—Case Reports—

Bacterial Meningitis Due to *Streptococcus pneumoniae* in a 7-Month-Old Girl Who Received Three Doses of 13-Valent Pneumococcal Conjugate Vaccine

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In Japan, pneumococcal vaccine has been routinely administered since 2010 to prevent invasive pneumococcal diseases such as *Streptococcus pneumoniae* meningitis. We describe a case of pneumococcal meningitis in a 7-month-old girl who had received three doses of 13-valent pneumococcal conjugate vaccine. Brain magnetic resonance imaging showed infarcts in the right frontal region, and she was treated with antibiotics, intravenous immunoglobulin, dexamethasone, and edaravone. On day 27, an enhanced brain CT scan showed improvement of abnormal findings in the frontal region, except for slight atrophy. The *S. pneumoniae* serotype was 12F, which is not included in the 13-valent pneumococcal conjugate vaccine. A future vaccine is expected to use cross-reactivity to target common antigens. (J Nippon Med Sch 2020; 87: 299–303)

Key words: bacterial meningitis, *Streptococcus pneumoniae*, serotyping, vaccine, infant

Introduction

In the past, *Streptococcus pneumoniae* and *Haemophilus influenzae* infections were the main causes of meningitis, and both can result in serious sequelae. However, the incidence of meningitis in children has decreased significantly since the introduction of the *H. influenzae* type-b (Hib) vaccine, in the 1990s, and the pneumococcal conjugate vaccine (PCV), in 2000 in the United States. The incidence of invasive pneumococcal disease (IPD) in children younger than 5 years decreased from 80 to 4.6 per 100,000 persons—a 94% decrease[1].

In Japan, the Hib vaccine was first administered in 2008, the 7-valent pneumococcal conjugate vaccine (PCV 7) was first given in 2010, and the 13-valent pneumococcal conjugate vaccine (PCV13) was first used in 2013. As a result, the incidences of *H. influenzae* meningitis and pneumococcal meningitis have significantly declined[2,3]. However, although the incidence of pneumococcal meningitis improved after introduction of these vaccines, it has not decreased further, and pneumococcal meningitis is more likely to be due to a serotype other than those contained in PCV7 and PCV13[4]. Here we report a case of pneumococcal meningitis in a 7-month-old girl who had received the PCV13 vaccine.

Case Description

A 7-month-old girl presented at a primary care clinic with fever and received a diagnosis of common cold. After returning home, she had repeated episodes of sursumvergence of about 1 minute, which were accompanied by vomiting. She was transported to our hospital by ambulance but returned home because she was energetic and had no disturbance of consciousness during an examination. However, she was later admitted to hospital because of inactivity on Day 2. Her past medical history was unremarkable, and she had received three doses of PCV13, in accordance with the standard schedule.

Vital signs at admission were body temperature, 40.0°C; heart rate, 150 beats/minute; systolic blood pressure, 70 mm Hg; and SpO_2, 100% in room air. No bulging anterior fontanel or neck stiffness was observed. The pharynx had mild redness. The findings of a heart and lung examination were normal. Initial laboratory findings (**Table 1**) showed a marked increase in white blood cell

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Table 1 Laboratory results on the day of admission showing blood levels consistent with bacterial infection; CSF abnormalities confirmed bacterial meningitis

WBC	25,800 /μL	AST	34 IU/L	PT-INR	1.38
Neut	71.5 %	ALT	19 IU/L	APTT	39.7 sec
Lymp	17.9 %	LDH	253 IU/L	Fib	612 mg/dL
RBC	447×10⁴ /μL	CK	47 U/L	D-dimer	5.4 μg/mL
Hb	11.4 g/dL	γGTP	11 U/L		
Plt	45×10⁴ /μL	BUN	10.7 mg/dL	CSF	
		Cre	0.27 mg/dL	Cell Count	2,693 /μL
Na	138 mEq/L	TP	6.3 g/dL	Protein	100 mg/dL
K	4.2 mEq/L	Alb	3.5 g/dL	Glu	54 mg/dL
Cl	104 mEq/L	CRP	8.33 mg/dL	LDH	27 IU/L
Glu	96 mg/dL	PCT	57.7 ng/mL		

count, with increased neutrophils, as well as elevated C-reactive protein and procalcitonin levels, which strongly suggested bacterial infection. However, no apparent source of infection was found. Examination of cerebrospinal fluid (CSF) showed a greatly elevated cell count, 2,693 /μL. Gram-positive cocci were present in the cerebrospinal fluid smear and blood cultures, suggesting pneumococcal meningitis, and meropenem (MEPM) and cefotaxime (CTX) were thus administered(**Fig. 1**). Bulging of the anterior fontanel began in the afternoon on the day of admission, and mannitol and dexamethasone (DEX) were added to treat increased intracranial pressure. Because of the persistent fever, intravenous immunoglobulin (IVIG) was administered on days 3 through 5. Brain MRI revealed a segmental hyperintense lesion in the right frontal lobe on diffusion-weighted images, which appeared as a diffusion-limited area on an apparent diffusion coefficient map on Day 3. (**Fig. 2A, B**)This was interpreted as a cerebral infarction caused by spread of inflammation to the meningeal arteries. Therefore, administration of edaravone—a free radical scavenger with a brain-protective effect—was started. On day 6, *S. pneumoniae* was isolated from cerebrospinal fluid and blood cultures. CSF cell counts normalized by Day 8. We confirmed normalization of elevated C-reactive protein and stopped MEPM and DEX on Day 10. On Day 27 enhanced brain CT was performed to evaluate the cerebral infarction(**Fig. 3A, B**). Slight atrophy was noted at the right frontal lobe, without enhancement, and the patient was discharged on Day 28. In Japan, all cases of IPD must be reported to a public health center, and the *S. pneumoniae* serotype was found to be 12F.

