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Relationship between occurrence of Guillain-Barre syndrome and mass campaign of measles and rubella immunization in Iranian 5–14 years old children

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ABSTRACT

Background: Case reports and epidemiologic studies have reported a relation between different vaccines including measles, rubella, mumps and Guillain-Barre syndrome (GBS). In this study we investigated relation between receiving measles and/or rubella vaccines and occurrence of GBS after national immunization campaign in 2003 in Iran.
Materials and methods: We used the national surveillance system for acute flaccid paralysis from the beginning of 2002 to the end of 2004 and studied the incidence of GBS disease among 5–14-year-old children. The 3-year time span of the study was divided into fifteen 10 weeks intervals and the number of reported and confirmed GBS case reports in each time period was analyzed supposing their distribution was according to Poisson distribution.
Results: From 2002 through 2004 there were 370 patients confirmed GBS case reports among persons 5–14 years of age. The annual incidence in this age group remained relatively constant over the 3-year period and ranged from 0.65 per 100,000 population in 2004 to 0.76 in 2003. The estimated average annual incidence of GBS in persons <15 years of age was 1/100,000 (CI 95%: 0.88–1.13), and 0.7/100,000 in persons 5–14 years of age (CI 95%: 0.58–0.83). No obvious seasonal pattern in GBS occurrence was observed. The mean number of GBS patients during each 10 week study interval was 23.8. Twenty-five patients with GBS were reported in the time period which coincided with national immunization campaign. The probability of occurring ≥25 cases of GBS in that time period according to Poison distribution with expected case numbers of 23-8 is equal to 0.43 ($p = 0.43$).
Conclusion: The yearly incidence rate of GBS in this study was similar to other studies. According to our results, there was no increase in GBS Incidence in the 4 weeks national Immunization campaign and 6 weeks after it in comparison to other 10 weeks periods before or after this time period.

1. Introduction

Guillain-Barre syndrome (GBS) is an autoimmune disorder characterized by a group of diverse clinical and pathologic findings. Epidemiologic studies in Europe, the United States and Australia report a GBS incidence rate 1/100,000 per year. The etiology of GBS is unknown yet, but several events have been observed which occur before development of disease including acute infections and immunizations. Numerous studies have documented an association of GBS and selected infections and it has been hypothesized that selected infections may activate immune system, leading to cross-reaction with myelin leading to demyelinization and axonal degeneration [1].

The most frequent infection associated with disease is gastroenteritis caused by *Campylobacter jejune*. Overall, approximately 20% of GBS patients report diarrhea before developing GBS; positive serology or culture exists in 26–36% of these patients. Cytomegalovirus (CMV) infection is also associated with GBS and is the second prevalent infection prior to GBS occurrence. In different studies between 5 to 22 percent of GBS cases show the evidences of CMV infection [1]. Several case studies and epidemiologic studies report a relation between GBS and receipt of different vaccines including rabies, poliomyelitis [2,3], influenza [4,5], measles [6], mumps-measles-rubella(MMR) [7], tetanus toxoid containing vaccines [8]. The American Academy of Neurology reported nearly a thousand cases of GBS to CDC between 1978 and 1979, of which only

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Table 1
Number of approved GBS in 5–14 years-old Iranians during the study and the GBS annual incidence rate

Time period	Year 2002	Year 2003	Year 2004
December	13	11	10
January	3	4	11
February	9	11	9
March	8	14	13
April	19	8	6
May	11	17	11
June	6	15	7
July	9	15	15
August	9	11	3
September	15	11	7
October	6	7	15
November	12	11	7
Whole year	121	135	114
Annual incidence per 100000	0.68	0.76	0.65
CI 95%*	0.57–0.82	0.64–0.90	0.53–0.77

* CI 95% has been calculated using exact binomial method.

45 cases (~4.5%) had history of an immunization during 8 weeks before GBS occurrence [9].

Later review studies did not find a causal relation between injection of measles or measles-rubella vaccines and development of GBS [10,11]. In a 5-year study in Finland in which admitted cases of GBS to hospitals have been compared to other recipients of measles, rubella, and mumps vaccines, no causal relation was seen between receiving any of these vaccines and occurrence of disease [12]. In the Australian National Immunization campaign against measles, rubella, and mumps in 1998, nearly two million school age persons were vaccinated; only three patients developed GBS consistent with previous rates in Australia and UK [13]. Several studies in different countries reported incidence of GBS as 0.4–2/100,000 [14,15].

