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BRIEF REPORT

Clinical and Microbiological Characteristics of Invasive Group A Streptococcal Infections Before and After Implementation of a Universal Varicella Vaccine Program

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Since the introduction of the varicella vaccine to the routine immunization schedule, we have observed a 70% reduction in the rate of varicella-associated invasive group A streptococcal infections (IGASI). In the mean time, the clinical presentation of IGASI and microbiological characteristics of GAS strains have changed significantly.

Keywords. invasive streptococcal infection; necrotizing fasciitis; pediatrics; varicella vaccine.

In recent decades, an unusually large number of invasive group A streptococcal infections (IGASIs), particularly those with concomitant necrotizing fasciitis (NF), have been reported in Montreal, Canada [1]. In children, varicella infection has been described as an important risk factor for developing IGASI and, more particularly, NF [2–4]. Therefore, it was predicted that increased use of the varicella vaccine (VV) would be associated with reduced rates of varicella-associated IGASI [2, 5]. In the province of Quebec, Canada, the VV was offered to high-risk persons in 2001 and was introduced as part of the routine immunization schedule in 2006. Here, our aim is to describe the clinical and microbiological characteristics of patients hospitalized with IGASI in our institution before and after the universal implementation of VV.

PATIENTS AND METHODS

Study Design

Sainte-Justine Hospital is the largest pediatric tertiary care teaching hospital in Quebec. Medical charts of all patients aged <18 years admitted for IGASI between January 1999 and December 2013 were reviewed. IGASI cases were identified from the microbiology laboratory and the hospital's diagnosis databases. A standardized data form was used to collect information on demographics, previous medical conditions, clinical features, and microbiological findings.

The study period was separated into 2 time intervals: January 1999 to December 2005, accounting for the first 7 years of the study period and representing the prevaccine era, and January 2006 to December 2013, representing the post-vaccine period.

The institutional review board and the local ethics committee approved the study.

Inclusion and Exclusion Criteria

IGASI included NF, streptococcal toxic shock syndrome (STSS), occult bacteremia, and focal infections such as pneumonia, osteomyelitis, septic arthritis, meningitis, and cellulitis with bacteremia. IGASI cases were defined as patients with compatible clinical presentation and for whom the GAS strain was isolated from blood or any other sterile body site [6]. Local complications of GAS infections (eg, retropharyngeal abscess, peritonsillar abscess, periorbital cellulitis, mastoiditis, or adenitis) were excluded. Varicella-associated IGASI was defined as IGASI that occurred within a maximum time span of 1 month after the onset of varicella infection. NF was assessed using the criteria defined by Kaul et al [7]. STSS was diagnosed according to the definition of the Working Group on Severe Streptococcal Infections [6].

Microbiological Analyses

Collected GAS isolates were analyzed by *emm* genotyping according to the Centers for Disease Control and Prevention method at the Robert Debré Hospital, Paris (France), Microbiology Department [8]. Expression of the streptococcal pyrogenic exotoxin genes A and C (*spe*A, *spe*C), streptococcal superantigen (*ssa*), and the allele 1 of streptococcal mitogenic exotoxin Z gene (*sme*Z) were detected using polymerase chain reaction as previously described [4].

Statistical Analyses

Results are presented as absolute numbers (percentages) for categorical variables, as means (standard deviation [SD]) for rates of IGASI per 1000 hospital admissions, and as median (interquartile) for continuous variables. Clinical and microbiological data were analyzed according to the time interval when IGASI occurred, that is, pre-implementation of the VV program as opposed to post-VV implementation. Statistical analyses were carried out using SPSS 19.0 software (SPSS Inc., Chicago, Illinois). Differences in group proportions and in mean values

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were compared using a univariate binary regression model. Any P value <.05 was considered significant.

RESULTS

Incidence

Over the 15-year study period, 165 patients hospitalized for IGASI met the inclusion criteria. The mean number of patients hospitalized for IGASI per year was 11.0 (SD, 6.2), reflecting an annual mean rate of 0.47 (SD, 0.28) IGASIs per 1000 hospital admissions. This rate varied over the study period and ranged from a low of 0.19 in 2000 to a high of 1.10 in 2003. The annual mean rate was not significantly different before and after VV implementation (0.49/1000 admissions; SD, 0.38 vs 0.46/1000 admissions; SD, 0.19; $P = .8$).

