（国内での検討：病原微生物検出情報（病原微生物検出情報：IASR より）

- 麻疹特異的 IgM 抗体は、発疹出現初期は陰性になる場合があります（偽陰性）。患者との接触状況、症状から麻疹が強く疑われるにも関わらず麻疹特異的 IgM 抗体が陰性であった場合は、日を改めて再度検査します。
- 麻疹特異的 IgM 抗体の検査と、地方衛生研究所での麻疹ウイルスの直接検出は同時並行で実施することが重要です。
- 国内で販売されている検査キット（デンカ生研（株）製）を用いて麻疹特異的 IgM 抗体が測定された場合、HHV-6/HHV-7 による突発性発疹、パルボウイルス B19 による伝染性紅斑、デング熱の急性期に弱陽性になる場合があります（偽陽性）。

④ 急性期と回復期のペア血清で麻疹特異的 IgG 抗体の陽転あるいは有意上昇の確認（急性期の血清検体を小分けして冷凍保管しておくことは、ウイルス感染症の診断すべてにおいて重要です）

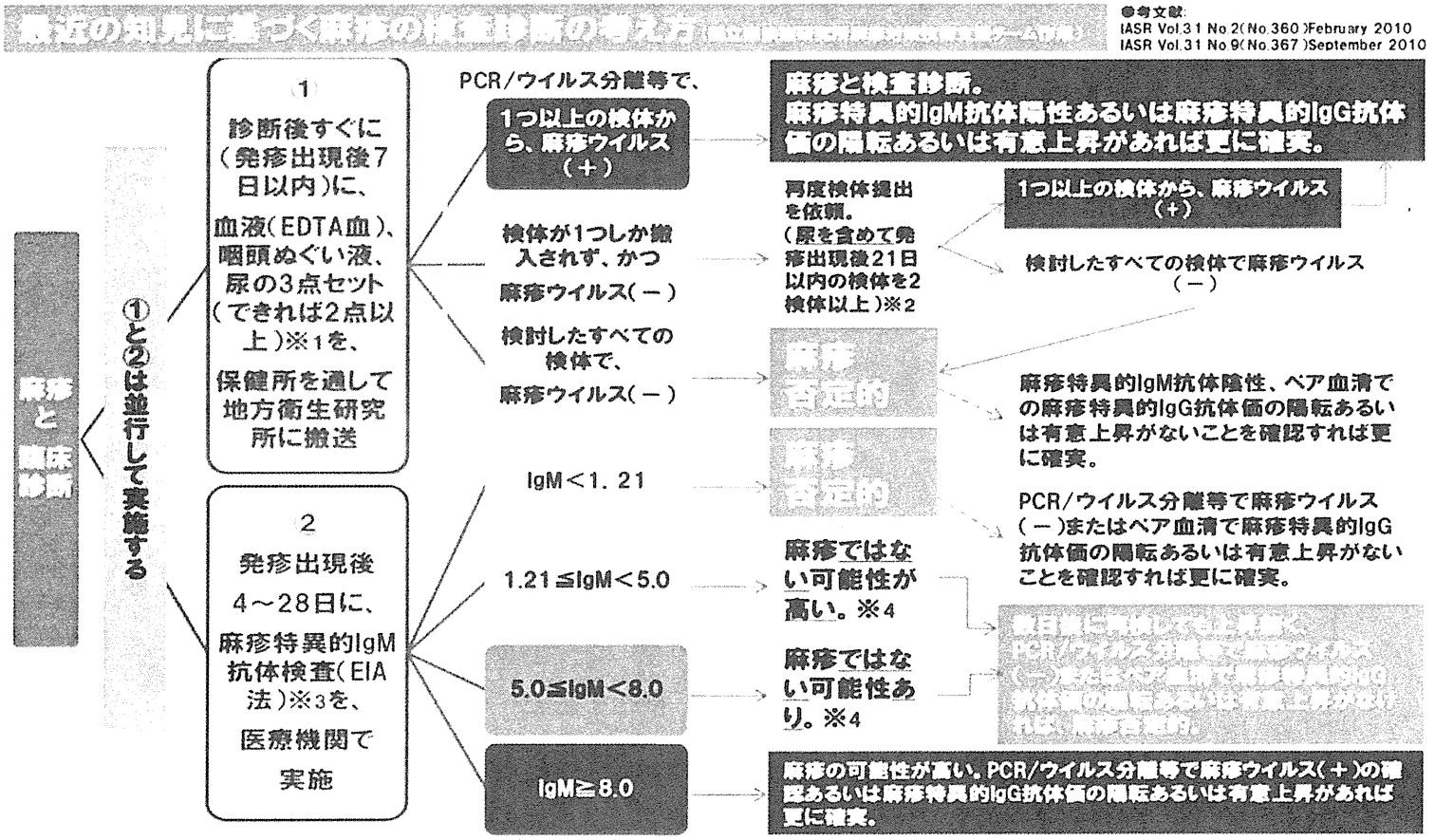
- ペア血清での抗体の検出において、有意上昇とは、被験血清を段階希釈して検査する抗体測定方法（HI 法、NT 法、PA 法、CF 法）で急性期の抗体価に比して、回復期の抗体価が4倍（2管という表現を使う場合もある。）以上の上昇を認めた場合、有意上昇と判定します。陽転は抗体価が陰性から陽性に転じることです。
- EIA 法は、＋、±、−のいずれかで EIA 価とともに結果が返却されますが、EIA 法で測定した抗体価の場合、「倍」という表現は用いません。庵原らによる厚生労働科学研究によると、EIA 価の場合、2 倍以上の上昇があれば、上記と同等に有意上昇と考えられると報告されています。

