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Rapid Communication

Serotype Changes in Adult Invasive Pneumococcal Disease in the Vaccine Era with Special Reference to Serotype 6E

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Abstract

Background: Despite the decreased incidence of pediatric Invasive Pneumococcal Disease (IPD) due to *Streptococcus pneumoniae* vaccine serotypes with the advent of pneumococcal vaccines, pediatric IPD cases due to non-vaccine serotypes have increased. However, it remains unclear whether similar trends exist among unvaccinated adult populations. In this observational study, we investigated the clinical and microbiological characteristics of adult patients with IPD.

Methods: Medical records of adult patients with documented IPD at Teine Keijinkai Hospital in Sapporo, Japan, were reviewed between January 2015 and December 2015. Serotypes and genotypes were verified by multiplex PCR and Multi-Locus Sequence Typing (MLST).

Results: Four of seven patients with IPD had a past history of malignancy. None of the patients previously received pneumococcal vaccination. The most common IPD manifestation was pneumonia (four patients). All patients received susceptible antibiotics as an initial therapy. Multiplex PCR and MLST showed non-vaccine serotypes in six cases; one of which was serotype 6E. Two patients infected with non-vaccine serotypes died during their hospital stay.

Conclusion: These findings suggested that changes in serotypes responsible for IPD in adults were potentially affected by pneumococcal vaccination and that improving pneumococcal vaccine coverage in both pediatric and adult populations might provide clinical benefit.

Keywords: *Streptococcus pneumoniae*; Invasive pneumococcal disease; Vaccine

Abbreviations

IPD: Invasive Pneumococcal Disease; MLST: Multi-Locus Sequence Typing; PCV7: 7-Valent Pneumococcal Conjugate Vaccine; PCV13: 13-Valent Pneumococcal Conjugate Vaccine; PCVs: Pneumococcal Conjugate Vaccines; PBP: Penicillin-Binding Protein; PPSV23: 23-Valent Pneumococcal Polysaccharide Vaccine

Introduction

Vaccination strategy for pneumococcal disease is the cornerstone for preventing life-threatening Invasive Pneumococcal Disease (IPD). In Japan, similar to that observed in most countries, 7-Valent Pneumococcal Conjugate Vaccine (PCV7) was incorporated into the national routine immunization program for children in April 2013 and was later replaced by 13-Valent Pneumococcal Conjugate Vaccine (PCV13) in November 2013. PCV13 coverage rate among children is over 90% [1], which is higher than that in other countries and responsible for the drastic decrease in the incidence of IPD due to vaccine serotypes in children. However, the incidence of IPD due to non-vaccine serotypes has increased [1,2]. Although some studies suggested that a decrease in the incidence of IPD due to vaccine serotypes in adults was an indirect effect of Pneumococcal Conjugate Vaccines (PCVs), the existence of such a trend remains unclear [2,3]. Thus, we conducted an observational study on adult IPD cases at a single tertiary center in Japan to elucidate the clinical and microbiological characteristics of patients.

Materials and Methods

Medical records of adult patients >18 years with documented IPD at Teine Keijinkai Hospital, Japan, were retrospectively reviewed (January 2015-December 2015). Vitek® 2 System (bioMerieux, France) was used for bacterial identification and antibiotic susceptibility testing of all *Streptococcus pneumoniae* isolates following the Clinical and Laboratory Standards Institute guidelines [4]. *S. pneumoniae* serotypes, macrolide resistance gene profile and Penicillin-Binding Protein (PBP) genotypes were determined by multiplex PCR; sequence analysis was employed for Multi-Locus Sequence Typing (MLST) [5].

Results

Seven patients (three males) with a mean age of 54 (range, 33-84) years were diagnosed with IPD during the study period (Table 1). Four patients had a history of malignancy. None were previously vaccinated with PCV13 or 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23). Four patients had clinical manifestations of

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Table 1: Clinical and microbiological characteristics of invasive pneumococcal disease among the study cohort.

