STM is an underdiagnosed and rare manifestation of *Schistosoma* infection, especially in children. Therefore, NS must be considered in the differential diagnosis of any patient presenting with unexplained myelopathy who has traveled to or lives in endemic disease areas.

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GUILLAIN–BARRÉ SYNDROME AFTER IMMUNIZATION IN CANADIAN CHILDREN (1996–2012)

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Abstract: Guillain–Barré syndrome (GBS) cases admitted to Canadian pediatric tertiary care centers were ascertained through active surveillance. From 1996 to 2012, 246 cases were identified, and 24 (10%) had onset ≤30 days after immunization. Annual rate of postimmunization GBS was 2.0 per 100,000 hospitalizations. Postimmunization GBS was an infrequent cause of pediatric hospitalization.

Key Words: adverse event following immunization, Guillain–Barré Syndrome, surveillance, vaccination

Accepted for publication September 7, 2015.

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This surveillance activity is conducted as part of the Canadian Immunization Monitoring Program Active (IMPACT), a national surveillance initiative managed by the Canadian Paediatric Society and conducted by the IMPACT network of pediatric investigators on behalf of the Public Health Agency of Canada's Centre for Immunization and Respiratory Infectious Diseases. Funding for Acute Flaccid Paralysis surveillance was provided by PHAC. PHAC was involved in the review and approval of the manuscript. K.A.T. was supported by an Investigatorship Award from the IWK Health Centre. J.A.B. was supported by a Career Investigator Award from the Michael Smith Foundation for Health Research. The authors have no conflicts of interest to disclose.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

DOI: 10.1097/INF.0000000000000903

Guillain–Barré syndrome (GBS) has an annual incidence of 1–2 cases per 100,000 population.[1] GBS can be triggered by viral or bacterial infections, including influenza and *Campylobacter jejuni*,[1–3] and has been reported as an adverse event following immunization (AEFI). The 1976 swine-type influenza A/New Jersey vaccine was associated with an excess risk of GBS of 1 per 100,000 vaccines.[4] Temporal associations between GBS and more recent influenza vaccines, diphtheria–tetanus–pertussis vaccines and measles–mumps–rubella (MMR) vaccines have been reported, but epidemiologic studies have not found consistent associations.[2,3,5]

Canada has 2 surveillance systems that capture GBS in children: the Canadian Paediatric Surveillance Program (CPSP) and the Canadian Immunization Monitoring Program Active (IMPACT). Since 1996, CPSP has conducted surveillance among community and hospital-based pediatricians for acute flaccid paralysis (AFP), which includes GBS, in children younger than 15 years to verify the success of polio eradication efforts.[6] From 1996 through 2012, CPSP received 773 reports of AFP cases (estimated annual incidence: 0.4–1.1 per 100,000 children), of whom 69% were diagnosed as GBS.[6] IMPACT conducts active surveillance for hospitalizations for selected AEFI including GBS, at 12 pediatric centers representing approximately 90% of pediatric tertiary care beds in Canada.[7]

The study objectives were 3-fold: (1) to describe the clinical features and outcomes of GBS with onset 0–30 days after immunization; (2) to compare the clinical features of postimmunization GBS cases with cases not recently immunized (>30 days); and (3) to estimate the annual rate of postimmunization GBS per 100,000 admissions at IMPACT hospitals.

MATERIALS AND METHODS

GBS cases reported to IMPACT and CPSP from 1996 through 2012 were reviewed. CPSP contacts >2500 Canadian pediatricians and subspecialists on a monthly basis to elicit reports of patients with AFP. At IMPACT centers, reporting of AFP cases to CPSP is delegated to IMPACT nurse monitors. GBS and AFP cases were identified using real-time searching of admissions and *International Classification of Diseases*, 9th and 10th Revision (ICD-9 and ICD-10, respectively) code searches (GBS: 357.0 or G61.0). Vaccination records were verified with the family physician or public health, and standardized reporting forms were completed for

each surveillance system.[7] Only CPSP cases admitted to IMPACT centers were included in this analysis to ensure consistency in case-finding and immunization record review procedures among postvaccine and nonvaccine-associated cases. Ethical approval was obtained at all participating hospitals.

