

Epidemiology of Guillain-Barré Syndrome in the Province of Quebec

Geneviève Deceuninck, Renée-Myriam Boucher, Philippe De Wals,
Manale Ouakki

ABSTRACT: Background: In the province of Quebec, a population-based study of Guillain-Barré syndrome (GBS) was conducted at the time of a mass immunization campaign against meningococcal disease, in 2001. **Methods:** The study population included residents aged 2 months to 20 years observed from November 1st, 2000 to December 31, 2002, representing 4 075 465 person-years of observation. GBS cases were identified in the provincial hospital database Med-Echo and medical records were reviewed. **Results:** Thirty-three incident GBS cases were identified, including 27 cases of acute inflammatory demyelinating polyradiculopathy. The overall GBS incidence rate was 0.8/100 000 person-years, higher in persons aged 1 to 4 years (2.1/100 000) than in those 5 years or more (0.6/100 000). There was a female preponderance and no significant seasonal variation. All patients survived. **Conclusion:** Results could be used to interpret reports of adverse events associated with the introduction of new vaccines in this age-group in Canada.

RÉSUMÉ: Épidémiologie du syndrome de Guillain-Barré dans la province de Québec. Contexte : Nous avons effectué une étude de population sur le syndrome de Guillain-Barré (SGB) dans la province de Québec au moment d'une campagne d'immunisation de masse contre le méningocoque en 2001. **Méthodes :** Les résidents âgés de 2 mois à 20 ans ont été inclus dans l'étude entre le premier novembre 2000 et le 31 décembre 2002, soit 4,075,465 personnes-années d'observation. Les cas de SGB ont été identifiés dans la base de données hospitalières provinciale Med-Écho et les dossiers médicaux ont été analysés. **Résultats :** 33 nouveaux cas de SGB ont été identifiés dont 27 cas de polyradiculopathie démyélinisante inflammatoire aiguë. Le taux d'incidence global du SGB était de 0,8/100,000 personnes-années, un taux plus élevé chez les enfants de 1 à 4 ans (2,1/100,000) que chez les enfants âgés de 5 ans ou plus (0,6/100,000), avec une prédominance féminine. Aucune variation saisonnière significative n'a été observée. Tous les patients ont survécu. **Conclusion :** Ces résultats pourraient être utilisés dans l'interprétation de rapports d'effets indésirables associés à l'introduction de nouveaux vaccins dans ce groupe d'âge au Canada.

Can. J. Neurol. Sci. 2008; 35: 472-475

The occurrence of Guillain-Barré syndrome (GBS) has been related to many exogenic factors including the administration of vaccines.^{1,2} In 1976-1977, an unusual number of GBS cases was reported following the administration of the inactivated "Swine" influenza vaccine, and the magnitude of the risk was estimated to approximately five to six cases per million vaccinees.³ However, a statistically significant association was not consistently found with more recent inactivated influenza vaccines.⁴ Following an extensive review of available data, the Institute of Medicine concluded that the evidence favoured acceptance of a causal relationship for oral polio vaccines, diphtheria and tetanus toxoids.⁵ In the UK, the analysis of a large general practice database indicated no increased risk of GBS following routine immunization.⁶ Recently, a possible association between GBS and receipt of a quadrivalent meningococcal conjugate vaccine

was reported in the United States, but the estimated attributable risk was very low (approximately one case per million vaccinees) and of borderline statistical significance.⁷ Because new vaccines are introduced in Canada, especially for use in school-age children and adolescents, it is important to collect

From the Public Health Research Unit, Quebec University Hospital Centre (GD), Department of Paediatric Neurology (RMB); Department of Social and Preventive Medicine, Laval University (PDW); Quebec National Public Health Institute (MO), Quebec City, Canada.

RECEIVED JANUARY 18, 2008. FINAL REVISIONS SUBMITTED MARCH 19, 2008.
Correspondence to: Philippe De Wals, Département de Médecine sociale et préventive, Université Laval, Pavillon de l'Est, 2180 chemin Sainte-Foy, Suite 1108, Québec, Canada, G1K 7P4.

valid data regarding the baseline incidence rate of potential adverse events, including GBS.⁸

In the province of Quebec, Canada, a mass immunization campaign using a serogroup C conjugate vaccine was implemented in 2001 and reached 82% of the targeted population.⁹ At the request of the Quebec Ministry of Health and Social Services, an investigation was carried out to assess the risk of GBS associated with vaccine administration in the population aged 2 months to 20 years and no excess risk was found.¹⁰ Results of this population-based investigation regarding the incidence and clinical presentation of GBS are presented.