Discussion

S. pneumoniae bacteria are classified into more than 90 serotypes based on the capsule antigens[5]. To prevent IPD, a vaccine containing multiple serotype antigens has been developed. In Japan, PCV7 (containing serotypes 4, 6B, 9 V, 14, 18C, 19F, and 23F) was introduced in 2010[6], followed by PCV13 (containing serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) in 2013. Children younger than 5 years have been routinely vaccinated with PCV13 since April 2013[7]. In October 2014, the 23-valent polysaccharide pneumococcal vaccine (pneumococcal polysaccharide vaccine 23 [PPSV23]: 2, 8, 9N, 10A, 11A, 12F, 15B, excluding 6A from PCV13, and including 17F, 20, 22F, and 33F) was introduced as a routine vaccine for elderly adults[8].

The present patient developed IPD, even though she had received her first three doses of PCV13 and had no evidence of immunodeficiency. The causative pneumococci serotype was 12F, a serotype not covered by PCV13. Since routine immunization with PCV13 began, there have been reports of increased IPD incidence attributable to serotypes not covered by PCV13[4]. In a Japanese national survey conducted from 2015 through 2017, the most common pneumococcal meningitis serotype was 24 F, followed by 12F and 15A. In 2017, 12F was the most frequently isolated IPD serotype, and the increase to 24.6% (42/171) was significant[7]. In Japan, the incidence of meningitis due to *H. influenzae* infection has decreased by 97%, whereas the incidence of meningitis due to *S. pneumoniae* infection has decreased by only about 70%[3]. The trends are similar in other countries[1]. In developed countries, bacterial meningitis has a fatality rate of 5%, and the incidence of neurological sequelae is approximately 15%[9,10]. In reports from Taiwan, approximately 10% of patients with bacterial meningitis had cerebral infarction, approximately 30% of which were due to *S. pneumonia*. Unfortunately, about 80% of patients with bacterial meningitis complicated by cerebral infarction had poor outcomes[11]. Sequelae include sensorineural hearing loss, epi-

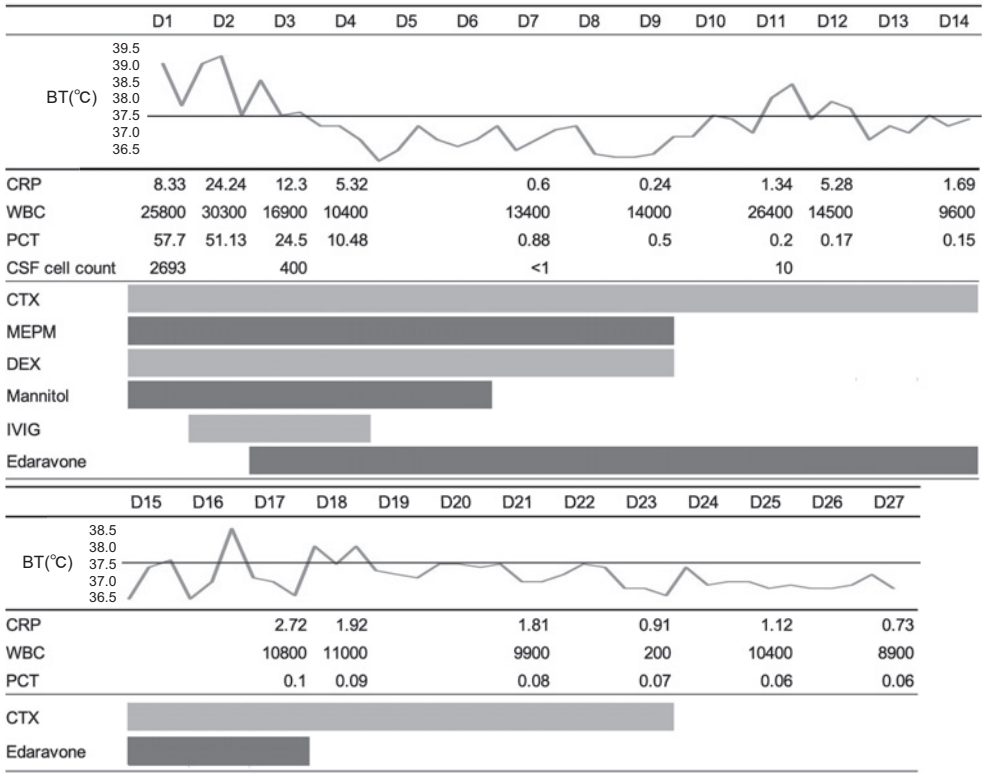

Fig. 1 The patient's clinical course.
Abbreviations: BT, body temperature; CRP, C-reactive protein; WBC, white blood cell count; PCT, procalcitonin; CTX, cefotaxime; MEPM, meropenem; DEX, dexamethasone; IVIG, intravenous immunoglobulin.