注1） 当該疾患が麻疹であるかどうかの確定診断には、CF 法や HI 法が用いられる場合がありますが、麻疹罹患後長期間経過した場合、あるいはワクチン既接種者で、被験者が麻疹に対する免疫を保有しているかどうかの検査に、CF 法あるいは HI 法は用いません。この場合は、NT 法、PA 法、EIA 法を用いて測定します。

注2） secondary vaccine failure（2次性ワクチン不全）で発症した修飾麻疹の場合、急性期から麻疹特異的 IgG 抗体価が著明高値となることが多いので、ペア血清での有意上昇の確認はできません。この場合の抗体価の判定には十分注意する必要があります。

文責：国立感染症研究所　感染症情報センター　多屋馨子

別添



※1 麻疹と臨床診断したら24時間以内を目途に保健所に麻しん発生届を提出し、それと同時に保健所を通して地方衛生研究所に検体を搬送する。取り扱う検体は自治体によって異なるため、保健所に確認する。
※2 発疹出現後8日以上経っている場合でも、麻疹ウイルス遺伝子は比較的長期に検出されるとの報告あり。麻疹に限ったことではないが、ウイルス感染症を疑った場合、その原因が明らかになるまでは、ペア血清での診断を可能にするため、急性期の血清の冷凍保管は、極めて重要である。
※3 1.21以上を「陽性」と判定している国内の検査キット（デンカ生研（社））での基準。麻疹含有ワクチン接種から8～56日の場合、麻疹特異的IgM抗体が陽性になる場合がある。地方衛生研究所に検体が搬入されていれば、検出される麻疹ウイルスの遺伝子型により、ワクチンによる反応か、麻疹の発症かを鑑別可能となる。ワクチンの場合は遺伝子型Aであり、Aが検出された場合は、麻しん発生届は削除となる。
※4 パルボウイルスB19による伝染性紅斑、HHV－6・HHV－7による突発性発疹、デング熱の急性期に麻疹IgM抗体が陽性になる場合がある。