METHODS

The study population encompassed all residents in the province of Quebec aged between 2 months and 20 years who were targeted by the mass immunization campaign against serogroup C meningococcal disease in the Fall of 2001 (those born between July 17, 1980, and November 30, 2001). The population size as of January 31, 2002 was estimated from a projection based on the 1996 census ($n = 1\,909\,734$). The observation period extended from November 1st, 2000, to December 31, 2002, for a total of 4 075 465 person-years of observation. The study was carried out in accordance with the Quebec Law on Public Health authorizing special investigations when there is a threat to the public safety and approval by an ethical committee was not requested.¹¹

The Med-Echo registry contains summary information on every patient admitted to an acute care hospital in the province of Quebec. After hospital discharge, medical archivists review medical notes and one main diagnosis and up to 15 secondary diagnoses are coded using the 9th Revision of the International Classification of Diseases (ICD-9). Records with a diagnostic

code compatible with GBS (ICD-9: 357.0) were extracted. Hospital medical directors were contacted to obtain a copy of patients' records, including medical notes and results of diagnostic investigations. All records were reviewed by a paediatric neurologist (RMB).

The clinical classification as proposed by Hughes and Cornblath² was applied and cases were categorized on the basis of the Brighton GBS Working Group's criteria (BGBSWG) as of September 12, 2007.¹² Confirmed GBS cases (BGBSWG level 1) had typical clinical features with electrophysiologic findings consistent with GBS and positive spinal tap (cerebrospinal protein concentration above the upper normal laboratory value, with cerebrospinal fluid (CSF) white cell count <50 cells/mm³) and no alternative diagnosis. Probable GBS cases (BGBSWG level 2 or 3) had typical clinical features and no alternative diagnosis (positive EMG or positive spinal tap may be present). Possible GBS cases had incomplete but compatible clinical presentation and no alternative diagnosis. Incidence density rates were calculated as the number of cases divided by the number of person-years of observation, and 95% confidence intervals (95% CI) were estimated by an exact method available in StatXact-6 (Cytel Software Corporation, Cambridge, MA). Differences in rates were tested using the Chi-square statistics.

RESULTS

A total of 46 records with a code compatible with GBS were identified, relating to 40 patients admitted in 23 acute care hospitals; six patients were excluded because the final diagnosis was another neurological condition other than GBS. One case of recurrence of GBS was also excluded. Finally, 33 incident GBS cases were included in the analysis. There were 21 female and 12 male patients (female proportion = 64%; 95% CI = 45% to 80%).

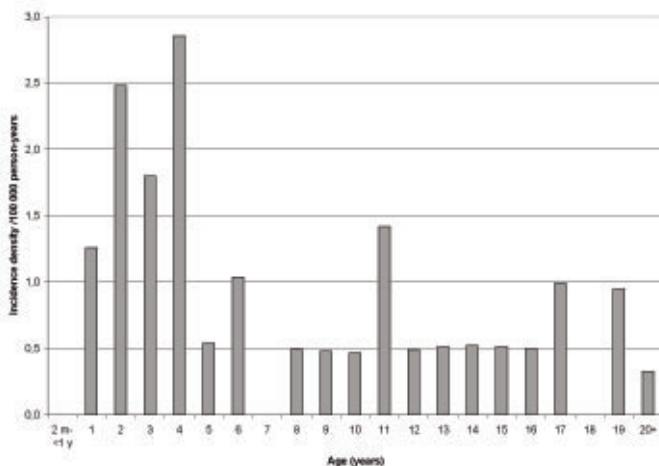


Figure 1: Incidence density of Guillain-Barré syndrome according to age, Quebec paediatric population, November 2000 to December 2002.

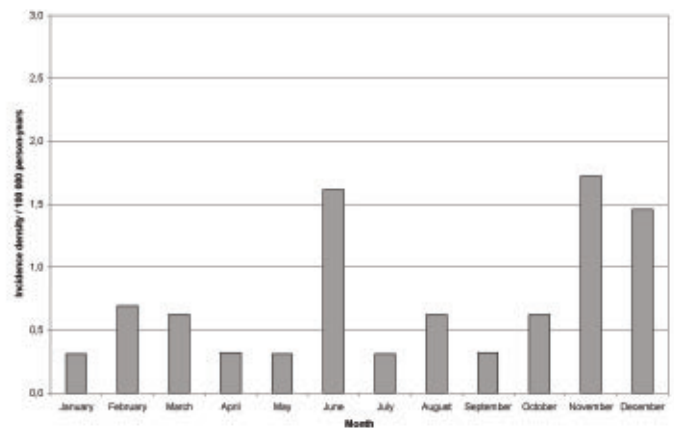


Figure 2: Incidence density of Guillain-Barré syndrome according to month, Quebec paediatric population, November 2000 to December 2002.

