Central Nervous System Complications of Varicella-Zoster Virus

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Objective To describe the spectrum of central nervous system complications of varicella-zoster virus (VZV) in children admitted to The Hospital for Sick Children between January 1999 and December 2012.

Study design Children aged 1 month to 18 years (n = 84) admitted with neurologic manifestations associated with a characteristic VZV rash or a confirmatory laboratory test (positive lesion scraping or cerebrospinal fluid polymerase chain reaction) were included in the study. Acute neurologic complications were included if they occurred within 4 weeks of VZV infection. Stroke was considered related to VZV if it occurred within 6 months of VZV infection, the neuroimaging was characteristic, and other causes were excluded.

Results Clinical syndromes included acute cerebellar ataxia (n = 26), encephalitis (n = 17), isolated seizures (n = 16), stroke (n = 10), meningitis (n = 10), Guillain-Barré syndrome (n = 2), acute disseminated encephalomyelitis (n = 2), and Ramsay Hunt syndrome (n = 1). In those with acute complications (nonstroke), neurologic symptoms occurred a median of 5 days after rash onset (range −6 to +16). The time between rash onset and stroke ranged from 2 weeks to 26 weeks (median 16.0 weeks). Three children with encephalitis died. Residual neurologic sequelae at one year occurred in 9 of 39 (23%) of children with follow-up data. Only 4 children were reported to have received the varicella vaccine.

Conclusion Neurologic complications of VZV infection continue to occur despite the availability of an effective vaccine. Neurologic symptom onset can predate the appearance of the VZV exanthem and in rare cases may occur in the absence of an exanthem. *(J Pediatr 2014;165:779-85)*.

Central nervous system (CNS) complications of varicella-zoster virus (VZV) are uncommon. Population-based epidemiologic studies undertaken in the pre-VZV vaccine era suggest an incidence of 1 to 3 per 10 000 varicella cases.[1,2] Such complications, although rare, are a leading cause of VZV-associated hospital admission[3-5] and can be associated with significant long-term morbidity and mortality.[6] Although a significant reduction in the incidence of chickenpox and its complications have been documented after the introduction of the VZV vaccine,[7,8] there remains a paucity of data specifically pertaining to the impact of vaccine availability on neurologic complications.

The live, attenuated VZV vaccine was approved for use in Canada in December 1998 to prevent VZV infection and its complications. Recommendations for its use in healthy, susceptible individuals older than 1 year of age were published by the National Advisory Committee on Immunization in May 1999.[9] Public funding of universal varicella vaccination in Ontario began in September 2004. The objective of this study was to describe the spectrum of neurologic complications associated with VZV, their clinical presentation, and outcome before and after the public funding of the VZV vaccine in Ontario.

Methods

All children ages 1 month to 18 years admitted to The Hospital for Sick Children (SickKids) between January 1999 and December 2012 with neurologic manifestations associated with a characteristic VZV rash or a confirmatory laboratory test (positive lesion scraping or cerebrospinal fluid [CSF] polymerase chain reaction [PCR]) were included in the study. Cases were identified using 4 independent sources: the SickKids Encephalitis Registry, the Infectious Disease inpatient consult service database, *International Classification of Diseases, 9th Revision* (ICD-9) or *International Classification of Diseases, 10th Revision* (ICD-10) discharge codes from the Health Records database and the Department of Pediatric Laboratory Medicine database.

The SickKids Encephalitis Registry is a prospective registry in place since 1994. Enrollment criteria, data collection, and investigations have been described previously.[10] The data for the Encephalitis Registry are collected by a dedicated study nurse who identifies patients by daily

ADEM	Acute disseminated encephalomyelitis
CNS	Central nervous system
CSF	Cerebrospinal fluid
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
PCR	Polymerase chain reaction
SickKids	The Hospital for Sick Children
VZV	Varicella-zoster virus

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review of admissions and quarterly review of ICD-9 or ICD-10 codes. All patients with the ICD-9 discharge codes "post-varicella encephalitis," "varicella with other specified complications," "varicella with unspecified complication," and the ICD-10 codes "varicella encephalitis," "varicella meningitis," or "varicella with other complication," were screened for possible inclusion. The Infectious Disease consult service database contains information on all patients with which the Infectious Disease team is involved when admitted to hospital. Finally, the Department of Pediatric Laboratory Medicine database was used to identify patients with positive CSF VZV PCR test results. Ethical approval for the study was obtained from the Research Ethics Board of at SickKids.

