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Adverse Reactions to Pneumococcal Vaccine in the Pediatric and Adolescent Sickle Cell Patients

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Abstract

Study Objective—To review five cases of severe adverse reactions after vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) in pediatric and adolescent patients with sickle cell disease (SCD), and evaluate the prevalence of adverse reactions to PPSV23 in the SCD patients by analyzing the data from Vaccine Adverse Event Reporting System (VAERS).

Design—Description of a case series and retrospective analysis of data from VAERS.

Data Sources—Medical records from a tertiary care hospital and VAERS database.

Measurements and Main Results—Five cases of severe adverse reactions after vaccination with PPSV23 in the pediatric and adolescent patients with SCD (age ranging from 2 to 22 yo) were described. The adverse reactions occurred within 24 hours after immunization, and required medical attention in all five cases. Comparing with the data from VAERS, PPSV23 is the most commonly reported vaccine in patients with SCD, accounting for 62% of total vaccine-induced adverse events. This rate is significantly higher than patients with HIV or asthma (62% vs 16%, $p < 0.0001$). The reported adverse reactions in the pediatric SCD patients (< 18 yo) were four times as many as the adult patients (18–39 yo).

Conclusion—The risk of developing severe adverse reactions to PPSV23 is greater in the SCD patients, especially in the pediatric and adolescent patients. Healthcare professionals should be aware of this potential vaccine adverse event and may consider avoiding concurrent administration of other vaccines with PPSV23.

Keywords

pneumococcal vaccine; sickle cell disease; adverse drug reaction; pediatric; adolescent; Pneumovax

Introduction

Streptococcus pneumoniae causes severe infection in children, such as pneumonia, meningitis, and acute otitis media (1). According to recommendation from Centers for Disease Control and Prevention (CDC), all children should receive a 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13) as a 4-dose series at ages 2, 4, 6, and 12–15 months (1). Due to functional asplenia, children with sickle cell disease (SCD) have increased susceptibility to invasive bacterial infection, especially encapsulated bacteria such as *Streptococcus pneumoniae* (2, 3). Pneumococcal infection was one of the leading causes of mortality in pediatric patients with SCD (4). Introduction of penicillin prophylaxis and pneumococcal immunization reduced the rate of pneumococcal infection by more than 90% (5). For children who are at increased risk of pneumococcal disease such as SCD patients, a 23-valent pneumococcal polysaccharide vaccine (PPSV23) should be administered at age 2–18 years with a second dose 5 years after the first dose. An optional dose of PCV13 may be administered among children aged 6–18 years with high risk conditions, even for those who have received 7-valent pneumococcal conjugate vaccine (PCV7) previously. For adult patients with high-risk conditions who have not previously received PCV13 or PPSV23, it is recommended to receive both, followed by a second PPSV23 dose 5 years after the first PPSV23 dose (6).

Although the benefits of pneumococcal vaccination are very large, adverse events can sometimes occur. One of the known adverse effects of PPSV23 is inflammatory reaction, especially when given in shortly after the PCV7 (7–10). Because the pathophysiology of SCD is now recognized to include baseline inflammation (11), it is possible that more adverse inflammatory reactions to immunizations occur in this population.

In this report, we describe five cases of severe adverse reactions in pediatric and adolescent patients with SCD after PPV23 vaccination, and analyze the data from Vaccine Adverse Event Reporting System (VAERS), showing that the adverse reactions to PPSV23 may be not rare in this patient population.

Case Series

Case 1

A two-year old male with SCD-SS presented to the emergency department (ED) with acute onset of fever and swelling of left thigh six hours after administration of PPSV23. A physical examination revealed mild erythema and generalized edema with warmth and tenderness to palpation of left thigh and knee. Patient was febrile to 38.9°C, resolved by one dose of ibuprofen. Laboratory tests revealed a WBC count of $39.8 \times 10^9/L$ (Table 1). The patient was admitted, and treated empirically with ceftriaxone, then vancomycin for suspected cellulitis. Patient continued to improve during hospitalization, and was discharged with clindamycin after 3 days. Symptoms completely resolved at the 3-day post-discharge follow-up visit.

Case 2

A three-year old female with SCD-SS presented to ED with pain and swelling of right leg one day after administration of PPSV23. The patient was febrile to 39.3°C with a WBC count of $17.2 \times 10^9/L$ on admission (Table 1). The patient was hospitalized for two days, and received empiric ceftriaxone. She was afebrile during the entire admission, and the swelling markedly decreased after 1 day, so that she was without pain upon discharge.