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研究成果の刊行に関する一覧表

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ORIGINAL ARTICLE

Anti-polyribosylribitol phosphate antibody in pediatric patients with *Haemophilus influenzae* type b invasive disease

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Abstract *Haemophilus influenzae* type b conjugate vaccine was recently introduced to Japan for voluntary immunizations. *H. influenzae* type b remains a leading cause of pediatric invasive diseases in Japan. The purposes of this study were to verify the suitability of the *H. influenzae* type b conjugate vaccine for immunizing children with a history of invasive *H. influenzae* type b disease and to determine whether *H. influenzae* type b conjugate vaccine is immunogenic in these children. The subjects comprised 64 children with a history of invasive *H. influenzae* type b disease. Serum samples from 64 patients with *H. influenzae* type b systemic infection in the acute and convalescent phases were analyzed. Serum anti-polyribosylribitol phosphate antibody responses of patients <2 years old were poorer than those observed in patients ≥2 years old. Nineteen of the 64 patients received a single dose of *H. influenzae* serotype b conjugate vaccine, and then follow-up serum was taken and analyzed. Eighteen of 19 patients had ≥1 μg/mL of anti-polyribosylribitol phosphate antibody titer after the first dose of *H. influenzae* type b conjugate vaccine. *H. influenzae* type b conjugate vaccine is immunogenic in children with invasive *H. influenzae* type b disease. Children <4 years old, and particularly <2 years old, with invasive *H. influenzae* type b disease should receive subsequent immunization with a *H. influenzae* type b conjugate vaccine.

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Keywords *Haemophilus influenzae* · Vaccine · Child · Polyribosylribitol phosphate

Introduction

Haemophilus influenzae is one of the leading causes of pediatric infectious disease, and *H. influenzae* type b (Hib) strains are known to constitute a major cause of invasive infections such as meningitis, sepsis and epiglottitis in children. More than 100 countries have introduced Hib vaccines as a part of routine immunization programs. As a consequence, the prevalence of infectious diseases caused by Hib has decreased dramatically [1, 2]. Hib vaccine is regarded as highly safe, and is widely used [3]. Hib vaccine has only recently been introduced into the voluntary immunization schedule in Japan, and Hib remains a leading cause of pediatric invasive infections, particularly meningitis, in Japan [4]. Most invasive Hib disease occurs in children <5 years old, with a peak incidence between 7 and 23 months old [5]. Hib is an encapsulated bacteria, with the capsule composed of polyribosylribitol phosphate (PRP). PRP antibody is an important protective antibody against invasive Hib disease. Children <2 years old may not develop protective antibodies to PRP after episodes of invasive Hib disease [6]. Furthermore, a subpopulation of children who have recovered from invasive Hib disease may also be at risk of developing a second episode of invasive Hib disease [7]. Strategies aimed at preventing a second episode of Hib disease in children with a history of Hib disease have included immunization with Hib conjugate vaccine.

The purposes of this study were to verify the suitability of the Hib conjugate vaccine for immunizing children with a history of invasive Hib disease and to determine whether

the Hib conjugate vaccine is immunogenic in these children.

