



Incidence study of Guillain-Barré syndrome in the province of Ferrara, Northern Italy, between 2003 and 2017. A 40-year follow-up

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Abstract

Background Guillain-Barré syndrome (GBS) is an acute/subacute autoimmune inflammatory polyradiculoneuropathy. Previous epidemiological studies carried out in the province of Ferrara, Italy, from 1981 to 2002 indicated that GBS incidence had tendency of increase in the period considered.

Objectives We aimed at updating the epidemiology of GBS in the years 2003–2017 and carrying on the work started in the 1980s.

Methods We conducted an incidence study, by adopting a complete enumeration approach. Cases were identified from administrative, medical records, and database of the Ferrara Hospital and other provincial structures of the study area. Case ascertainment and definition are analogous to those adopted in previous surveys.

Results In the period 1 January 2003 to 31 December 2017, 73 patients living in the province of Ferrara (mean population 353,142) were found to be new cases of GBS fulfilling the NINCDS criteria. Male/female ratio 1.15. The mean incidence rate was 1.38 per 100,000 (95% CI 1.08–1.74), 1.54 per 100,000 for men and 1.23 per 100,000 for women, a nonsignificant difference. During the period considered, the rates had slow increase or mild decrease, without nonsignificant difference. The highest rates were observed for the age groups 70–79 years for both sexes. A half of patients reported infectious events in the weeks before the onset of symptoms.

Conclusion In line with many epidemiological data, in the whole period 2003–2017, we observed a trend towards increase or decrease in incidence and periods of relative stability. Similar temporal heterogeneity with the comparison to our previous works was found.

Keywords Guillain-Barré syndrome · Epidemiology · Incidence · Ferrara · Italy

Introduction

Guillain-Barré syndrome (GBS) is an acute-subacute autoimmune inflammatory polyradiculoneuropathy [1]. The pathophysiology of the disease is intimately correlated for at least

two thirds of cases with a previous infection of the upper respiratory tract or gastrointestinal system (usually 4 weeks prior to the onset of GBS symptoms) [2].

GBS is characterized by an ascending flaccid paralysis, with reduction or absence of muscle reflexes; the paralysis

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could develop acutely, within few days, or subacutely, within weeks [3]. The muscle weakness reaches a plateau and then shows a spontaneous and mostly complete recovery. In about 15% of cases however, even with an adequate immunomodulatory treatment, the outcome is poor after 1 year of follow-up. In a considerable number of cases (20–30%), respiratory muscle is severely involved and patients need mechanical ventilation, an event considered to be an important risk factor of poor outcome [3, 4].

GBS is now the most common cause of acute or subacute flaccid paralysis in the western countries, after the eradication of poliomyelitis [5].

The incidence of GBS has been worldwide and extensively studied, estimating a mean incidence of 1–2 cases per 100,000, but with a relatively wide range of 0.16 to 4.0 per 100,000 population [3, 4, 6]. This considerable difference could be due to a factual variable incidence across different world regions, but also to methodological differences in case definition and ascertainment, and in the size of the population studied.

The results of previous epidemiological studies carried out in the province of Ferrara, Northern Italy, performed by this same research group from 1981 to 2002 indicated that GBS risk had a tendency to increase in the period considered, with mean rates which vary from 1.26 per 100,000 over the years 1981–1987 [7] to 1.87 per 100,000 in the years 1988–1993 [8] and 1.97 per 100,000 over the years 1994–2001 [9]. Therefore, our intent was to update the GBS incidence estimates in the same area, considering its favorable conditions, namely, the stable availability and quality of medical services and the greater experience in the epidemiological field of our research group over time.

