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Meningitis Due to *Haemophilus influenzae* Type *e* Biotype 4

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Haemophilus influenzae type *e* biotype 4 was isolated from the cerebrospinal fluid of a 16-month-old child with meningitis. This is the first isolation, from a case of meningitis, of this organism that has been biotyped.

There have been very few reports of serious *Haemophilus influenzae* infections due to typable strains other than type *b* in infants and children (1). It has also been described that type *b* causes more than 95% of serious *H. influenzae* infections, especially meningitis, in young children (12). In two separate and extensive surveys of *H. influenzae* infections at Boston City Hospital (8) and in England and Wales (5), type *e* was not recorded among 79 patients with meningitis and 72 patients with bacteremia without meningitis in the first survey and 41 meningeal strains in the second. In 1976, Buck and Douglas (2) merely referred to a previous case of meningitis due to *H. influenzae* type *e* described as having been isolated from the cerebrospinal fluid (CSF; 9). Recently, a case of bacteremia reported by Cawthern et al. (4) has been suggestive of the increasing importance of *H. influenzae* type *e* biotype 4 in the etiology of human disease. The following case represents the first, to our knowledge, in which *H. influenzae* type *e* biotype 4 has been isolated from the CSF of a patient with meningitis.

Case report and results. A 16-month-old female was admitted to Sendai National Hospital with a history of 3 days of fever, nausea, and a convulsion. Upon admission, she was semicomatose with exaggerated deep tendon reflexes, as well as nuchal rigidity, having slight upper respiratory tract infection. The leukocyte count was 16,600/mm^3, with a left shift; the C-reactive protein was 6+. A lumbar puncture was performed after meningitis was suspected, and cloudy CSF was obtained. The CSF contained 368 cells per mm^3 (predominantly polymorphonuclear leukocytes). The CSF glucose was 18 mg/dl, and the protein was 200 mg/dl. *H. influenzae* was isolated from the CSF on heated blood (chocolate) agar. The organism was identified as *H. influenzae* since it showed the following typical characteristics: gram-negative, nonmotile pleomorphism; a requirement for both X and V factors; no hemolysis on 7% rabbit blood agar; and acid production from glucose. The serotype determination by the slide agglutination and capsule swelling technique with antisera *a* to *f* (Difco Laboratories) demonstrated that the isolate was type *e*. The isolate was subjected to taxonomic biotyping by the method of Kilian (6). The organism was urease and ornithine decarboxylase positive, but indole negative; consequently, by these differential characteristics of biotypes 1 to 5, it was identified as *H. influenzae* biotype 4 (Table 1). Blood cultures were negative, and cultures of throat swabs were also negative for *H. influenzae*. No viruses were isolated from the CSF. The administration of piperacillin, a new semisynthetic piperazine penicillin derivative that has greater in vitro activity than does ampicillin against clinical isolates of *H. influenzae* (7, 11), was started on day 1 of admission. A dose of piperacillin, 750 mg (74.3 mg/kg), was infused intravenously for 1 h every 6 h. The minimum inhibitory concentration of piperacillin was 0.1 μg/ml and that of ampicillin was 0.39 μg/ml by the agar plate dilution method (7). Beta-lactamase production could not be demonstrated by the method of Catlin (3). None of the repeated CSF cultures yielded growth. Piperacillin was discontinued on day 25 of administration, when CSF findings and body temperature had returned to be normal. No complications were present. Simultaneous CSF and serum levels of piperacillin were measured during treatment. The CSF levels ranged from 1.0 to 6.65 μg/ml and CSF/serum ratios varied from 0.25 to 1.9 at 2.5 to 6 h after the infusion was started on days 2 to 22 of administration. On follow-up, no neurological or developmental abnormalities were found, including electroencephalographic normalization and normal Gesell development scales after discharge. No immunodeficiencies were noticed when se-

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TABLE 1. *Abbreviated biochemical characteristics of H. influenzae biotypes*

H. influenzae biotype	Indole production	Urease activity	Ornithine decarboxylase activity
1	+	+	+
2	+	+	−
3	−	+	−
4	−	+	+
5	+	−	+

rum immunoglobulin values and delayed hypersensitivity skin reactions were considered.

Discussion. A longitudinal study on natural infections with *H. influenzae* of 104 normal children by Sell and her co-workers (10) revealed that at least one of the six serotypes was recovered from nasopharyngeal cultures of every child by the age of 5 years. On the other hand, it is well known that almost all serious *H. influenzae* infections have been caused by type *b*. An investigation by Dawson and Zinnemann (5) showed that all of the meningeal strains were type *b*, but that during the same period of observation all six types were isolated from the nasopharynx of 31 children out of 650 cases examined. The clinical significance of serotypes other than type *b* and nontypable strains is not fully understood. In Japan, the reported serotypes of *H. influenzae* responsible for meningitis have been only type *b*, this being the first case reported in this country of serious *H. influenzae* infection due to another type. Since no work on the proportion of serotypes in nasopharyngeal carriers of *H. influenzae* has been reported in Japan, we have not discussed the relationship between localized or surface infections and systemic infections. Our patient, however, provided an important clue to considering epidemiological features of *H. influenzae* infections in this country.

In a taxonomic study, subdividing *H. influenzae* into five biotypes, Kilian (6) described that biotype 4 had been the least satisfactory biotype of *H. influenzae*. This case demonstrates the clinical importance of *H. influenzae* type *e* biotype 4 as the causative organism in meningitis, in addition to bacteremia (4), although it is an extremely rare pathogen as reported in the literature.

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