Postvaccine IMPACT GBS cases meeting the following definition were included in the analysis: rapidly progressive, symmetrical motor weakness with loss of tendon reflexes, with or without sensory loss or increased protein level in the cerebrospinal fluid (CSF) in children younger than 15 years and with onset ≤30 days after immunization. Postvaccination cases were reported to the IMPACT data center and the national AEFI surveillance system operated by the Public Health Agency of Canada (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php).

Nonvaccine-associated CPSP AFP cases meeting the following definition were analyzed: acute onset of focal weakness or paralysis characterized as flaccid without other causes (eg, trauma) in children younger than 15 years, diagnosed with GBS, who were not immunized within 30 days of onset and were admitted to IMPACT hospitals. AFP cases were reported to CPSP and then forwarded to the investigator at the Public Health Agency of Canada for verification.

Both IMPACT and CPSP reporting forms captured age, sex, neurologic history, immunizations received ≤30 days of symptom onset, neurologic features (cranial nerve involvement and areas of weakness), results of CSF examination, viral culture or molecular testing, neuroimaging, duration of hospitalization, outcome and final diagnosis. IMPACT also captured any presenting nonneurologic features (eg, fever, upper respiratory, gastrointestinal symptoms). CPSP captured fever at presentation and acute respiratory infections within 30 days of paralysis onset. Only fever and respiratory symptoms were compared between postvaccine and nonvaccine cases.

Reporting of weakness differed between IMPACT and CPSP: both had separate categories for weakness of each extremity (eg, right leg), but while CPSP captured respiratory muscle weakness, IMPACT categorized neck, trunk and generalized weakness separately. In this analysis, weakness was categorized as quadrilateral (4 extremities involved), bilateral legs, bilateral arms, unilateral leg and/or arm (without bilateral weakness) and other (respiratory muscles, neck, trunk or generalized without specified limb involvement). Weakness severity was not analyzed because IMPACT and CPSP used different grading scales.

Outcomes were reported by IMPACT based on the status at hospital discharge and by CPSP based on the status at the time of initial reporting and 60 days after onset of paralysis. Only 60-day outcomes were reported for nonvaccine-associated cases because of a wide range (1–793 days) between symptom onset and initial reporting. Outcomes were categorized as fully recovered (normal or baseline status), not yet recovered (partial recovery, persistent neurologic abnormality whether improving or not), fatal or unknown.

The analysis was descriptive. Differences in proportions were assessed by χ^2 test or Fisher exact test, as appropriate. Rate of postimmunization GBS cases per 100,000 hospital admissions was calculated using mean annual admissions at the 12 IMPACT centers (1996–2012). Statistical analysis was conducted using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Twenty-four cases of GBS were reported with onset 0–30 days after vaccination, and 222 cases of GBS were reported with onset >30 days postimmunization. Approximately 10% of patients admitted with GBS had received an immunization within 30 days of symptom onset. The annual rate of postimmunization GBS was 2.0 per 100,000 admissions (95% confidence interval: 1.4–3.0 per 100,000).

Clinical features of postvaccine and nonvaccine cases were similar, including age, sex, results of CSF analysis and neuroimaging and duration of hospitalization (Table, Supplemental Digital Content 1, http://links.lww.com/INF/C272). Patterns of weakness differed between groups ($P < 0.001$) with 96% of nonvaccine-associated cases reporting quadrilateral or bilateral limb weakness versus 63% of postvaccine cases. Fever and/or respiratory symptoms were frequently reported in both groups. Nineteen (79%) postvaccine cases presented with ≥1 nonneurologic symptom. Infection was confirmed by culture, polymerase chain reaction or serology in 5 (21%) postvaccine cases and 23 (11%) nonvaccine cases ($P = 0.17$). Among postvaccine cases, 2 (8%) had fully recovered at discharge (median: 14 days after onset, range: 4–69 days) and 22 (92%) had not yet recovered. Among nonvaccine cases, 43 (19%) had fully recovered by 60 days after onset, 174 (78%) had not yet recovered, 1 (0.5%) had a fatal outcome from an underlying condition unrelated to GBS and outcome was unknown in 4 (2%).