Case 3

A six-year old male with SCD-SC presented to ED with left thigh pain and swelling 9 hours after PPSV23 administration. The patient was febrile to 38.7°C with a WBC count of $12.4 \times 10^9/L$ on admission (Table 1). The patient was admitted, and received penicillin and clindamycin. He was afebrile throughout the course of admission, and was discharged after 4 days when swelling completely resolved.

Case 4

An eighteen-year old female with SCD-SS presented to the clinic with severe pain and swelling of the left deltoid one day after PPSV23 vaccination. The area surrounding the injection site was mildly warm with red and edematous tenderness from mild-clavicular to upper humerus. Patient received ibuprofen for pain, and was evaluated during the office visit. The patient was not admitted to the hospital (Table 1).

Case 5

A twenty-two year old female with SCD-SS presented to ED with painful swelling of the right arm one day after PPSV 23 vaccination. The patient was afebrile with a WBC count of $13.6 \times 10^9/L$. She received hydromorphone and hydration, and was discharged home from ED (Table 1).

Discussion

PPSV23 was licensed in the United States in 1983, and it is effective against 23 different pneumococcal serotypes. It is available as a 0.5 mL dose containing 25 µg of each polysaccharide in isotonic saline solution with 0.25% phenol as a preservative (7). Since 1997, the Advisory Committee for Immunization Practices (ACIP) from CDC has recommended use of PPSV23 for patients more than 2 years who are at increased risk for pneumococcal disease (12). Pediatric patients with underlying medical conditions, such as SCD, are recommended to receive PPSV23 after PCV7 or PCV13 (1, 13).

The most common adverse events associated with PPSV23 administration are mild local reactions in adults (1, 10). In pediatric populations, the safety profile appeared similar to adults (1, 14). Previous trials studying use of 14-valent pneumococcal vaccination in children with SCD reported mild local reactions, and increased pre-immunization pneumococcal antibody titers were associated with an increase in adverse event rates after first-time immunization and after revaccination (8, 9). A recent study reported a case of severe limb swelling in a pediatric patient with SCD after re-immunization with PPSV23 (15). The authors attributed administering PPSV23 earlier than the recommended period and

repeated exposure to polysaccharide antigens as potential contributing factors. But our case series showed that the severe reactions to PPSV23 had no clear correlation with previous immunization history or waiting period between first immunization and re-vaccination (Table 1).

The allergic reactions presented in this report are most likely non-IgE-mediated reactions based on the clinical manifestations and the timing of the appearance of symptoms. The patients received pain medications such as ibuprofen, and empiric antibiotics such as ceftriaxone, vancomycin, clindamycin, or penicillin for suspected cellulitis, which is commonly prescribed to treat local allergic reactions to vaccines (16). Other medications such as corticosteroid or antihistamines are infrequently used (16). Hospitalization is rarely indicated for the injection site reaction due to vaccines in the general population (16), but three out of five patients presented here were admitted to the hospital because SCD is considered an immunocompromised condition, and local allergic reaction may trigger vaso-occlusive pain crisis. Therefore, medical interventions such as emergency room visit and/or hospitalization are warranted in this patient population.

A total of 75 PPSV23 vaccines were administered in our pediatric and adolescent sickle cell clinic during the period of 2012–2014, and thus the five cases of severe reactions reported here represented approximately 7% of total PPSV23 vaccinations. It is possible that additional severe reactions were unreported, but unlikely because this population follows up very closely with the clinical team. In the same time span, approximately 40 doses of PPSV23 vaccinations were given in our adult sickle cell clinic, and there were no reports of severe reactions to the immunizations. In the Vaccine Adverse Event Report System (VAERS) co-sponsored by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), one hundred and twenty-three serious vaccine-related adverse events involving patients with SCD have been reported, and among them 76 cases (62%) were associated with PPSV23 (Table 2), representing the most commonly reported vaccine associated with SCD. Asthma and HIV, another two eligible conditions for PPSV23 immunization before 65 yo, have only 16% adverse events related to PPSV23, whereas all other conditions have 7% cases related. The incidence of serious adverse events related to PPSV23 was significantly higher in patients with SCD ($p<0.0001$). When analyzing different age groups, fifty-six serious adverse events involving pediatric patients (<18 yo) with SCD after PPSV23 vaccination have been reported compared to only 14 cases in the older population (18–39 yo) (Table 3). Asthma has 212 (<18 yo) and 407 (18–39 yo) severe adverse reactions reported when using the same search criteria, whereas HIV has 8 (<18 yo) and 46 (18–39 yo), respectively. Eligible conditions other than SCD, asthma, or HIV have 1,155 (<18 yo) and 1,433 (18–39 yo) adverse events reported. The proportion of adverse reactions reported associated with pediatric SCD patients was significantly higher than that with adults compared to asthma/HIV or other conditions ($p<0.0001$, Table 3). One caveat with VAERS is that it is a voluntary reporting system, thus underreporting is likely to occur, which means that only a small fraction of adverse events were reported. In reality, there may be more serious adverse events associated with PPSV23. Based on the analysis of the data from our center and VAERS, it appears that severe adverse events after PPSV23 administration are much more common in the patients with SCD, and pediatric and