Patients and methods

Subjects comprised 64 children with a history of invasive Hib disease. The children were admitted to either the Department of Pediatrics at Chiba University Hospital or to 25 other hospitals located in various areas throughout Japan between 1997 and 2009. Diagnoses included meningitis ($n = 38$), epiglottitis ($n = 13$), sepsis ($n = 4$), cellulitis ($n = 3$), arthritis ($n = 3$), pneumonia ($n = 1$), endocarditis ($n = 1$), and osteomyelitis ($n = 1$). Five of the 64 children had a history of recurrent invasive Hib disease. These 5 children did not suffer from congenital immunodeficiency or congenital anomalies, for example cerebrospinal fluid fistula and Mondini anomaly. Serum samples from 64 children with invasive Hib disease in the acute phase and convalescent phase (2–3 weeks after admission) were analyzed. The number of serum samples in the acute phase obtained <24 h, 1–2 days, and 3–5 days after onset of symptoms were 16, 38, and 10, respectively. Nineteen of the 64 children received a single dose of Hib conjugate vaccine. Serum for analysis was taken just before vaccination and at follow-up (4–8 weeks after vaccination). Serum samples were transported to our laboratory and stored at −20°C until needed. Informed consent was obtained from the parents and permission from the health care provider of each child was obtained. All study protocols were approved by the Chiba University Institutional Review Board for Clinical Investigations. Anti-PRP antibody titers were analyzed using a Bindazyme anti-haemophilus B enzyme immunoassay kit (The Binding Site, Birmingham, UK). This is the only commercially available EIA kit for measurement of anti-PRP antibody. Schauer et al. measured anti-PRP antibody in serum samples of 386 age-stratified subjects using this EIA kit. They reported that in all unimmunized infants below 1 year of age the concentration of anti-PRP antibodies was <1.0 μg/mL [8]. To date, there has been no comparative data between standard radioantigen-binding assay and this EIA kit. Statistical analyses were performed using SPSS software (SPSS, IL, USA). Fisher's exact test was used to compare the proportion of children in the convalescent phase of infection with ≥1.0 μg/mL of anti-PRP antibody. Geometric mean titers (GMTs) were calculated for pre and post-immunization titers. Titers <0.1 μg/mL (the low cutoff of assay sensitivity) were considered equal to 0.1 μg/mL for the purposes of data analysis. Pre and post-immunization GMTs were compared using a paired t test on log-transformed data.

Results

Anti-PRP antibody titers were <0.15 μg/mL for 40 of the 64 children with invasive Hib disease in the acute phase, and <1 μg/mL for 63 of the 64 children. Anti-PRP antibody titer for one 3-year-old child with endocarditis was ≥1 μg/mL in the acute phase (1.13 μg/mL). Table 1 shows immune responses after Hib invasive disease according to age. All 5 children ≥4 years old responded with ≥1 μg/mL of anti-PRP antibody titer after invasive Hib disease. Anti-PRP antibody titers were <0.15 μg/mL for 19 of the 59 children <4 years old with invasive Hib disease in the convalescent phase, and <1 μg/mL for 42 of the 59 children.

Three of 5 children with recurrent Hib invasive diseases did not respond with anti-PRP antibody titer ≥1 μg/mL after a second episode of invasive Hib disease. Anti-PRP antibody responses of children <2 years old were poorer than those of patients ≥2 years old. Anti-PRP antibody responses of children with meningitis were poorer than those of children with epiglottitis. Nineteen of the 64 children had been given one dose of Hib conjugate vaccine.

Table 1 Immune response after Hib invasive disease according to age group

Diagnosis	0 Year	1 Year	2 Years	3 Years	4 Years	≥5 Years	Total
Meningitis	14 (1)	13 (0)	4 (0)	3 (0)	1 (1)	3 (3)	38 (5)
Epiglottitis	0	1 (1)	6 (6)	5 (4)	1 (1)	0	13 (12)
Sepsis	3 (0)	1 (0)	0	0	0	0	4 (0)
Cellulitis	1 (0)	1 (1)	1 (1)	0	0	0	3 (2)
Arthritis	0	2 (0)	1 (1)	0	0	0	3 (1)
Endocarditis	0	0	0	1 (1)	0	0	1 (1)
Pneumonia	0	0	0	1 (0)	0	0	1 (0)
Osteomyelitis	0	0	1 (1)	0	0	0	1 (1)
Total	18 (1)	18 (2)	13 (9)	10 (5)	2 (2)	3 (3)	64 (22)

Numbers in parentheses are the number of children with anti-PRP antibody ≥1.0 μg/mL in the convalescent phase

Table 2 Characteristics and antibody responses of children with Hib invasive disease