Clinical Features of IGASI

Table 1 summarizes the characteristics of the 165 children hospitalized as a result of IGASI.

Prior to VV implementation, skin and soft tissue infections (SSTIs), including NF and cellulitis with bacteremia, represented the most frequent clinical presentations of IGASI, accounting for 50.0% of cases (41/82). Among the 82 children with IGASI, 24 (29.3%) had a recent history of varicella. Most of them (88.5%) presented with SSTI. STSS was present in 9 patients (11%) and associated with NF in 6 cases.

After VV implementation, 7 children (8.8%) were hospitalized for the following varicella-associated IGASIs: SSTI, 2; pleural empyema, 2; meningitis, 1; osteoarthritis, 1; and occult bacteremia without focal infection, 1. None of the children had NF. Among these 7 cases of varicella-associated IGASI, 6 developed 2 years after VV implementation.

The proportion of children hospitalized for streptococcal SSTI decreased significantly from 50.0% to 18.1% ($P < .001$), which was associated with a decline in NF from 29.3% to 3.6% ($P < .001$). However, during this time interval, children were more likely to present with pleuropulmonary or osteoarticular IGASI (odds ratio [OR], 2.17; 95% confidence interval [CI], 1.16–4.05; $P = .02$). The overall case fatality rate was 4.2% (7/165).

Table 1. Demographics and Clinical Characteristics of the Patients With Invasive Group A Streptococcal Infections and Microbiological Characteristics of the Strains

Characteristic	Before Implementation of VV	After Implementation of VV	*P* Value
N	82	83	
Age (mo), Median (interquartile range)	49.0 (22.7–74.0)	52.0 (27.0–84.0)	.95
Gender			
Female, N (%)	42 (51.2)	28 (33.7)	.03
Male, N (%)	40 (48.8)	55 (66.3)	
Varicella-related IGASI, N (%)	24 (29.3)	7 (8.8)	.001
Underlying chronic disease, N (%)	7 (8.5)	9 (11)	.34
Clinical features of IGASI, N (%)			
SSTI	41 (50.0)	15 (18.1)	<.001
NF	24 (29.3)	3 (3.6)	<.001
SSTI other than NF	17 (20.7)	12 (14.5)	.31
IGASI other than SSTI	41 (50.0)	68 (81.9)	<.001
Pleuropulmonary	15 (18.3)	24 (28.9)	.14
Osteoarticular	14 (17.1)	21 (25.3)	.25
Streptococcal toxic shock syndrome	9 (11)	3 (3.7)	<.001
Death, N (%)	3 (3.7)	4 (4.8)	1
*Emm*1 genotype,[a] N (%)	13 (26.0)	28 (38.4)	1.18
Virulence factor genes,[a] N (%)			
*spe*A	18 (32.7)	34 (46.6)	.15
*spe*C	21 (38.2)	32 (43.8)	.59
ssa	11 (20)	45 (61.6)	<.001
smeZ	55 (43.3%)	72 (56.7%)	.002

Abbreviations: IGASI, invasive group A streptococcal infection; NF, necrotizing fasciitis; SSTI, skin and soft tissue infection; VV, varicella vaccine.

[a] *Emm*1 genotype and presence of virulence factor genes were screened in 140 and 128 Group A Streptococcal strains, respectively.

Microbiological Characteristics

A total of 140 and 128 GAS strains were available for genotyping and analysis of virulence factor genes, respectively. Over the study period, *emm*1 represented 24.8% of the strains. The *spe*A, *spe*C, and *ssa* genes were present in 40.6%, 41.4%, and 43.8% of the strains, respectively. The percentages of strains containing the *spe*A or *spe*C genes did not change over the study period (Table 1), although strains isolated after VV implementation were more likely to contain the *ssa* gene (OR, 6.43; 95% CI, 2.85–14.48; $P < .001$) and *smeZ* (OR, 3.16; 95% CI, 1.52–6.57; $P = .002$).

GAS strains isolated from patients with NF were more likely to contain the *spe*C gene (OR, 4.54; 95% CI, 1.63–12.67; $P = .004$), although strains isolated from patients with pleuropulmonary infection were more likely to contain the *ssa* gene (OR, 3.72; 95% CI, 1.58–8.79; $P = .003$). We did not find any association between the *smeZ* gene and clinical syndrome. Strains isolated from patients with varicella-associated IGASI were less likely to contain the *spe*A gene (OR, 0.10; 95% CI, .02–.46; $P = .003$).