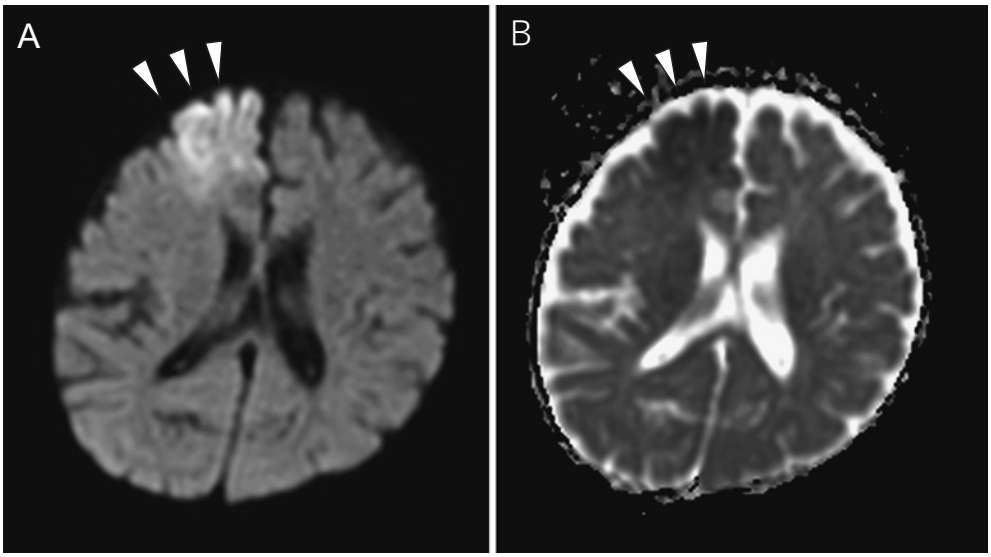

Fig. 2 Brain MRI images suggesting cerebral infarction in the right frontal lobe.
A, diffusion-weighted images; **B**, apparent diffusion coefficient map. White arrows indicate the abnormal lesion.

leptic seizure, hydrocephalus, intellectual disability, greater dysfunction, and behavioral abnormalities. Because of this high risk of serious sequelae, vaccine development is extremely important for preventing disease onset and progression. Although the current PPSV23 covers many capsular antigens, it has lower immunogenicity and a shorter duration of effect, as compared with PCV. However, PCV results in local reactions in as many as

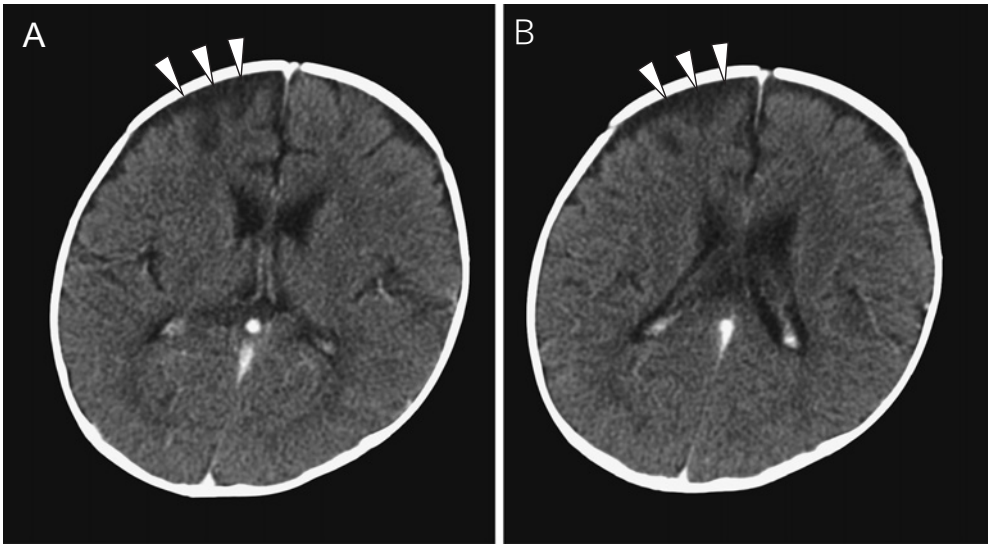

Fig. 3 Enhanced brain CT on Day 27 (**A** and **B**).
Unenhanced images showing mild atrophy in the right frontal lobe.

10% of patients[12].

In the future, common antigens such as pneumococcal surface protein A[13] and plasmin and fibronectin binding protein A will be targteted[14], thereby enabling development of a vaccine with fewer side effects and cross-reactivity to many capsular types.

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Conflict of Interest: The authors declare no conflict of interest.

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