Diagnosis	Age at diagnosis (months)	Age at vaccine (months)	Pre-GMT (μg/mL)	Post-GMT (μg/mL)
Meningitis	5	10	<0.1	1.31
Meningitis[a]	5	20	0.82	8.90
Meningitis	6	8	<0.1	9.14
Meningitis	6	33	<0.1	9.42
Meningitis	7	15	<0.1	3.20
Meningitis	7	15	0.35	4.83
Meningitis	8	34	<0.1	9.50
Sepsis	10	41	0.35	0.45
Meningitis	12	14	<0.1	1.68
Meningitis	12	29	<0.1	14.0
Meningitis	13	53	<0.1	9.22
Meningitis	14	19	<0.1	8.92
Meningitis	15	24	0.27	16.05
Meningitis[a]	16	29	<0.1	8.64
Sepsis[a]	17	39	0.47	15.90
Meningitis	19	23	0.86	8.80
Meningitis	24	36	0.1	10.18
Meningitis[a]	29	30	3.82	6.15
Pneumonia	41	43	<0.1	7.36
GMT			0.198	6.20[b]

[a] Second episode of Hib invasive disease

[b] $P < 0.001$, Pre-GMT versus Post-GMT

Eighteen of the 19 children had anti-PRP antibody titer ≥1 μg/mL after administration of Hib conjugate vaccine (Table 2). No serious adverse reactions to the vaccine occurred in any child who received Hib vaccine.

Discussion

The most important factor for susceptibility to Hib is young age. This is explained by the inability of children <24 months old to produce PRP antibodies in sufficiently large amounts to protect against the disease [9, 10]. Anti-PRP antibody titers of 0.15 and 1 μg/mL have been established as the minimum levels required to achieve protection and long-term protection, respectively [11]. In our study, 19 (29.7%) of the 64 children had antibody levels <0.15 μg/mL after invasive Hib disease and 42 (65.6%) of the 64 children had <1 μg/mL antibody. In particular, 15 (41.7%) of 36 children <2 years old had <0.15 μg/mL antibody after invasive Hib disease and 33 (91.7%) of these 36 children had <1 μg/mL antibody, confirming previous observations that young children typically do not develop protective levels of antibodies to invasive Hib disease. Similarly, Walter et al. [12] reported that only 1 of 10 children ≥12 months old and none of 13 children <12 months old had significant antibody responses after recovering from invasive Hib disease. Furthermore, 9 (39.1%) of 23 children 2–4 years old with invasive Hib disease in our study did not have ≥1 μg/mL antibody and 4 (80.0%) of 5 children with recurrent invasive Hib diseases likewise did not achieve ≥1 μg/mL after a second episode of invasive Hib disease. Interestingly, the proportion of children with ≥1 μg/mL anti-PRP antibody in the convalescent phase was significantly higher for the 13 children with epiglottitis than for the 38 children with meningitis. Johnson et al. compared levels of anti-PRP antibody in a larger group of children with either epiglottitis or meningitis. According to their results, children with epiglottitis respond more vigorously in convalescence than those with meningitis, a finding that cannot be explained by age alone. They suggested that the poor convalescent-phase response was not a general feature of children with Hib meningitis, but was instead attributable to a sub-group of poor responders [13]. Host factors related to lower antibody responses with invasive Hib disease have yet to be determined and further studies are warranted.

The Hib conjugate vaccine is currently indicated for voluntary immunization of children at 2–59 months old in Japan. In this study we also measured the immunogenicity of the Hib conjugate vaccine (tetanus toxoid conjugate) in children with previous invasive Hib disease. Hib conjugate vaccine induced an immunogenic response in 18 of the 19 children tested. The mean age at vaccination was 27.1 months (range, 8–53 months). In a study similar to ours, Kaplan et al. [14] reported that 15 of 17 children responded with ≥1 μg/mL anti-PRP antibody after a single dose of Hib conjugate vaccine and all children responded