This study was conducted to assess any relation between measles and/or rubella vaccination in national immunization campaign and occurrence of GBS. From 6 December 2003 to 3 January 2004, the Ministry of Health and Medical Education in Iran conducted a nationwide immunization campaign targeting 33,579,082 people between the ages of 5–25 years with a combined measles (edmonston-zagreb strain) and rubella (wistar ra 27/3 strain) live attenuated vaccine; 98% of the target population were vaccinated. We hypothesized that if there is a causative relation between immunization against measles and/or rubella and GBS, it's incidence would increase after the immunization campaign period comparing to the time before the campaign.

2. Materials and methods

In this study we used national surveillance system for acute flaccid paralysis data from the beginning of 2002 to the end of 2004. This system is established to detect occurrence of poliomyelitis cases. One of differential diagnoses for acute flaccid paralysis is GBS, and case definition in this system is the occurrence of any acute flaccid paralysis in persons <15 years of age without any history of trauma. All case-reports are gathered from health centers, medical offices, clinics and registered in a standardized format according to guidelines from the World Health Organization protocols. These data are categorized using guidelines through special committees of the universities of medical sciences (UMSs) across the country, and finally verified by a national committee in Center for Disease Control. Data for all acute flaccid paralyses cases in all UMSs are entered into a computerized database for analysis and reporting. The occurrence of any GBS case is verified by national committee.

As the common age range between immunization campaign against measles and rubella (5–25 years olds) and acute flaccid paralysis surveillance system (under 15 year-olds) was 5–14-years age group, we compared the national incidence of GBS in this age group during the immunization campaign with the other time periods. The population of persons under 15 years of age and persons 5–14 years of age were derived from estimates of Iranian Center for

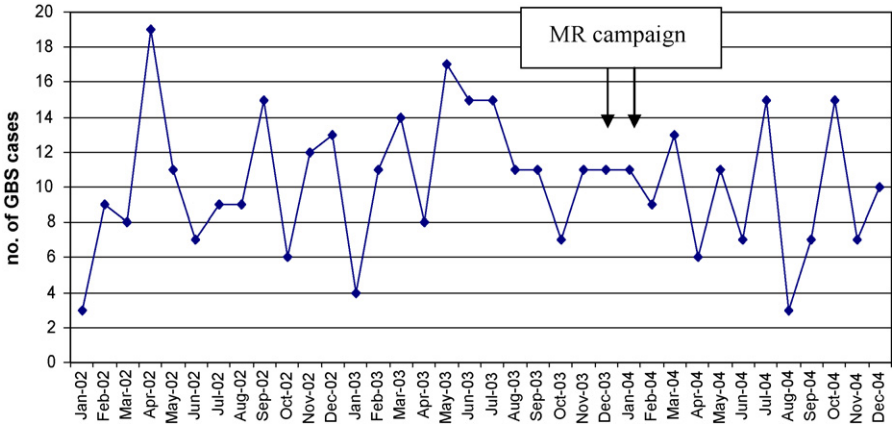

Fig. 1. Monthly distribution of 5–14-year-old patients with Guillain-Barre syndrome in Iran from January 2002 to December 2004.

Table 2
Trends in Guillan-Barre in 5–14-year-old children in each 10-weeks time period from January 2002 through September 2004

10-weeks time period	Number of GBS cases
January 5–March 16, 2002	17
March 16–May 24, 2002	31
May 25–August 2, 2002	18
August 3–October 11, 2002	26
October 12–December 20, 2002	23
December 21, 2002–February 28, 2003	20
March 1–May 9, 2003	27
May 10–July 18, 2003	40
July 19–September 26, 2003	24
September 27–December 5, 2003	20
December 6, 2003–February 13, 2004	25
February 14–April 24, 2004	22
April 25–July 3, 2004	20
July 4–September 11, 2004	20
Sep 12–November 20, 2004	24
Total	357

Statistics for this age groups for the year 2004, which was mode of time duration of the study. According to these estimates, the populations for these age groups were 26,259,600 and 17,683,680, respectively. The time of onset of paralysis symptoms was proposed as the time basis for age of affected persons.

