Journal of Rural Medicine

Original article

Comparison of the clinical features of invasive pneumococcal disease with those of pneumococcal pneumonia in adults

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Abstract

Background: Invasive pneumococcal disease (IPD) is an infectious disease where Streptococcus pneumoniae can be detected in the cerebrospinal fluid or blood.

Methods: Eight patients presented to our hospital with adult IPD. We compared with 69 cases of pneumococcal pneumonia treated in our department between 2012 and 2014. None of the patients had a history of pneumococcal vaccine administration.

Results: Hematological examination showed the platelet count was significantly lower and the serum C-reactive protein level was significantly higher in the IPD group. There was a significant difference in the use of a respirator and mortality in the IPD group. About antibiotics, Carbapenem and quinolone were used for the treatment of many patients in the IPD group. In the fatal three cases of IPD, the age of all members were 65 years or younger. Two of three had no underlying disease.

Conclusion: IPD develops without elderly people and in those without underlying disease. Also, the patients who took a sudden course may result in death. In line with previous studies that have reported the effectiveness of the pneumococcal vaccine, our study findings emphasize the need of administering vaccination for prevention of IPD in person who was younger than 65 years old.

Key words: bacteremia, pneumococcal pneumonia, Invasive pneumococcal disease (IPD), underlying disease

(J Rural Med 2022; 17(1): 29–32)

Introduction

Pneumonia is the third leading cause of death in Japan. Pneumococcal disease, as the primary cause, is assumed to account for 23–39% of cases[1]. The most severe form of pneumococcal infection, invasive pneumococcal disease (IPD), is defined as the presence of *Streptococcus pneumoniae* in the blood or cerebrospinal fluid. The fatality rate of IPD in adults has been reported to be between 10–15%[2]. Recently, Chen *et al.* conducted a systematic review and meta-analysis of the prognostic factors for mortality in adults[3]. Our study aimed to determine the clinical characteristics of IPD in adults by comparing it with pneumococcal pneumonia.

Received: July 19, 2021
Accepted: October 8, 2021
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Patients and Methods

Subjects and diagnostic criteria

We retrospectively investigated eight patients with IPD and 69 patients with pneumococcal pneumonia who presented to our hospital between 2012 and 2014. We assessed the patients' age, sex, history of smoking, severity of pneumonia (determined using the ADROP system: A, age; D, dehydration; R, respiration; O, orientation; P, pressure), underlying diseases, initial treatment, and treatment outcomes. Hematological tests included white blood cell (WBC) count, platelet count, C-reactive protein, and procalcitonin levels. Pneumococcal pneumonia was diagnosed based on the presence of pneumococcal antigens in a urine sample or the growth of pneumococcal colonies in a sputum culture. IPD was defined as an illness occurring in association with the isolation of *Streptococcus pneumoniae* from normally sterile body specimens, including blood, cerebrospinal fluid, pleural or synovial fluid, or abscess separates

or tissue specimens/swabs obtained intraoperatively, but excluding bronchoalveolar lavage.

Statistical analysis

Student's *t*-test was used to compare continuous variables (hematological tests). The χ^2 test was used to compare categorical variables between the treatment groups, including age, sex, smoking index, ADROP value, use of a respirator, frequency of change of the antimicrobial agent, and mortality. Statistical significance was set at $P<0.05$.

Results

The variables for each group are presented in Table 1. The incidence of IPD was higher in men, but the difference was not significant. The differences in patient age and smoking history were not significant. Hematological examination showed no significant difference in the WBC count, but the platelet count was significantly lower in the IPD group ($P<0.05$). Moreover, serum C-reactive protein levels were significantly higher in the IPD group ($P<0.05$). There were no significant differences between groups in the evaluation with the ADROP system, which measures the severity of pneumonia (≥3 points indicate serious illness). There was a significant difference in the use of a respirator (7% in the pneumococcal pneumonia group and 63% in the IPD group ($P<0.05$).

We examined the incidence of underlying diseases and found that 50% of the patients in both groups had respiratory disease, cardiovascular disease, or diabetes, but there was no significant difference between the groups. In the IPD group, two patients had no underlying disease (Table 2).

Carbapenem and quinolones were used to treat many patients in the IPD group. In contrast, 50% of the patients in the pneumococcal pneumonia group received ampicillin sodium/sulbactam sodium (Figure 1). The antimicrobial agent was changed at a frequency of 14.5% (10/69) in the pneumococcal pneumonia group and 75% (6/8) in the IPD group, showing a statistically significant difference ($P<0.05$, Figure 1). The average serum procalcitonin level was 46.5 ng/mL in the IPD group and 5.8 ng/mL in the pneumococcal pneumonia group (Table 1). The mortality rate in the pneumococcal pneumonia group was 13%, while that in the IPD group was 37.5%. This difference was statistically significant ($P<0.05$, Table 1).