with ≥1 μg/mL anti-PRP antibody after two doses of Hib conjugate vaccine. Conversely, Walter et al. reported that only 9 of 19 children <15 months old responded with ≥1 μg/mL anti-PRP antibody after a single dose of vaccine. They suggested that a two-dose regimen should be considered for children <15 months old who are recovering from an episode of invasive Hib disease [12]. Hib conjugate vaccine is immunogenic in children with no anti-PRP response to invasive Hib disease, because children are most at risk of developing a second episode of Hib invasive disease within 6 months of the initial illness [7]. Indeed, our study included 5 children who experienced recurrent episodes of invasive Hib disease. Hib conjugate vaccine should optimally be used promptly after recovery from invasive Hib disease in any child <4 years old, particularly in those <2 years old, in Japan.

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ORIGINAL ARTICLE

Direct detection by real-time PCR of *ftsI* gene mutations affecting MICs of β-lactam agents for *Haemophilus influenzae* isolates from meningitis

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Abstract One resistance mechanism of *Haemophilus influenzae* to ampicillin involves decreased affinity of penicillin-binding protein (PBP) 3 for β-lactam antibiotics reflecting amino acid substitutions in PBP3 encoded by the *ftsI* gene. Three amino acid substitutions, Ser385Thr, Arg517His, and Asn526Lys, are especially responsible for β-lactam resistance. We constructed a new real-time polymerase chain reaction (PCR) to directly detect these substitutions in addition to 16S ribosomal RNA (rRNA), *cap*, and bla_{TEM} genes. Our real-time PCR was evaluated using 206 clinical *H. influenzae* strains isolated from pediatric patients with meningitis. Relative sensitivities and specificities of real-time PCR were 90.5–100% and 96.3–100% for all resistance classes compared with our previously reported conventional PCR. In addition, real-time PCR shortened time required from 3 h by conventional PCR to 1.5 h. When correlations between combinations of amino acid substitutions in the *ftsI* gene detected by real-time PCR and minimum inhibitory concentrations (MICs) of β-lactam antibiotics were evaluated, MIC_{90}s of ampicillin for β-lactamase-nonproducing ampicillin-intermediate-resistant strains with Asn526Lys, β-lactamase-nonproducing, ampicillin-resistant strains with Ser385Thr, and β-lactamase-nonproducing ampicillin-resistant strains with both Asn526Lys and Ser385Thr, respectively, were two, four, and eight times higher than those for sensitive strains. Similarly, MIC_{90}s of cephalosporins for these strains, respectively, were two, 16–32, and 16–32 times higher than those for sensitive strains. Thus, real-time PCR can guide antibiotic use.

Keywords *Haemophilus influenzae* · Penicillin-binding protein 3 · Rapid real-time PCR

Introduction

Haemophilus influenzae has attracted much attention world wide for reduced susceptibility to many oral and parenteral β-lactam antibiotics [1–3]. Consequently, acute otitis media (AOM) and respiratory tract infections (RTIs) are increasing. In Japan, where serotype b *H. influenzae* (Hib) vaccine had not been introduced clinically by the end of 2008, *H. influenzae* is an important pathogen causing meningitis as well as AOM and RTIs. Prevalence of β-lactamase-nonproducing ampicillin (AMP)-resistant (BLNAR) *H. influenzae* exceeded 60% among isolates from pediatric patients with Hib meningitis in 2009.

Two well-known mechanisms are implicated in resistance of *H. influenzae* to AMP. One is enzymatic hydrolysis of β-lactam agents resulting from production of TEM-1 or ROB β-lactamase [4–7]. A strain producing β-lactamase is termed β-lactamase-producing AMP-resistant (BLPAR) *H. influenzae*. The other mechanism is decreased affinity of penicillin-binding protein (PBP) 3 for β-lactam antibiotics reflecting amino acid substitutions derived from mutations in the *ftsI* gene encoding PBP3 [8]. Substitutions in PBP3 surrounding the conserved amino

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