

RESEARCH ARTICLE

CHILDHOOD GUILLIAN-BARRE SYNDROME IN THE IRAN'S EAST AZERBAIJAN PROVINCE: 2001-2005

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Abstract

Objective

This study aims at determining the epidemiologic, presenting symptoms, clinical course and electrophysiologic features of childhood Guillain-Barre Syndrome (GBS) in the East Azarbaijan province over a period of five years.

Materials & Methods

All the patients, aged < 15 years, referred/admitted to Tabriz Children Hospital with GBS between January 2001 and December 2005 were investigated.

Results

One hundred and twelve subjects were enrolled during this period. The average annual incidence rate was 2.21 per 100000 population of children aged <15 years (CI 95%: 1.8-2.6); the highest proportion of 29% was observed in winter (P=0.10); mean age (SD) of subjects was 5.1 (3.3) years, while 61.6% were ≤5 years. The male/female ratio was 1.3. Antecedent events were identified in 80 (71.4%) patients. The most common manifestation was limb weakness; at the peak of the disease course, only 8 (7.1%) patients were able to walk without assistance. Cranial nerve involvement was found in 37.5%. Fifteen percent of patients had autonomic dysfunction, and 32.2% complained of neuropathic pain. Artificial ventilation was needed in 10.7% of patients, and three patients (2.7%) died due to cardiac arrest. Electrophysiological examination showed the demyelinating type of the disease in 54.5%; axonal type in 35.7% and 9.8% as unclassified or normal pattern. Short time to reach nadir (P=0.008), cranial nerve involvement (P=0.000), autonomic involvement (P=0.001), and axonal pattern on electro diagnosis (P=0.043) were found as risk factors for respiratory failure. In follow-up, at the end of one year, 95% of patients could walk without aid.

Conclusion

The axonal type of GBS is a relatively common form of childhood GBS occurring in East Azerbaijan.

Keywords: Guillian-Barresyndrome, Childhood, Epidemiology, Electrodiagnosis, Clinical features, East Azarbaijan

Introduction

Gullain-Barre syndrome (GBS) is an acute polyneuropathy which is most commonly characterized by rapidly progressive symmetric weakness and hypo or areflexia. It is now the main cause of acute flaccid paralysis in children (1). The annual incidence of typical GBS reported worldwide is between 0.6 and 4 cases (per

100000 populations) (2).

Most previous studies report males as being more at risk than females (2-5).

The syndrome is an autoimmune disease most frequently triggered by preceding infection. Many studies have reported that 50-75% of patients had had an infectious illness, 1-4 weeks prior to neurologic symptoms (2-5). Overall, it is believed that GBS has a favorable course and prognosis; however a mortality rate of 2-12 % has been reported. Some patients (4-30 %) may also require respiratory support (2-8). Therefore GBS patients seemingly require initial respiratory and autonomic monitoring to prevent fatal outcomes. Prompt recognition and optimal treatment of respiratory failure and autonomic dysfunction hence play key roles in successful management of the syndrome.

The GBS can be classified into the demyelinating and axonal types based on electrophysiological criteria (2). Frequency of the axonal form of GBS varies considerably in different countries, its incidence being less than 10% in Europe and North America, 65% in northern China, and 40% in Japan (9-11).

Majority of large studies on GBS in developed countries have focused on both children and adults. There are not many reports on pediatric GBS in Iran (12-13).

The purpose of this study was to document the epidemiologic data, clinical course and electrophysiologic features and outcome of childhood GBS in a defined geographic area in the Northwest of Iran.

Materials & Methods

The setting of the study was Tabriz Children's Hospital, the largest pediatric medical center in the Northwest of Iran; this 200-bed acute care university hospital provides tertiary referral care for critically ill patients. For this study, children must be <15 years old at the onset of weakness, and onset of disease should have been occurred during 2001 to 2005. Inclusion criteria were age over <15 years at onset of weakness, and onset of disease should have occurred between 2001 and 2005.

As part of the World Health Organization (WHO) certification process for polio eradication, Iran has been systematically notifying/registering children under 15 years old with acute flaccid paralysis since 1995. According to the local policy for acute flaccid paralysis

(AFP) surveillance program, all cases of AFP must be referred to this hospital, where they are examined by an expert child neurologist (M.B.) within 7 days of notification. GBS is then diagnosed and ascertained based on the criteria defined by Asbury and Cornblath (1). One hundred and twelve cases of GBS were diagnosed and confirmed. Data recorded at admission, were: age, sex, and date of onset of the disease, preceding illness, clinical manifestation, and course of disease during hospitalization, results of CSF analysis and neurophysiologic evaluation, specific treatment and early outcome.