Discussion

A protocol for IPD in Japan was previously reported by Chiba[4]. This report indicated that severe pneumonia was frequent among adults with IPD who were older than 50 years. Patients with an underlying disease had an increased risk of death and neurological sequelae. The laboratory findings in the IPD group showed a WBC count of $\leq 5.0\times10^9$ cells/L. The probability of a poor prognosis, including but not limited to adults, was reported[4] in cases with platelet levels of $\leq 1.30 \times 10^9$ cells/L.

In our study, the WBC and platelet counts were similar to those in the conventional report on IPD in adults. Serum procalcitonin levels were also significantly higher in the IPD group. This is an extremely useful marker because the procalcitonin level specifically increases only in systemic bacterial infections, according to Kushimoto[5]. According to Assicot *et al.*[6], serum procalcitonin levels increase remarkably in severe bacterial infections and decrease immediately after treatment. This remarkable increase was not observed in local bacterial or viral infections.

We examined the characteristics of IPDs in adults in our department. A systematic review and meta-analysis of IPD in adults by Chen *et al.*[3] reported a mortality rate of 20.8%. They also reported that the factors associated with mortality were age, being in nursing home, nosocomial infections, septic shock, chronic diseases, solid organ tumor, immunosuppression, and alcohol abuse. Of these factors, alcohol abuse and septic shock were detected in two of the three patients that died in the current study (Table 2). All the pa-

Table 1 Patient characteristics

	Pneumococcal pneumonia (n=69)	IPD (n=8)	*P* value
Age (years)	74 ± 2	65 ± 3	N.S
Sex (F/M)	22/47	2/6	N.S
Pack year	31 ± 5	27 ± 8	N.S
Underying disease	64/69 (93%)	6/8 (75%)	N.S
WBC (/μL)	11,943 ± 843	7,443 ± 3,760	N.S
Plt (/μL)	23.2 ± 1.6	15.2 ± 2.7	$P<0.05$
CRP (mg/dL)	16 ± 1	28 ± 4	$P<0.05$
PCT (ng/mL)	5.8 ± 1.4	46.5 ± 16.6	$P<0.05$
Pneumonia, ADROP >3	22/69 (32%)	4/8 (50%)	N.S
Intubation	5/69 (7%)	5/8 (63%)	$P<0.05$
Fatal case	9/69 (13%)	3/8 (37.5%)	$P<0.05$

tients who died required artificial respiratory support (Table 3). We administered broad-spectrum antibiotics, such as carbapenem or quinolones, as first-line treatment in the IPD group (Table 3); however, the outcomes were poor. Despite switching to a high dose of ampicillin sodium/sulbactam sodium, the case fatality rate remained high (three of eight cases, 37.5%).

Our results differed from those of the conventional re-

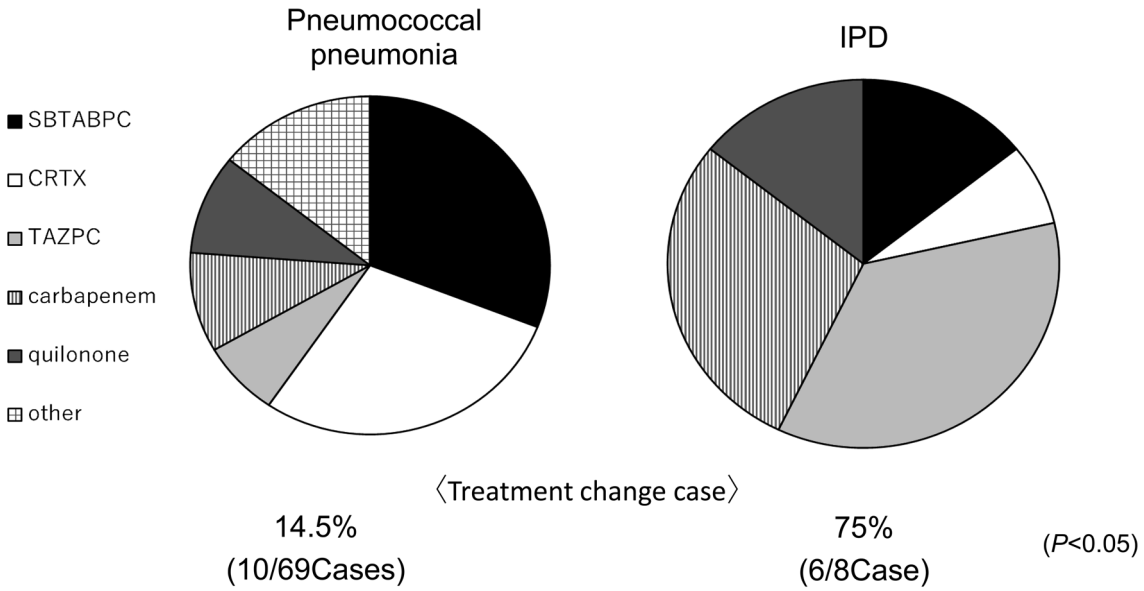

Figure 1

Table 2 Characteristics of IPD (1)

