)
Respiratory	38 patients (50%)
Electrodiagnostic characteristics	
Demyelination	46 patients (60.5%)
Axonal degeneration	19 patients (25%)
Mixed pattern	11 patients (14.5%)
Mean Hughes score on admission	3.25±0.77
Mean disability score on discharge	2.74±1.33
Mortality	6 patients (7.59%)

very young, which is reflected in the age of the patients and the age-specific incidence of the disease (Figure 2, 3). There was not significant a difference in mean age between sexes (women, 30.72±22.29; men, 37.14±24.90; $P=0.24$). The mean time from onset of symptoms to nadir was 5.6 (±4.9) days (median time, 7 days), with no significant difference between urban (5.1±5.6) and rural patients (5.7±7.5 days, P =not significant).

Fifty patients (65.8%) reported a history of infection in the 4 weeks preceding the onset of symptoms: an upper respiratory infection was detected

in 38 patients (50%) and a history of gastroenteritis in 12 patients (15.8%). Table 1 shows the results of electrophysiologic studies. No correlation was found between previous gastrointestinal infections and axonal or demyelinating EMG pattern ($P<0.5$, but not statistically significant). Cerebrospinal fluid (CSF) examination was performed in 74 cases. All patients underwent only one lumbar puncture and usually in the first week of admission. Elevated CSF protein levels (greater than 45 mg/dL) were noted in 15 cases (19.7%). The mean level was 75.5 mg/dL (SD, 38.5). Autonomic dysfunction was recorded in 32 (42.1%) cases and predominantly affected the cardiovascular system. Sphincter muscles were involved in 7 cases (9%). Forty-nine (64.5%) patients were admitted to ICU for better supervision but only 25 patients (32.9%) were supported by mechanical ventilation. The mean ICU care period was 13.19±21 days, including 21±32.5 days for axonal damaged cases and 9.9±12.96 days for demyelinating type nerve injuries ($P<0.04$).

The mean GBS score on admission was 3.25±0.77 with a maximum disability of 3.97±0.923 during the following days. The mean disability score on discharge was 2.74±1.33. Thirty-four patients (44.7%) were very weak with a GBS score of >3, but on discharge 23 patients (30.3%), including 5 patients who died, were in this severe weakened group. In 6 months of follow up only 15 patients (19.7%) had a GBS score of >3.

A worse GBS score (>3) at nadir was not related to the presence of axonal or demyelinating nerve damage ($P=0.132$), autonomic nervous system involvement ($P=0.53$), or age ≥50 years ($P=0.32$). Also we found no significant relationship between diarrhea or respiratory infection history and disability score on admission ($P=0.76$ for diarrhea and $P=0.5$ for respiratory tract infection). There was a significant correlation between a history of diarrhea and a further need for mechanical ventilation in the univariate analysis ($P<0.05$), and mechanically ventilated patients had a low GBS scores on discharge compared with patients who were not mechanically ventilated ($P=0.05$). Neither age, disability on admission, autonomic dysfunction nor early EDX study results were important factors for prediction of mechanical ventilation need in the days following admission, but those with axonal EMG had low scores on discharge and follow-up examinations (OR=3.19, 95%CI, 1.65 to 6.16).

A total of 6 (7.9%) patients died acutely within 21 days from the onset of the disease. The mean age

of fatal cases was slightly older (40 ± 28.6 years for fatal cases and 34 ± 23.7 years for surviving cases; $P > 0.5$). These patients reported a similar frequency of previous respiratory infection or diarrhea (47.1% vs. 38.7%; $P > 0.5$). Fatal cases had no more autonomic abnormalities than survivors (57% vs. 40.6%; $P > 0.5$). One of the fatal cases (20%) and 21 nonfatal cases (29.6%) had an axonal or mixed EMG pattern ($P > 0.5$). Two cases died due to ventilator-associated pneumonia. One had sudden death that was attributed to severe autonomic disturbance and the two other cases had multiple complications, sepsis and aspiration pneumonia in particular. The last patient had sudden death that was attributed to a pulmonary embolus because she had a deep venous thrombosis before respiratory arrest.

The most frequently used therapy was plasma exchange (PE) in 31 patients (40.8%), followed by IVIG in 30 patients (39.5%). Both methods were used in 12 patients (15.8%). In 3 cases, a conservative approach and supervision alone was enough. We found no differences in outcome when comparing main treatments (PE vs. IVIG). The mean GBS grade at discharge was 2.9 ± 1.27 for patients receiving IVIG and 2.81 ± 1.37 for plasma-exchanged cases ($P > 0.5$).