The functional status at the time of maximum deficit was graded according to Hughes scale of disability as follows: 0: healthy, 1: minor signs and symptoms and ability to run; 2: ability to walk 5 meters without assistance, but unable to run. 3: ability to walk with assistance, 4: confined to bed or chair bound, 5: requiring assisted ventilation, and 6: died (14).

Poliovirus infection was excluded by cultures that are routinely performed for patients with acute flaccid paralysis as a requirement of the national program of poliomyelitis eradication in the country.

All children underwent at least one electrodiagnostic evaluation at the acute phase of disease, for which a Medelec Synergy electromyography machine was used. Nerve conduction studies included motor nerve conduction (MNC), sensory nerve conduction (SNC); F-wave response assessments were performed using the standard techniques while keeping the temperature under control. MNC studies were carried out on the ulnar, Median, tibial and deep peroneal nerves, and SNC on median and sural nerves. Each value of nerve conduction was compared with age matched normal data reported by Parano and colleagues (15). Needle EMG was done for any denervation potentials and motor unit action potentials (MUAP) changes in all patients in at least two proximal and two distal limb muscles. Patients were classified as having either the axonal or demyelinating type on the basis of the electro diagnostic criteria reported by Cornblath and colleagues (16); for each patient, the first neurophysiologic study was reviewed.

In addition to the general supportive management, specific therapy with 400 mg/kg of intravenous immunoglobulin for five days, were administered in

most cases. All patients followed until they achieved independent walking (maximum 12 months).

Data from the Ministry of Health, Statistics office, were used to estimate frequencies of the GBS in the region. Differences between proportions were statistically tested by Chi-square or Fisher's exact test. All other numerical or quantitative comparisons were performed using student's unpaired t-test or Mann-Whitney U test. All values were two tailed and were considered statistically significant if $P \leq 0.05$. This study approved by the Ethics Committee of Tabriz University of Medical Sciences.

Results

Between 2001 and 2005 one hundred and twelve cases of GBS were diagnosed in Tabriz Children Hospital. Occurrence of GBS (per 100 000) in the Northwest of Iran by year and gender is shown on table 1. Based on data from the region's general population, the average annual incidence rate was 2.22 per 100000 population of <15 years children (CI 95%: 1.8-2.6) ranging from 1.5 to 3.4 in 2001 and 2003, respectively. The lowest and highest portion of the syndrome occurred in summer (21.4%) and winter (28.6%), respectively ($P > 0.10$).

The most common manifestations in all subjects on admission were limb weakness, with various degrees of motor weakness, and areflexia or hyporeflexia. Demographic and clinical features of patients are presented in Table 2. The mean (SD) age of patients was 5.1 (3.3) years, 61.4% of patients were aged ≤ 5 years. The sensory symptoms, mostly pain in the limbs were noted in 36 patients (32.2%). Because of younger age of most patients', numbness and parasthesia were not very reliable. Cranial nerve involvement was found in 37.5% of patients. Bulbar weakness (hoarseness of voice, dysphonia, dysphagia, choking) (22.3%) were the most common type followed by facial palsy (17.9%). Only 8 of 112 patients (7.1%) were able to walk independently at the peak of illness (grade 0-2).

CSF studies were conducted in all patients (over the days 1 to 16 of admission); levels of CSF total protein ranged between 10-850 mg/dl with white blood cell (WBC) count of 0-30 cells/mm³. The mean (SD) CSF protein concentration was 85.3(87.8) mg/dl while in 74.1% it was ≥ 40 mg/dl. In 25.9% of patients, whose CSF was obtained only in the first week of illness, protein levels

were normal.