Neurologic complications were grouped as acute nonstroke complications and stroke (acute or nonacute). A VZV-associated acute nonstroke neurologic complication was defined as the onset of neurologic symptom(s) 4 weeks before to 4 weeks after the VZV rash or detection of VZV within the CSF and the absence of an alternative explanation for the symptom(s). Encephalitis was defined as the presence of encephalopathy (altered level of consciousness including lethargy, irritability, or personality or behavioral change persisting ≥24 hours) and 2 or more of the following: fever (≥38°C), seizure, focal CNS findings, CSF pleocytosis (>5 white blood cells/mm^3), electroencephalogram abnormalities, or diagnostic imaging abnormalities consistent with encephalitis.[10] The presence of ataxia without evidence of encephalitis was diagnostic of acute cerebellar ataxia. VZV-associated stroke was defined as the development of focal neurologic deficits accompanied by neuroimaging abnormalities indicating cerebral ischemia, infarction, or hemorrhage with angiographic evidence of the characteristic vasculopathy (narrowing or beading in cerebral arteries)[11] within 6 months of VZV infection and exclusion of other causes. Six months was chosen on the basis of a recent study in which the authors found that children with chickenpox were at increased risk of stroke in the subsequent 6 months.[12]

Neurologic impairment was considered "minor" if near full recovery was expected, there was minimal or no impact on function, and strength was ≥4 of 5 on the motor strength scale. Neurologic outcomes were considered to be "major" if they had significant impact on function or there was focal weakness with strength <4 of 5 on the motor strength scale.

Statistical Analyses

Statistical analysis was performed using SPSS version 20 (SPSS Inc, Chicago, Illinois). Medians and proportions were used to describe continuous and categorical variables, respectively. Admission rates to SickKids were compared before and after September 1, 2004. The total number of admissions related to VZV-neurologic complications for each time period was divided by the total number of hospitalizations to the inpatient units over the same time period.

Results

A total of 84 children with neurologic complications associated with VZV infection were admitted to SickKids between January 1999 and December 2012 (Figure 1). The rate of admission with VZV-related CNS complications to SickKids was 55 per 100 000 before full vaccine coverage in Ontario (September 1, 2004) and 20 per 100 000 after full coverage. The median age was 7.3 years (range, 4 months to 16.5 years); 49% were male. Most had no underlying medical conditions (n = 68; 81%). The remainder had neurologic or

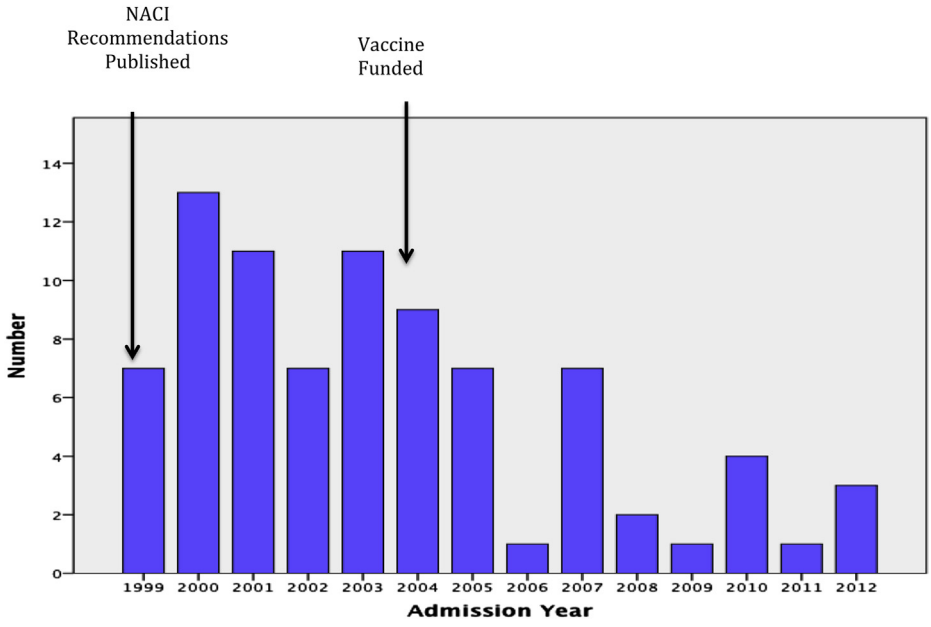

Figure 1. Number of admissions for VZV-associated CNS complications per year. *NACI*, National Advisory Committee on Immunization.