Table: Distribution of Guillain-Barré cases according to clinical presentation and confirmation of diagnosis

Clinical presentation	Confirmation of diagnosis			Total
	Confirmed	Probable	Possible	
Acute inflammatory demyelinating polyradiculopathy	12	13	2	27
Acute motor axonal neuropathy		1	1	2
Acute motor and sensory axonal neuropathy	1			1
Acute sensory neuropathy with pandysautonomia			1	1
Undetermined			2	2
Total	13	14	6	33

The overall annual incidence rate was 0.8 per 100 000 person-years (95% CI: 0.56 to 1.14). As shown in Figure 1, the peak incidence was observed in the age group 1 to 4 years (2.1/100 000 person-years; 95% CI = 1.2 to 3.6). In the age group 5 to 22 years, the incidence rate was significantly lower ($p < 0.001$) with 0.6 case per 100 000 (95% CI = 0.3 to 0.9). There were no cases in infants.

The monthly distribution of cases is shown in Figure 2, and there was no significant heterogeneity in incidence ($p = 0.18$).

A CSF examination was performed in 32 out of 33 patients and cytoalbumin dissociation was present in 20 of them (63%). The mean delay between the onset of symptoms and the CSF examination was 6.4 days (median = 4 days). Cytoalbumin dissociation was present in 10 of the 19 patients with a lumbar puncture in the first four days after disease onset (53%), and in 9 out of the 11 patients tested more than four days after disease onset (82%) ($p=0.11$). An EMG examination was available for 25 out of 33 patients (76%) and the average delay after disease onset was 8.8 days (median = 5 days). Electrophysiologic findings consistent with GBS were observed in 22 patients (88% of those tested).

The distribution of GBS cases according to the clinical presentation and the confirmation of diagnosis is shown in the Table. Acute inflammatory demyelinating polyradiculopathy was the most frequent presentation (27 cases), and there were two cases of acute motor axonal neuropathy, one case of acute motor and sensory axonal neuropathy, and one case of acute sensory neuropathy with pandysautonomia. In two other cases, a precise classification could not be made, for lack of details. In 13 cases, the GBS was considered as confirmed, as probable in 14 cases, and as possible in the remaining six cases.

The mean length of hospital stay was 12.3 days (median = 9 days; range = 1 to 57 days). Assisted ventilation was required for four patients and 22 other patients developed a paralysis of the lower limbs and were unable to walk (12 cases) or required assistance to walk (10 cases). Autonomic disturbances were

noted in 9 patients, including 2 cases with cardiac arrhythmia and 4 cases with arterial hypertension. Facial nerve paralysis was observed 11 cases. None of the patients died. Unfortunately, follow-up examinations were not available to assess the prevalence of long-term sequelae.

DISCUSSION

Our study is based on hospitalized GBS cases identified in the Quebec hospital administrative database Med-Echo. In Quebec, the accessibility of medical services remains high for potentially life-threatening conditions and the recommended practice is to admit any young patient with suspected GBS. Because the ICD-9 357.0 code category is covering all types of acute infective polyneuritis, medical records were reviewed to exclude diagnoses other than GBS. However, we cannot exclude some under-ascertainment resulting from gross diagnostic misinterpretation or punching error in the data processing. The validity of hospital discharge database has been assessed in a study in Northern Italy using three other independent sources, and high sensitivity was found for GBS identification (more than 90% of GBS cases identified under the 357.0 code) with relatively poor specificity (positive predictive value of 55% for the 357.0 code).¹³ In a previous study based on hospital service databases in Quebec and Ontario, in 1983-1989, only a sample of records was reviewed and age-specific rates were not adjusted for misclassification.¹⁴ The same methodological issue was present in a more recent study in Alberta relying on the provincial hospital discharge database without any attempt to review medical records.¹⁵

Guillain-Barré syndrome is rare in infancy and the incidence tends to increase with age.¹ In a study relying on voluntary notification from sentinel neurologists in the U.S., a peak was observed in persons aged 15 to 34.¹⁶ In another study based on a large U.S. hospital discharge database, there were two peaks, respectively, in the age groups 2-4 years and 15-19 years.¹⁷ In the paediatric population in Quebec, the peak was in persons aged 1-4 years. A male preponderance is generally observed,² but this was not found in persons aged less than 30 years in the US.^{16,17} Although a female preponderance was observed in our study, the statistical precision was relatively low and an equal risk cannot be excluded. Guillain-Barré syndrome is also known to occur with minor or no seasonal variation,¹ and the same pattern was observed in Quebec.