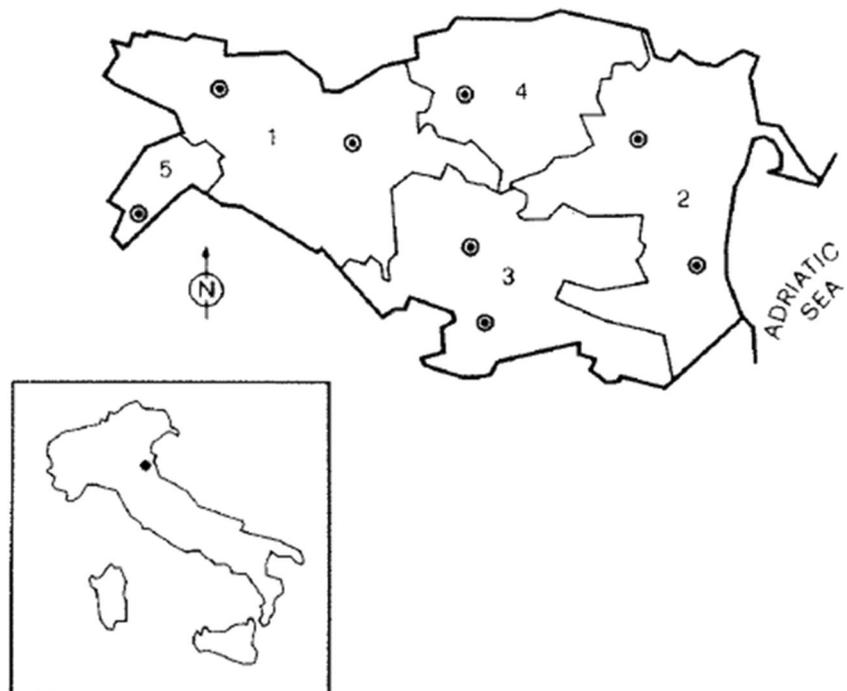
Materials and methods

Study population and area

The province of Ferrara is located in Emilia Romagna, a region in north-eastern Italy; the population is mixed but the vast majority is Caucasian. It covers a surface of 2632 km² and the mean population density is 133 inhabitants/km². The geographical, political, and socioeconomical characteristics and medical facilities of the study area were described in detail in previous epidemiological studies (Fig. 1) [7–9]. The standard of living is on the average high; in the last decades, the level of medical organization has also become more efficient. Health care is free for all residents, whether Italian citizens or not. The public health system allows a wide availability of data, from both paper and computerized administrative records.

Ferrara University Hospital provides first- and second-level medical and surgical care and comprises two neurological units with day-hospital, outpatient services, relying on clinical neurophysiology, neuroimaging (MRI), laboratory facilities for cerebrospinal fluid (CSF) analyses, and a neurorehabilitation unit. Neurological patients of the province of Ferrara and neighboring areas are routinely referred to the Neurological Clinic and Unit and the Motor Rehabilitation of Ferrara University Hospital. Other three hospitals in the province have services of neurology, neurophysiology, and neuroimaging which all have a strict connection with the services of the Neurological Units of the Ferrara University Hospital. All the hospitals of the province make use of the neurochemistry laboratory located in Sant'Anna University Hospital, Ferrara.

Fig. 1 Province of Ferrara. Area of investigation. Borders of the various public health districts are indicated. (1 = Ferrara; 2 = Comacchio; 3 = Portomaggiore; 4 = Copparo; 5 = Cento; • neurological centers)



The local authority service of the province (Azienda Sanitaria Locale, ASL) supplies domiciliary assistance such as medical assistance, nursing homes for bedridden patients, motor rehabilitation, and occupational therapy.

We studied the incidence of GBS on the population living in the province of Ferrara between January 1, 2003, and December 31, 2017. In that period, a mean of 353,142 people per year lived in the province.

Case selection

We adopted the same methodological approach of previous studies [7–9], in order to have reliable comparisons, even if a larger population was considered in this study compared to previous papers. We searched the health system administrative database for patients who were discharged from hospital with a primary or secondary diagnosis of “acute infectious polyneuropathy” codified by the code 357.0 of the International Classification of Diseases 9th edition (ICD-9); then, we excluded the patients who were not resident in the province of Ferrara.

Moreover, we could screen the database of medical records of the main hospitals of the bordering provinces and regions, with particular regards to the Veneto and Romagna regions with the aim to find possible GBS patients residing in the Ferrara Province at the incidence period. No patient residing in the province of Ferrara was found.

Many patients have acute infectious polyneuropathy only as a secondary diagnosis; all the data of these patients were reviewed, and those found to have only sequelae of a previous history of GBS were also excluded. Two patients showed a replication of the attack, 3 and 5 months after the first relapse; in the selection of incidence cases, they were considered only once, at the first attack.

All the cases which were used for the analysis fulfilled the GBS diagnostic criteria codified by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) [10].

Data collection and analysis

All the medical records of patients selected were reviewed, in particular to find any previous infectious event: the season in which the symptoms started, the number of patients who require mechanical ventilation and admission to the intensive care unit, and the mortality during hospitalization. We also considered the area where the patient lived (rural or urban).