Neurophysiological examination was performed 1 to 27 (mean 6.5 days) days after the onset of weakness and usually near the peak of illness. Three patterns emerged: the demyelinating type (AIDP) in (54.5%) patients, the axonal type in (35.7%) patients and the unclassified or normal type in 9.8% of patients. Comparing the axonal and AIDP forms, no significant differences were found in the CSF protein levels, gender, clinical manifestation and age between axonal and AIDP forms. However the time taken to reach nadir was shorter in the axonal compared to the AIDP forms (mean \pm SD): 4.2 ± 2.7 vs. 5.9 ± 4.9 days ($P = 0.045$). Axonal pattern was observed to be a risk factor for respiratory failure ($P = 0.043$).

In addition to the general supportive management, specific therapy with 400 mg/kg of intravenous immunoglobulin for five days, was administered in 93 patients, IVIG plus methylprednisolone succinate (20mg/kg maximum 500mg) for five days administered in 13 patients; 6 patients received only supportive care due to unavailability of IVIG.

Autonomic involvement occurred in 17 (15.2%) patients including: cardiac arrhythmia in 7, hyper or hypotension in 5 patients, urinary incontinence in 3 and excessive sweating in 2 patients.

Twelve (10.7%) patients required mechanical ventilation for an average of 20.9 days (SD=20.8, and range: 1-75 days). Risk factors for respiratory failure found were: short time to reach peak disability ($P = 0.008$), cranial nerve involvement ($P = 0.0001$), autonomic involvement ($P = 0.001$), and axonal pattern on electrodiagnosis ($P = 0.043$). In 15 patients (13.4%), some complications, mostly pulmonary, occurred. In this study, three (2.7%) patients died due to cardiac arrest as a result of autonomic dysfunction.

We evaluated the outcome at 6 months and 12 months of follow-up. At six months, 92.5 % of patients with the demyelinating form and 77.8% of patients with an axonal pattern, were able to walk independently ($P = 0.047$). However, at end of 1 year, 95% of patients were capable of independent walking with no significant difference between two groups.

Table 1: Occurrence of Guillan-Barre syndrome (per 100 000) in the Northwest of Iran by year and gender

	Total	Frequency	Rate			Frequency	Rate			Frequency	Rate	
Year	Population	of GBS	(100 000)	CI 95%	Male	of GBS	(100 000)	CI 95%	Female	of GBS	(100 000)	CI 95%
2001	1003605	15	1.49	(0.7,2.3)	514399	10	1.94	(0.7,3.1)	489206	5	1.02	(0.1,1.9)
2002	1004684	20	1.99	(1.1,2.9)	514952	12	2.33	(1.0,3.6)	489732	8	1.63	(0.5,2.8)
2003	1004633	34	3.38	(2.2,4.5)	514926	16	3.11	(1.6,4.6)	489707	18	3.68	(2.0,5.4)
2004	1007195	22	2.18	(1.3,3.1)	516239	14	2.71	(1.3,4.1)	490956	8	1.63	(0.5,2.8)
2005	1018038	21	2.06	(1.2,2.9)	521796	12	2.3	(1.0,3.6)	496242	9	1.81	(0.6,3.0)
Total	5038155	112	2.22	(1.8,2.6)	2582311	64	2.48	(1.9,3.1)	2455843	48	1.95	(1.4,2.5)

Table 2: Basic characteristics of the study subjects with Guillain-Barre syndrome

		Mean	Standard Deviation
Age (years)		5.1	3.3
Median time to peak disability(days)		5.1	4.2
		Number	Percent
Sex	Male	64	57.1
	Female	48	42.9
Preceding events	Upper Respiratory infection	63	56.3
	Gastroenteritis	13	11.6
	other	4	3.6
	None	32	28.6
Seasonal incidence	winter	32	28.6
	spring	26	23.2
	summer	24	21.4
	Autumn	30	26.3
Functional Grading of disease	2	8	7.1
	3	14	12.5
	4	75	66.9
	5	12	10.7
	6	3	2.3
Cranial nerve Involvement		42	37.5
Autonomic dysfunction		17	15.2
Sensory symptoms pain (limbs)		36	32.2

Discussion

This study reports the clinical and epidemiologic characteristics of GBS over a 5-year period, as observed at a large pediatric tertiary care center in the Northwest of Iran. The epidemiology of GBS is not easy to investigate because of the difficulties in case definition and the absence of a reference standard diagnostic test. Objective physiologic abnormalities of nerve dysfunction may also be difficult to detect in the early stages.