adolescent SCD patients tend to have significantly higher incidence associated with PPSV23 than adult patients.

PPSV23 appears to be the most commonly reported vaccine associated with adverse events in SCD (Table 2). Although there is no clear explanation for the seemingly high rates of adverse events associated with PPSV23 vaccination in SCD, especially in the pediatric patients, it may be desirable to avoid concurrent administration of other vaccines with PPSV23 so that the immune system will not be further amplified. Additionally, the timing for recommended revaccination of PPSV23 after the first dose needs to be at least 5 years after the 1st dose due to the repeated exposure to polysaccharide antigens.

Conclusion

Adverse reactions to PPSV23 vaccination are usually mild and manifest locally in general populations. In this report, we showed five cases of severe adverse reactions to PPSV23 immunization in the pediatric and adolescent patients with SCD. Analysis of data in our institution and VAERS showed significantly higher rate of severe adverse events associated with PPSV23 in the SCD patients, especially in pediatric and adolescent patients compared to the adult counterparts. PPSV23 appeared to be the most commonly reported vaccine associated with adverse events in SCD patients in VAERS database. The healthcare professionals should closely monitor the potential adverse events after PPSV23 vaccination or revaccination, adhere to the recommended time interval between PCV13 and PPSV23, and may consider avoiding simultaneous administration of other vaccines with PPSV23.

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Table 1

Five Cases of Adverse Vaccine Events

Case	Gender	Age (y)	Sickle Cell Disease Type	Baseline WBC (10 ⁹ /L)	Previous Pneumococcal Vaccine Exposure	Concurrent Vaccination	Symptoms	Interventions
1	M	2	Hgb-SS	11.0	PCV13: 1 and 2 years prior PPSV23: 6 weeks prior	meningococcal vaccine	erythema, edema, fever, and leukocytosis	Hospitalization
2	F	3	Hgb-SS	17.2	PCV13: 1 year prior	None	edema, fever, and leukocytosis	Hospitalization
3	M	6	Hgb-SC	8.9	None	None	edema, pain, and fever	Hospitalization
4	F	18	Hgb-SS	10.5	PPSV23: 5 years prior	meningococcal vaccine	erythema, edema, and pain	Office visit
5	F	22	Hgb-SS	6.5	PCV13: 4 months prior	None	erythema, edema, and pain	ED visit

Table 2

Adverse Events Related to PPSV23 and Other Vaccines.

	SCD	Asthma	HIV	All	p-value
PPSV23	76(62%)	1,231(16%)	106(16%)	23,070(7%)	<0.0001
Other vaccines	47(38%)	6,538 (84%)	538 (84%)	307,875(93%)	
Total	123	7,769	644	330,945	

Keyword “sickle” or “asthma” or “HIV” was used to search VAERS database in current illness, history, or description field. Vaccine Products field: PNEUMOCOCCAL VACCINE, POLYVALENT (PPV) or ALL. Unique results were sorted out with results containing “sickle trait” excluded. Search was conducted on Aug. 15, 2014. P-value was calculated using Chi-square test.

Table 3

Adverse Events Related to PPSV23 in Different Age Groups.

	<18 yo	18–39 yo	Ratio	p-value
SCD	56	14	4	<0.0001
asthma	212	407	0.52	
HIV	8	46	0.17	
Other	1,155	1,433	0.81	

Keyword “sickle” or “asthma” or “HIV” was used to search VAERS database in current illness, history, or description field. Vaccine Products field PNEUMOCOCCAL VACCINE, POLYVALENT (PPV). Unique results were sorted out with results containing “sickle trait” excluded. Ratio represents the incidence of adverse events in <18 yo group divided by that in 18–39 yo group. Search was conducted on Aug. 15, 2014. P-value was calculated using Chi-square test.