The crude rate of incidence was sex- and age-adjusted to the Italian and European populations [11, 12]. Ninety-five confidence intervals (95% CI) were computed, assuming a Poisson distribution [13]. Continuous variables were presented as means and standard deviations (SD) and Student's *t* test was used for comparison. Categorical variables were reported

as percentages or ratios, and comparisons were made by the chi-square test. A two-tailed probability distribution at 95% was chosen and *p* was set at < 0.05.

Results

A total of 164 medical records were found using the case selection method described above; of these, 43 were excluded because the patients were not living in the province of Ferrara; out of the other 121 records, in the whole period 1 January 2003 to 31 December 2017, 73 cases (39 men and 34 women) were actually found to be new cases of GBS fulfilling the NINCDS criteria. The male/female ratio was 1.15. Among the examined records, no patients diagnosed with Miller-Fisher syndrome were found. Three patients (4.11%) had the axonal subtypes; the other 70 subjects had classical acute inflammatory demyelinating polyneuropathy (AIDP).

The mean age at onset was 52.57 years (range 2–85 years, SD 17.2), 53.62 years for men (range 8–84 years, SD 17.7) and 48.29 years for women (range 2–85 years, SD 16.8), a nonsignificant gender difference.

In 2013, we only found one GBS case, while the maximum number was 9 cases in 2016, with a mean of 4.87 cases/100,000/year (Table 1).

The mean incidence crude rate during the study period was 1.38 per 100,000/year (95% CI 1.08–1.74), 1.54 per 100,000 for men (95% CI 1.09–2.11) and 1.23 per 100,000 for women (95% CI 0.85–1.72), a nonsignificant gender difference.

The incidence rates adjusted to the Italian population were 1.33 per 100,000 (95% CI 1.04–1.68), 1.49 per 100,000 (95% CI 1.6–2.04) for men and 1.30 per 100,000 (95% CI 0.90–1.82) for women, respectively. The incidence rates adjusted to the European population were 1.25 per 100,000 (95% CI 0.98–1.57), 1.31 per 100,000 (95% CI 0.93–1.79) for men and 1.25 (95% CI 0.98–1.57) for women, respectively.

During the period considered, the rates showed an increase: the mean annual incidence in the years 2003–2006 was 1.37 per 100,000 (95% CI 0.82–2.13), 1.13 per 100,000 (95% CI 0.65–1.83) in the period 2007–2010, 1.41 per 100,000 (95% CI 0.86–2.17) in the period 2011–2014, and 1.71 per 100,000 (95% CI 1.01–2.70) in the years 2015–2017 (Table 1). The difference in rates was not significant from the other periods considered.

Sex- and age-specific crude mean annual incidence rates are reported in Table 2. The highest rates were observed for the age group 70–79 years (2.31/100,000/year) for both sexes.

Based on 4 incidence cases, the mean annual incidence among children (0–9 years old, mean population 25,278) was 1.05 per 100,000 (95% CI 0.29–2.69). In the subset of children aged 0–9 years, the annual incidence rates were highest among children aged 2 years.

Over the entire study period, the mean annual incidence was higher in urban areas (52 cases, mean population

Table 1 GBS incidence in the province of Ferrara and mean rate in years 2003–2017

Year	Males (cases)	Females (cases)	Total (cases)	Men	Women	Total	Men rates per 100,000 (95% CI)	Women rates per 100,000 (95% CI)	Total rates per 100,000 (95% CI)
2003			4	165,937	181,423	347,360			
2004			2	167,139	182,635	349,774			
2005			6	168,195	183,257	351,452			
2006			7	169,298	184,005	354,073			
Total	7	12	19	167,642	182,830	350,665	1.05 (0.42–2.17)	1.65 (0.86–2.89)	1.37 (0.82–2.13)
2007			4	170,423	185,386	355,809			
2008			8	171,399	186,581	357,980			
2009			2	171,696	187,277	358,972			
2010			2	171,912	188,082	359,994			
Total	8	8	16	171,357	186,831	358,188	1.19 (0.51–2.34)	1.08 (0.47–2.13)	1.13 (0.65–1.83)
2011			7	168,047	184,809	353,303			
2012			7	168,281	184,442	352,856			
2013			1	169,587	185,514	352,723			
2014			5	169,208	184,865	355,101			
Total	13	7	20	168,781	184,907	353,496	1.92 (1.02–3.28)	0.95 (0.38–1.96)	1.41 (0.86–2.17)
2015			3	168,148	183,288	351,436			
2016			9	168,073	182,786	350,859			
2017			6	166,883	181,479	348,362			
Total	11	7	18	167,571	182,518	350,219	2.19 (1.09–3.92)	1.28 (0.51–2.02)	1.71 (1.01–2.70)
Total	39	34	73	168,838	184,271	353,142	1.54 (1.09–2.11)	1.23 (0.85–1.72)	1.38 (1.08–1.74)