In our study, the average incidence rate was 2.22 per 100000 populations of children aged < 15 years, which was within the range reported from most areas worldwide (0.2-4 cases per 100000) (2-6, 8). In our area the incidence ranged between 1.5 and 3.5 in different years. A similar fluctuation of annual incidence of GBS has been reported in some studies (3, 17-19).

The syndrome occurred at all ages. However the age distribution showed that it predominantly affects children aged 1-5 years, which is consistent with the findings of some studies (5,20,21). In children the incidence of GBS may decrease by age while in adults it shows the opposite pattern. Immunological status and vulnerability of myelin in both early/late life may explain the increased susceptibility to GBS (22). The male to female ratio (1.3) in our study is in accordance with other reports (2-6,8,13,20,21).

Although the disease is considered to be sporadic without significant variation between seasons and months, small clustering of patients, in this study, during winter could be related the higher frequency of upper respiratory infections during the cold weather(winter). GBS is the prototypic post infectious disease with 50 to 75% of patients with an antecedent illness. Respiratory infection was the most frequently reported preceding illness, followed by gastrointestinal infections (2-6, 8, 20, 21). In our study, 71.4% of patients had a history of acute infectious illnesses preceding the onset of neurologic symptoms, including URI (56.3%) and GI infections in 11.6% of cases.

No remarkable differences in clinical presentation were found between our findings and previously published reports (2-6, 8, 12, 13, 20, 21). However our case material shows a trend toward severe cases (71.4% were in grade ≥ 4); mostly due to the availability of pediatric intensive

care at our hospital.

In a study on 254 patients conducted over 8 years, only 4.7% were able to walk independently throughout their entire course of GBS (23). In our study this statistic was 7%. In recent years, it has been shown that GBS includes at least two distinct conditions: acute demyelinating inflammatory polyneuropathy (AIDP) and acute motor or motor sensory axonal neuropathy (AMAN or AMSAN) (2). There have been some reports on the incidence of AIDP and axonal types of childhood GBS; the axonal pattern was found in up to 65% in China (9), 40% in Japan (10), 30% in Argentina (8), 35% in Turkey (24), 31% in Pakistan (25) and 10% in North America (11). The percentage of cases with the axonal type in our study was higher than in western countries and lower than that of Chinese population; it is however consistent with figures of the axonal type GBS, observed in the neighboring countries (i.e. Turkey and Pakistan) and the Latin American regions. These findings suggest that the incidence of the axonal type in childhood GBS varies considerably among countries, the reason still unknown. However various populations have different genetic background and environmental exposures (2,9). On the other hand, differences in the frequency of various subtypes of GBS might be related to different sets for electrophysiologic identification of demyelination. At least 5 different sets of criteria have already been used by investigators (16, 26-29). We used the Cornblath set for this study.

Respiratory failure is the most serious short-term complication of GBS and may require invasive mechanical ventilation in 4-30% of patients (6-8). Moreover 60% of intubated patients developed major complications including pneumonia, sepsis, gastrointestinal bleeding and pulmonary embolism. Anticipation of respiratory failure is crucial to avoid respiratory distress and aspiration. In most studies, cranial nerve involvement especially bulbar weakness and time between onset of the disease and reaching peak disability was less than 7 days; electrophysiological evidence of axonal degeneration and vital capacity of less than 60% of that were considered as risk factors for developing respiratory failure (7,30-31). In our study, the short time to reach peak disability, cranial nerve involvement, and autonomic involvement

were risk factors for developing respiratory failure. When patients with the normal or unclassified type are excluded, patients with axonal involvement are more likely to need assisted ventilation.

The prognosis of childhood GBS is generally favorable (5,8,20,21). In our study only 3 patients (2.7%) died. According to research reports, cardiac arrest, resulting from autonomic dysfunction, is the most common cause of death. Other causes of death include chest infection, pulmonary embolism and respiratory failure (6, 13, 27). Long term outcomes of GBS are quite good, with an excellent functional recovery. Although in our study cranial nerve, autonomic involvement, rapid progression of illness and axonopathy were risk factors for a poor, early outcome (i.e. respiratory failure), these factors did not have adverse effects on long term outcomes.

In conclusion, Epidemiological and clinical features of our subjects were relatively similar to those documented in other studies. The axonal type of GBS is a relatively common form of childhood GBS in East Azerbaijan, Iran. Further studies are needed to investigate patterns of childhood GBS in other regions of Iran.

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