Guillain-Barré syndrome may be a severe acute condition in children and teenagers, but the vital prognosis remains good thanks to high quality intensive care as confirmed in our study. This is an important issue when dealing with vaccine risks and benefits. For example, the current risk of meningococcal disease from age 15 to 19 years in Canada is approximately 7 per 100 000 and 7% of those affected will die.¹⁸ Such risk is far greater than the potential (and still unconfirmed) one per million GBS risk associated with a highly effective meningococcal conjugate vaccine.⁷ As other vaccines are introduced in Canada for school-age children and adolescents (i.e. HPV, Hepatitis A), it is important to obtain valid baseline rates of potentially selected neurological conditions in order to interpret alleged associations.⁸ Assuming a GBS frequency comprised between 0.3 and 0.9 per 100 000 person-years in teenagers, up to six GBS cases could occur within six weeks of HPV vaccination among

two million female Canadians receiving three doses each. Any case series below this threshold should not raise concern regarding HPV vaccine safety.

ACKNOWLEDGEMENTS

This study was supported by the Quebec National Public Health Institute and an unrestricted research grant was received from Chiron (now Novartis) Vaccines.

REFERENCES

- Hahn A. Guillain-Barré syndrome. *Lancet*. 1998; 352: 635-41.
- Hughes RA, Cornblath DR. Guillain-Barré syndrome. *Lancet*. 2005; 366: 1653-66.
- Langmuir AD, Bregman DJ, Kurland LT, Nathanson N, Victor M. An epidemiologic and clinical evaluation of Guillain-Barré syndrome reported in association with the administration of swine influenza vaccines. *Am J Epidemiol*. 1984; 119: 841-79.
- Lasky T, Terracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, et al. The Guillain-Barré syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *N Engl J Med*. 1998; 339: 1797-802.
- Stratton KR, Howe CJ, Johnston RB Jr. Adverse events associated with childhood vaccines other than pertussis and rubella. Summary of a report from the institute of medicine. *JAMA*. 1994; 271: 1602-5.
- Hughes RA, Charlton J, Latinovic R, Gulliford MC. No association between immunization and Guillain-Barré syndrome in the United Kingdom, 1992 to 2000. *Arch Intern Med*. 2006; 166: 1301-4.
- Woo EJ, Ball R, Braun M, Clark T, Rosenstein Messonnier N, Wharton M, et al. Update: Guillain-Barré syndrome among recipients of Menactra® meningococcal conjugate vaccine—United States, June 2005–September 2006. *MMWR*. 2006; 55 (41): 1120-4.
- Siegrist CA. Autoimmune diseases after adolescent or adult immunization: What should we expect? *CMAJ*. 2007; 177: 1352-4.
- De Wals P, Deceuninck G, Boulianne N, De Serres G. Effectiveness of a mass immunization campaign using serogroup C meningococcal conjugate vaccine. *JAMA*. 2004; 292: 2491-4.
- De Wals P, Deceuninck G, Boucher RM, Ouakki M. Risk of Guillain-Barré syndrome following serogroup C Meningococcal conjugate vaccine in Quebec, Canada. *Clin Infect Dis*. In press.
- Assemblée nationale. Loi sur la santé publique. Québec city (province of Quebec, Canada): Editeur officiel du Québec, 2001.
- The Brighton Collaboration GBS Working Group. The Brighton Collaboration Guillain Barre' Syndrome case definition draft, version 20. Atlanta, GA [updated 2007 September 12; accessed 2008 March 13]. Available from: http://www.brightoncollaboration.org/internet/en/index/definition___guidelines/document_download.html.
- Bogliun G, Beghi E, Guillain-Barré Syndrome Registry Study Group. Validity of hospital discharge diagnoses for public health surveillance of the Guillain-Barré syndrome. *Neurol Sci*. 2002; 23: 113-7.
- McLean M, Duclos P, Jacob P, Humphreys P. Incidence of Guillain-Barré syndrome in Ontario and Quebec, 1983-1989, using hospital service databases. *Epidemiology*. 1994; 5: 443-8.
- Hauck LJ, White C, Feasby TE, Zochodne DW, Svenson LW, Hill MD. Incidence of Guillain-Barré syndrome in Alberta, Canada: an administrative data study. *Neurol Neurosurg Psychiatry*. In Press 2007.
- Kaplan JE, Schonberger LB, Hurwitz ES, Katona P. Guillain-Barré syndrome in the United States, 1978-1981: additional observations from the national surveillance system. *Neurology*. 1983; 33: 633-7.
- Prevots DR, Sutter RW. Assessment of Guillain-Barré syndrome mortality and morbidity in the United States: implications for acute flaccid paralysis surveillance. *J Infect Dis*. 1997; 175 Suppl 1: S151-5.
- Navarro C, Deeks SL, Medaglia A, Tsang RSW. Enhanced surveillance of invasive meningococcal disease in Canada: 1 January, 2004, through 31 December, 2005. *CCDR*. 2007; 33 (10): 1-15.