Case	Age	Sex	Diagnosis	Comorbidities	Vaccine Status	Treatment	Outcome	Serotype	pbp genotype*	Macrolide resistant gene	ST	PCG MIC (μg/mL)
1	61	Male	Lung Abscess	Malignancy	None	CFPM →VCM	Died	6C	gPISP (*pbp2x*)	*ermB*	2924	0.06
2	79	Male	Pneumonia	DM	None	ABPC	Cured	6E	gPRSP	*ermB*	90	0.12
3	84	Female	Pneumonia	Cirrhosis	None	CTRX →ABPC	Cured	23F	gPRSP	*mefA/E*	10409	1
4	38	Female	Peritonitis	Malignancy	None	CFPM →CTRX→CLDM	Died	23A	gPSSP	*ermB*	2572	0.25
5	33	Female	Iliopsoas Abscess	None	None	CTRX →LVFX	Cured	15B	gPISP (*pbp2x*)	*ermB*	199	0.12
6	54	Female	Pneumonia	Malignancy	None	CTRX	Cured	38	gPISP (*pbp2x*)	*mefA/E*	6429	0.06
7	60	Male	Tumor Infection	Malignancy	None	CFPM →LVFX CFPM →LVFX	Cured	15A	gPRSP	*ermB*	63	2

PCG: Penicillin G; ST: Sequence Type; MIC: Minimal Inhibitory Concentration; DM: Diabetes Mellitus; CFPM: Cefepime; VCM: Vancomycin; ABPC: Ampicillin; CTRX: Ceftriaxone; CLDM: Clindamycin; LVFX: Levofloxacin, PSSP: Penicillin-Susceptible Streptococcus Pneumoniae; PISP: Penicillin-Intermediate S. Pneumoniae; PRSP: Penicillin-Resistant S. Pneumoniae

*Penicillin-Binding Protein (PBP) gene genotype was presented as gPSSP (presence of three normal pbp genes: pbp1a, pbp2x, and pbp2b), gPISP (presence of one or two altered pbp genes) and gPRSP (three altered pbp genes).

pneumonia. All patients received susceptible antibiotics as an initial therapy. Except for one *S. pneumoniae* isolate, the remaining six isolates belonged to the non-PCV13 serotypes. One isolate was serotype 6E. All seven isolates carried macrolide resistance genes; six isolates exhibited PBP mutations. Two patients with IPD due to non-vaccine *S. pneumoniae* serotypes died during the course of hospitalization.

Discussion

Here IPD occurred in unvaccinated patients, including those with malignancies. The incidence of IPD due to PCV13 serotypes was 54% [1]. Here non-PCV13 serotypes caused IPD in six cases. These results were consistent with a study by Lexau, et al. who reported that PCVs had an indirect effect on the adult population [6]; PPSV23 vaccination of elderly people >65 years and immunocompromised individuals should be encouraged to facilitate coverage for non-PCV13 serotypes. IPD due to serotypes 22F, 6C, 23A and 15C are increasing since PCV introduction [1]. Here two cases with serotype 6C and 23A had poor outcomes; further supporting concerns of increased mortality risk in patients with IPD due to virulent non-vaccine serotypes despite the overall decreased the incidence. Because certain proportion of *S. pneumoniae* is known to harbor chemo-resistance genes with reduced susceptibility to cephalosporin agents, caution is advised during initial treatment with ceftriaxone, which is often used. Thus, IPD prevention by vaccination is critical.

With the advent of PCVs, the incidence of IPD due to vaccine serotypes, most notably serotype 6B was drastically decreased. *S. pneumoniae* serogroup 6 comprises four different serotypes (6A-6D). The incidence of a new *S. pneumoniae* serotype (genotype) 6E was recently reported [7]. Studies investigating the clinical and microbiological characteristics of *S. pneumoniae* serotype 6E are limited [8,9]. To the best of our knowledge, this is the first report of an IPD case due to serotype 6E in Japan. Serotype 6E cross-reacts with serotype 6B by the quellung reaction and can only be detected by sequencing of the cps locus [10]. Therefore, it remains possible that a subset of serotype 6B isolates reported previously was in fact serotype 6E. As observed here, serotype 6E isolates tend to be more resistant to antibiotics than other serogroup 6 isolates and typically carry the ST90 genotype [8,9]. Since serotype 6B included in PCV formulations can provide cross-protection against serotype 6E, the incidence of patients with IPD due to serotype 6E may decrease with PCVs [8]. Conversely, a selective expansion of serotype 6E might also occur because of its higher chemo-resistance than the other serogroup 6 types. However, based on our observations, the virulence and mortality of serotype 6E might be limited. Future studies are required for elucidating the clinical characteristics of *S. pneumoniae* serotype 6E including the mortality.

Conclusion

Findings in the current study suggested that changes in *S. pneumoniae* serotypes responsible for pneumococcal disease in adults might be affected by pediatric PCV13 vaccination. Consequently, increase in the incidence of IPD due to non-vaccine serotypes, including 6E, following PCV13 worldwide remains a concern. Improvement of pneumococcal vaccine coverage for both pediatric and adult populations might be beneficial in preventing unwanted seroconversion in IPD.

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