The number of reported and approved GBS patients 5–14 years of age in each month were used to evaluate any changes in GBS incidence. We compared these data with expected incidence rates in the same time period according to Poisson distribution to identify if there was an increase in GBS incidence in the time period of national immunization campaign compared to similar time periods before and after the campaign. As GBS is rare and study population was very large, the distribution of GBS cases in the studied time period was assumed to be according Poisson distribution. A 6 weeks period has been considered as maximum time between immunization and the onset of paralysis symptoms (the latent period of GBS) [12,16,17]. Taking into account that the national immunization campaign lasted for 4 weeks, a 10-weeks time periods was used as the interval in which GBS cases were compared to the other time periods. In the time span of the study, we calculated GBS disease rates for fifteen 10-weeks time periods from 5 January 2002 to 20 November 2004.

The mean number of GBS cases in all 10 weeks periods was considered as expected number of GBS cases in Poisson distribution. The exact Poisson measure has been used to determine the confidence interval of the annual incidence of GBS. Population of the target group (denominator of the fraction) was considered equal to one fifth of annual population of the target group.

3. Results

In the time span of the study, 1218 reports of acute flaccid paralysis were identified including 785 patients (~64.5%) classified as having GBS. During this time interval, there were 370 patients confirmed GBS case reports among persons 5–14 years of age. The annual incidence in this age group remained relatively constant over the 3 year period and ranged from 0.65 per 100,000 population in 2004 to 0.76 in 2003 (Table 1). The estimated average annual incidence of GBS in persons <15 years of age is 1/100,000 (CI 95%: 0.88–1.13), and 0.7/100,000 in persons 5–14 years of age (CI 95%: 0.58–0.83). No obvious seasonal pattern was seen in GBS occurrence (Fig. 1).

The mean number of GBS patients identified per 10-week period was 23.8 during the study period (Table 2). The highest reported occurrence of GBS was for 10 May to 18 July 2003, before the immunization campaign. Twenty-five patients with GBS were reported in the time period which coincided with national immunization campaign. The probability of 25 cases of GBS occurring in the immunization campaign including time period according to Poisson distribution with expected cases number of 23.8 is equal to 0.43 ($p = 0.43$). In the time period of the immunization campaign, the annualized incidence rate of GBS in 5–14-year-old children was 0.71/100,000, which is in concordance with expected incidence rate of 0.67/100,000 (CI 95%: 0.44–1) that was computed based on occurrence of 23.8 cases of GBS in each 10-weeks time period. Thus, during the national immunization campaign, the number of reported cases of GBS was not more than expected incidence rate.

4. Discussion

In this study, the annual incidence rate of GBS is similar to other studies [18–21]. We observed no increase in GBS occurrence in the 4 week period of the national immunization campaign and the 6 week period following the campaign. In measles-rubella mass immunization campaign in Albania, 867,000 doses of vaccine were administered to children 1–14 years of age; 1 case of GBS was reported with a GBS incidence rate of 0.12/100,000 (CI 95%: 0.003–0.64) [1,22].

In a 5 years study between 1982–1986 in Finland, the average annual incidence rate of GBS after measles-mumps-rubella vaccination reported as 0.93/100,000 in 1–12 years-old children [12].

When evaluating poliomyelitis surveillance system of four contries in Latin America, Silveira et al. [16] estimated an average annual incidence of GBS among children 5–14 years of age as 0.52/100,000 (CI 95%: 0.49–1.53). In this study in the 72 days time period containing 1-month measles mass vaccination and 6 weeks afterwards 97 cases of GBS were reported in Argentina, Brazil, Chile, and Colombia, which was not significantly different from expected occurrence of GBS (93 cases) presuming Poisson distribution of GBS occurrence in 72 days time periods.

In a case-control study for evaluating risk factors of GBS occurrence, Liu et al. did not find any relation between vaccination and occurrence of GBS [23].

The above mentioned studies have used different methods to assess any relationship or causation between measles and rubella vaccination and GBS occurrence in different age groups among children. Our results were in concordance in time periods and similarly found no relation between vaccination and occurrence of GBS.

Since this study, as most of other similar studies, used acute flaccid paralysis surveillance system data, the validity (sensitivity and specificity) of the surveillance system would have a significant influence on the findings. The World Health Organization has suggested reporting 1 or more cases of acute flaccid paralysis per 100,000 under 15 years old children as evolution land mark for sensitivity of such a surveillance system [24]. In Iran average of this index is 1.6 in each year of the study which is acceptable. Showing a causative relation between measles and rubella vaccination, and the occurrence of GBS needs prospective studies and follow up of probable complications of the vaccines. Therefore, we propose precise analysis of immunization complication registration system data while controlling variables such as symptoms of infections like diarrhea and respiratory infections, and etc.

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