Mean rates in the periods 2003–2006, 2007–2010, 2011–2014, and 2015–2017

238,258 inhabitants, average annual rate 1.45 per 100,000, 95% CI 1.08–1.90) than in rural areas (21 cases, mean population 114,884 inhabitants, average annual rate 1.21 per 100,000, 95% CI 0.75–1.85) with nonsignificant difference.

A tendency of incidence increase was observed in winter periods, but no significant seasonal clustering was found during the period considered: according to the seasons, the number of GBS cases varied, but the differences were not statistically significant. In particular, 24.9% of the patients

manifested symptoms in autumn, 36.7% in winter, 26.1% in spring, and the remaining 12.3% in summer.

Sensory disturbances were present but to a lesser degree (60.3%). Antecedent events were noted in the clinical files for 40 patients (54.8%) within 1 month before GBS onset. They included influenza-like illness (16.5%), gastrointestinal infections (15.9%), upper airway infections (14.6%), and other disorders of unknown origin (7.8%). No patients reported previous vaccinations. No therapies—parental infusion of bovine

Table 2 Gender- and age-specific incidence rate (per 100,000) of GBS in the province of Ferrara, Northern Italy, 2003–2017

Age groups	<i>n</i>	Women (mean population)	Rate (95% CI)	<i>n</i>	Men (mean population)	Rate (95% CI)	<i>n</i>	Total mean population	Rate (95% CI)
0–9	2	12,468	1.07	2	12,810	1.04	4	25,278	1.05
10–19	1	12,626	0.53	–	13,956	–	1	26,582	0.25
20–29	1	15,077	0.44	–	15,176	–	1	30,253	0.22
30–39	4	25,111	1.06	5	25,607	1.30	9	50,718	1.18
40–49	5	29,096	1.15	11	29,165	2.51	16	58,261	1.83
50–59	6	26,590	1.50	6	24,683	1.62	12	51,273	1.56
60–69	6	24,905	1.61	6	22,577	1.77	12	47,482	1.68
70–79	8	24,171	2.21	7	19,174	2.43	15	43,345	2.31
> 80	1	18,038	0.37	2	9032	1.48	3	27,070	0.74
Total	34	184,271	1.23 (0.85–1.72)	39	168,838	1.54 (1.09–2.11)	73	353,142	1.38 (1.08–1.74)

brain ganglioside therapies—for various neurological disorders were found to precede GBS.

All patients were treated with plasma exchange or intravenous immune globulins.

Ten patients (13.7%) had a severe respiratory muscle weakness and required mechanical ventilation in the intensive care unit; 4 of them (5.48%) died during the hospitalization.

Discussion and conclusions

The mean annual GBS incidence in the province of Ferrara for the period 2001–2017 was 1.38 per 100,000 population.

This is the fourth investigation of GBS incidence in the area of Ferrara where the same group of researchers carried out the first investigation in the period 1981–1987 [7] and the last with incidence data in 2002 [8, 9]. Over this period, GBS incidence in this population showed fluctuations with no significant trends. The highest incidence rates were found in the period 1990–1998, i.e., more than 2 per 100,000 population. With the present study, we observed a slow decrease and gradual increase in incidence during the period 2011–2014 and then relative high rates in the last 3 years considered (2015–2017) with rates of 1.71 per 100,000. In 2016, nine cases were registered. Since the time lag between clinical onset and diagnosis is usually expressed in weeks, and since only three and six cases were registered in 2015 and 2017, respectively, the rate for 2016 is an isolated report and likely due to chance fluctuation. Interestingly, the rate reported for 2016 does not differ from that found in the multicentric GBS incidence survey in Italy (ITANG Study) based on a prospective data collection and in a population aged 18 years and older [14].