Among the postvaccine cases, the median interval from vaccination to symptom onset was 18 days (range: 4–30 days). Nineteen cases (79%) had received a single vaccination within 30 days of symptom onset: diphtheria–tetanus–pertussis vaccine (5 cases), influenza vaccine (5), hepatitis B or combined hepatitis A and B vaccine (4), meningococcal conjugate vaccine (3) and MMR vaccine (2). Vaccines co-administered during the same visit before GBS onset included DPT + MMR (3 cases), DPT + MMR + pneumococcal conjugate vaccine (1) and influenza + meningococcal vaccine (1).

DISCUSSION

GBS occurring within 30 days after immunization was a rare cause of hospitalization among Canadian children, representing approximately 10% of GBS admissions at IMPACT centers and occurring at a rate of approximately 2 per 100,000 hospital admissions. Temporal associations between GBS onset and immunization were observed for several routine vaccinations. Most postvaccine cases also presented with symptoms suggestive of recent infection, and 5 (21%) had microbiologically confirmed infection, suggesting an alternate etiology for their GBS.

Clinical characteristics were similar between cases reported after vaccination and nonvaccine-associated cases. The 1 difference observed was the pattern of weakness ($P < 0.001$), with a higher proportion of nonvaccine-associated cases reporting involvement of all 4 limbs. This could be explained by differences in the categories of weakness on the IMPACT and CPSP reporting forms. "Generalized" weakness was reported for 7 postimmunization cases, a category not present on CPSP reporting forms.

Similar to this study, previous reports identified infectious etiologies in 18% of GBS cases and 14% of AFP cases in Australia and Hong Kong, respectively, but immunization status was not reported.[8,9] One prospective study of children with GBS identified infectious etiologies in 75% (6 of 8) of cases vaccinated within 6 weeks of onset and 46% (40 of 87) of nonvaccine-associated cases, most commonly coxsackieviruses and *Chlamydophila pneumoniae*.[3]

This study had limitations. IMPACT and CPSP captured immunizations received 0–30 days before onset, rather than the current standard of 0–42 days; the case definitions used by IMPACT and CPSP differed from the current Brighton Collaboration case definition and the data were not population based.[10] These factors might limit the generalizability of the results. The diagnostic evaluation and microbiologic work-up were not standardized, which could have contributed to misclassification of GBS cases and underestimation of the frequency of concurrent infection. Because the children in this study were admitted to pediatric tertiary care centers, we expect that cases were evaluated by a neurologist, and

evaluation of postvaccine and nonvaccine-associated cases was comparable, strengthening the validity of the diagnosis. The study's strengths included the use of trained nurse monitors to identify and verify cases and review immunization records, and periodic audits using ICD codes, which contributed to high data quality and complete reporting.

This study provides reassuring evidence that postimmunization GBS is rare in children. The high frequency of symptoms of recent infection suggests that a temporal association between vaccination and GBS onset is most likely coincidental rather than causal.

ACKNOWLEDGMENTS

The authors thank the expert assistance of Tiffany Smith (Public Health Agency of Canada), the Monitor Liaison (Heather Samson), Canadian Immunization Monitoring Program Active (IMPACT) nurse monitors, staff of the IMPACT Data Centre (Kim Marty, Shu Yu Fan) and Melanie Laffin (Canadian Paediatric Society and Canadian Paediatric Surveillance Program).

APPENDIX

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