Discussion

We found a higher incidence of GBS in our society in the cold seasons, but the study period was too short to determine an absolute seasonal correlation with the prevalence of GBS. Our province in the northwest of Iran is a cold region and temperatures of -10 to -20°C in winter are common. Viral infections are very common in the community and close contacts are a usual route for epidemics of upper respiratory tract infections.¹⁰ Also Winner et al. reported that rates of upper respiratory tract infections tended to be higher in the winter and early spring.¹¹ Lyu et al, in a study of the clinical characteristics of various forms of Guillain-Barre syndrome in Taiwan, found a seasonal preponderance, especially for the AIDP type cases in spring (March to May).¹² Others did not find this seasonal pattern.¹³⁻¹⁴

The outcome of GBS is still uncertain, possibly because most studies are analyzed retrospectively or focus on severely affected individuals admitted to hospitals. Retrospective studies may have selection biases or difficulty in correctly determining the risk factors and the progression of the disease. Differences in epidemiological results may also be due to differences in diagnostic criteria used in defining the

Figure 2. Age distribution of patients with Guillain-Barré syndrome.

Figure 3. Age-specific incidence rates of Guillain-Barré syndrome in northwest Iran.

disorder. The annual incidence rate of GBS based on NINCDS diagnostic criteria (see <http://www.neurology.org>) observed in the northwest of Iran in 2003 was in the range of the values reported in the other countries. This finding shows that the disease, independently from ethnic, socioeconomic, and environmental characteristics, is evenly distributed in all parts of the world, although less severe cases may not be present in our study as in most other studies.

A higher incidence of GBS in males has been reported in most studies, with a male-to-female ratio ranging from 1.1:1 to 2:1. This finding is similar to what we observed, 1.45:1. Similar findings have been reported in the two other autoimmune disorders of the peripheral nervous system: multifocal motor

neuropathy with conduction blocks¹⁵ and chronic inflammatory demyelinating neuropathy.¹⁶⁻¹⁷ The incidence rates in our series increased with age, with a peak in the 60 to 69 year and 70 to 79 year age groups. We found a bimodal shape in the age-specific curve observed in other studies (Figure 2)¹²⁻¹³. Some authors relate the higher incidence of GBS in the elderly to the supposed increased susceptibility to autoimmune disorders in old age.¹

A positive history of infectious events was found in 65.8% of patients, which is in the range of other published studies using the same diagnostic criteria. However, in our study the frequency of gastrointestinal infections was 15.8%, which is lower than values in other studies.¹³

Axonal involvement in our study was found in about 25% of cases which is slightly higher than that reported in other epidemiological reports.¹⁸ This could be related to the fact that we used definite criteria and an electrophysiological protocol for defining the type of nerve involvement and more uniform evaluation of patients. Also, the criteria used for defining demyelinating and axonal damage greatly influence the relative frequency of the various forms in GBS.¹⁹ We did not find any significant correlation between axonal damage and previous infections.

In our survey, the early mortality rate of 6.6% is in the range of 3.2% to 8%, which has reported in other published studies. Determinations of the factors affecting early mortality are necessary to plan more effective therapeutic programs, especially selection of those patients who probably have a worse prognosis. We found no significant relationship between older age, axonal damage,

autonomic system involvement and previous infection and early mortality. However, our results showed that those patients with severe weakness on admission and those patients with previous infection were more likely to need mechanical ventilation and so had a poorer prognosis. In our survey, deaths generally were related to ventilator-associated pneumonia and other infective complications.

According to previous reports the overall recovery (i.e., GBS grade <2) of patients with GBS ranges from 54% to 64% at 6 months.¹³⁻¹⁸ We found that axonal damage and a previous history of infection, especially diarrhea, were significantly related to a worse outcome at 6 months. Several factors related to a worse recovery have been described, including severity at admission and axonal EMG5, reduction of CMAP amplitude^{14,18,20,21} severity at nadir^{5,18,22}, latency to nadir,⁵ age over 40 or 50 years^{5,23,18,14,20,24,25} longer duration of the plateau phase²² and previous gastroenteritis.^{5,26} These differences are likely due to the different study designs from single specialized centers to series based on pharmacologic trials. High mortalities and morbidities in some studies are likely due to the inclusion of patients with more serious disease. In our survey, about 80% of patients had a good recovery at 6 months.

In conclusion, we found that acute mortality in GBS was mostly due to the poor respiratory care of patients and infective complications, but disability and probably late mortality were due to the axonal type involvement of nerve injury. Also a history previous infection had prognostic value for late disability.

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