In agreement with other studies, men were more frequently affected than women, with a sex ratio of 1.15 [6, 15–19]. A male preponderance was found in all previous investigations in the area of Ferrara, but it never reached a statistical significance. The male predominance is unusual for an autoimmune disease, and it might imply a protective effect of estrogen operating at a level of susceptibility against infection or for the control of an autoimmune response [2, 4].

The likelihood of GBS was found to be higher in the adolescent and young female population than in the male population of comparable age. This is in line with similar findings where a higher prepubertal incidence of GBS in girls than in boys was reported [20–23].

GBS incidence progressively increases with age, in accordance with some of our previous studies in Ferrara and most surveys from Europe [14–24], the USA [25, 26], Australia [27], China [28], and Japan [29]. In the age group 70–79 years, incidence rates are the highest for both sexes, 2.31 per 100,000. In the most ancient groups (> 80 years), the risk declined to 1.36 per 100,000 in both sexes. Although conclusions cannot be drawn because of the very limited number of cases (3 patients)

and the lack of statistical significance, similar results have been obtained in recent studies [27–30] making the incidence of GBS in people over 80 years still a matter of debate.

The incidence of GBS in children and patients under 15 years of both sexes is 0.69 per 100,000; the rate is 1.05 per 100,000 when we consider children in the age group 0–9 years. Among the four children included for estimation, one was the age of 2 years. These data are comparable with those reported in literature reviews which show the annual incidence in children (0–15 years) between 0.34 and 1.34 per 100,000. The incidence among children is lower than that among adults [5, 16, 19, 31].

As in previous surveys in Ferrara, GBS was somewhat more frequent in urban areas than in rural areas, but without a significant difference, which may indicate that no specific physical or biological exposures to exogenous risk factors are associated to the disease. With regard to seasonal clustering, the frequency of the disease is higher in winter compared to that in summer, but not if the comparison is made with the other seasons. It is likely that the winter season favors the onset of infections which in turn trigger the onset of GBS. Similarly to the results of our survey, in most GBS studies, predominant symptoms of preceding infections were reported as fever or infections in the upper respiratory tract or gastrointestinal tract [4, 32–34]. No peak of incidence was observed in winter 2011 during the H1N1 influenza pandemic nor in relation to the vaccination campaign against influenza virus, unlike what was reported in the ITANG Study [14]. However, whether the retrospective nature of our study may have accounted for this difference cannot be ruled out. Vaccination has been implicated in GBS pathogenesis, and the attributable risk in adults ranges from 2 to 5 GBS cases per 1,000,000 vaccinations [35]. However, this association is still controversial. During the period considered, no preceding recent history of vaccination (any) was registered in our patients.

Due to the retrospective nature of the study, an underestimation of incident cases is possible. However, due to multiple assessments over time, the multiple sources scrutinized for ascertainment and inclusion criteria, the organizational layout of the health services in the province of Ferrara and the traditional local practice of referral, and the underestimation of incidence rates for the period considered seem unlikely. Moreover, the NINCDS diagnostic criteria for GBS were adopted homogeneously over the entire study period allowing a comparison of incidence rates with other studies using these criteria. All clinical files were reviewed by expert neurologists, and the diagnosis of GBS was based on the consensus within the same team, also considering the electrodiagnostic as well as the cerebrospinal fluid features as supportive for the diagnosis. This methodological approach gave an average annual incidence estimate which is similar to those from other community-based studies that have followed the NINCDS criteria for diagnosis of GBS [1, 6, 16, 17] and also to

prospective studies [14]. In France, a nationwide epidemiological analysis recently registered an incidence of GBS of 2.42 per 100,000 person-years (world standardized IR = 2.00), rates among the highest reported in Europe [19].

Evidence from our incidence studies on GBS over the past 40 years of observation supports a greater risk for adulthood GBS among the elderly with recent exposure to respiratory infections and an irregular, somewhat unpredictable, frequency in the winter months, mimicking outbreaks. No specific public health measures for GBS surveillance are available in Italy. In the light of the disease epidemiological pattern, time point reliable estimates are needed—and GBS epidemiological studies should be prioritized—to face seasonal incidence peaks in the fragile population through adequate planning and prioritization of care services to ultimately reduce the overall burden of the disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Ethics approval for the study was obtained.

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