	Prognosis	Age	Sex	Smokimg status	BI	Alcohol abuse	Underlying disease	Vaccination	WBC	CRP	PLT	PCT
1	death	58	M	ex	600	yes	yes*	no	900	29.8	6.5	152.1
2	death	58	M	cu	570	no	no	no	1,200	9.91	10.9	55.9
3	death	61	M	cu	515	yes	no	no	600	26.09	3.8	55.73
4	alive	59	M	un	un	no	yes**	no	17,200	41.66	18.7	10<
5	alive	61	F	ne	0	yes	yes***	no	6,300	11.38	21.6	0.12
6	alive	69	M	ex	1,000	yes	yes[&]	no	1,600	37.72	13.6	37.96
7	alive	71	M	ex	un	no	yes[#]	no	29,700	34.21	23.6	53.14
8	alive	81	M	un	un	un	yes[$]	no	7,100	30.72	10.6	26.84

ex: experience; cu: current; un: unknown; ne: never. *: Gastric Ca., **: Rheumatoid arthritis, Hypertension, ***: Thymona, Myastheniia gravis, [&]: Ischemic heart disease, Cerebral infarcion, [#]: Chronic obstructive pulmonary disease (COPD), [$]: COPD.

Table 3 Characteristics of IPD (2)

	Age	Sex	Pneumonia	A	D	R	O	P	Severity	Intubation	Primary tretment	Regimen change	Prognosis	Hospitalization days
1	58	M	yes	0	1	1	0	1	3	yes	MEPM+CPFX	yes	death	10
2	58	M	yes	0	1	1	0	1	2	yes	MEPM+LVFX	yes	death	23
3	61	M	yes	0	1	1	0	0	2	yes	MEPM+LVFX	yes	death	20
4	59	M	yes	0	1	1	0	0	2	yes	MEPM+AZM	yes	alive	48
5	61	F	yes	0	0	1	0	0	1	no	ABPC/SBT	no	alive	32
6	69	M	yes	1	1	1	0	1	4	yes	MEPM+LVFX	no	alive	88
7	71	M	yes	1	1	1	0	0	3	no	ABPC/SBT	yes	alive	39
8	81	M	yes	1	1	1	0	0	3	no	TAZPC+VCM	yes	alive	55

port in two aspects: age at disease onset and fatal characteristics. Regarding the former, all patients were 50 years or older, and only two patients were 70 years or older (Table 3). For the latter, the three patients who died were all younger (58, 58, and 61 years old), and only one patient had a history of a solid organ tumor. That patient had a rapid course and died within one month (Table 3). In the patients who survived, the median duration of hospitalization was 48 days, which is a long duration of hospital stay (Table 3).

The 23-valent pneumococcal vaccine was recommended for inoculation in adults in March 1988. Adaptation of the sedimentation the 13 valen pneumococcal conjugate vaccine (PCV13) for patients aged ≤65 years was approved in June 2014. Periodic inoculation with the 23-valent pneumococcal vaccine for adults aged ≤65 years was recommended in October 2014[7].

There have been some reports on the effects of pneumococcal vaccines on IPD. The heptavalent pneumococcal conjugate vaccine (PCV7) was introduced in the United States in 2000[8]. An indirect effect was found in the non-vaccinated population as IPD of the serotype of the vaccine largely decreased in 2003, resulting in a decrease in transmission[9]. This study also reported that IPD in older adults by the vaccine serotype decreased by 75%.

In Japan, the introduction of periodic inoculation to promote PCV7 vaccination in children was implemented using public funding. Serotype substitution of the causative organism in adult IPD is suggested by the herd immunity effect.

Because this was a retrospective study conducted at a municipal hospital, we could not identify the pneumococcal capsule type. All cases in which the capsule type was not identified and were considered not to have been incculated by the pneumococcus vaccine. Therefore, it was difficult to evaluate the efficacy of the vaccine and the cause of death in the patients with IPD included in the current study. However, Chiba states that vaccination is required to control IPD infection[4]. Ito *et al.*[10] reported three cases of kidney transplant recipients who developed IPD. The non-inoculated patient died, while another patient had a history of inoculation with a capsular serotype not included in the vaccine. The authors concluded that the vaccine appeared to be efficacious. In our study, none of the patients had been inoculated with the pneumococcal vaccine. There is a possibility that prior vaccination in people younger than 65 years may prevent the onset of IPD.

Conclusion

IPD can develop in younger people and those without underlying diseases. In addition, patients who have a rapid course may die. In line with previous studies that have reported the effectiveness of the pneumococcal vaccine, our findings emphasize the benefit of vaccination in preventing IPD in people younger than 65 years of age.

Ethical approval: The study was approved by the ethics committee of Obihiro Kosei General Hospital, 2020-022.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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