DISCUSSION

In pediatric patients, varicella is a well-documented risk factor for IGASI, associated with approximately 15% to 30% of such infections [2–4]. In January 2006, 1 dose of VV at the age of 12 months was introduced to the routine immunization schedule in Quebec, without a catch-up policy. Although the immunization coverage rate was less than 25% in children aged ≤24 months before implementation of the universal VV, it reached 91.5% in 2012 [9]. As expected, we observed a significant decline of 70% among patients hospitalized with varicella-associated IGASI at our institution, reinforcing the importance of universal VV use in children. In our hospital, this decline was associated with a significant reduction in the number of GAS-induced SSTIs and, more particularly, with a dramatic decrease

in NF. Only 3 cases of NF required hospitalization after VV implementation (none associated with varicella) compared with 24 cases of NF before VV implementation, with 15 (62.5%) associated with varicella. A decline in the incidence of varicella-related IGASI following VV implementation has been described by others [5]. However, previous work focused on SSTI and did not comment on the absence of reduction in the annual rate of IGASI, nor were the clinical characteristics of IGASI described.

In our study, although the rate of varicella-associated IGASI decreased significantly after the implementation of VV, the annual mean rate of IGASI per 1000 admissions did not change significantly. Moreover, IGASI clinical presentation changed, with an increase in pleuropulmonary and osteoarticular infections.

Here, we present further evidence that varicella is not the only risk factor for IGASI in children. While the increasing frequency of pleuropulmonary IGASI may suggest a possible role of respiratory viruses in facilitating the occurrence of IGASI, our experience suggests otherwise. During the novel influenza A (H1N1) pandemic in 2009, we did not observe a particular increase of pleuropulmonary IGASI [10].

Host susceptibility could be involved in the occurrence and severity of IGASI [1]. In our study, fewer than 10% of patients had an underlying chronic disease. Although some children were evaluated for an underlying immune deficiency, we did not identify any immune susceptibility that could explain the severity of the infection [11]. However, the real influence of host susceptibility needs to be clearly defined with further studies.

Finally, particular GAS virulence factors (eg, *emm* type or specific exotoxin production [as for *spe*A or *spe*C]) are prominent in IGASI. We previously described an association between NF and *spe*C (OR, 4.0; 95% CI, 1.2–13.9) [4]. Others have reported an association between *emm*-type (*emm*1, *emm*12, *emm*4) virulence factor (*ssa*) and varicella-associated IGASI cases [12]. The 2 predominant *emm* types found in our study were *Emm*1 and *emm*12. Although *Emm*1 has previously been described as a main genotype in IGASI, our finding of the *Emm*12 genotype likely reflects the frequency of this *emm* type in the community.

Here, strains containing the *spe*A and *spe*C genes represented 40.6% and 41.4% of the isolates, respectively. The *spe*C gene was significantly associated with NF isolates, while strains isolated from patients with pleuropulmonary infection were more likely to express the *ssa* gene. These results could suggest that the expression of virulence factor genes in the GAS strain may lead to specific clinical expression of IGASI. Indeed, the association between NF and the presence of the *spe*C gene in isolates before the implementation of VV, as well as the association between the presence of the *ssa* gene in the strains and the development of pleuropulmonary IGASI, may be a reflection of the temporal epidemiology of GAS. These changes in the epidemiology of GAS could be due to temporal trends in IGASI and streptococcal types, as it has been described over decades for pneumococcal infections and serotypes [13], or we may hypothesize that it could be due, in part, to selection pressure induced by VV.

Our study has limitations due to its retrospective design and the use of a single-center setting. It was not designed to assess the direct impact of VV on individual risk for developing IGASI, given that information about individual immunization against varicella was often missing in the files, nor to assess the impact of the immunization program on the incidence of varicella since we focused exclusively on IGASI requiring hospitalization. However, this study shows that VV was effective in reducing varicella-related IGASI and streptococcal SSTI including NF. However, it also suggests that VV is not sufficient to reduce the overall frequency of IGASI.

Note

Potential conflicts of interest. All authors: No potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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