Mixed Bacterial Meningitis Due to *Streptococcus pneumoniae* and *Neisseria meningitidis* in an 18-Month-Old Child

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We report an unusual case of culture-proven pneumococcal and meningococcal mixed meningitis in an 18-month-old girl. The patient responded well to antimicrobial therapy and recovered completely without sequelae. No underlying condition could be demonstrated except a rhinitis of unknown etiology 2 days before the onset of the symptoms suggesting meningitis.

CASE REPORT

An 18-month-old girl was admitted to the emergency unit of the Montpellier Teaching Hospital in November 2003 for deteriorating general condition in the previous 48 h, with fever at 40°C, asthenia, and vomiting in a context of rhinitis. She had no previous medical history. On admission, she was lethargic and algetic but had no identified hemodynamic dysfunction. Physical examination revealed clear meningeal syndrome with stiff neck and Kernig and Brudzinsky signs. No focal signs or purpura were observed. She presented with pharyngitis, bilateral serous mucosal otitis, and cervical adenopathy of less than 1 cm. Laboratory evaluation revealed a C-reactive protein value of 170.5 mg/liter and a white blood cell count of 16,500/mm³. Lumbar puncture revealed turbid cerebrospinal fluid (CSF) with a white cell count of 750 cells/mm³ with 83% polymorphonuclear leukocytes. Gram staining of CSF revealed very rare gram-positive diplococci. A latex particle agglutination test for the detection of bacterial antigen was done on the CSF with Wellcogen tests (Remel, Dartford, United Kingdom) and was negative for serogroup B *Neisseria meningitidis*, *Escherichia coli* K1, *Streptococcus pneumoniae*, *Haemophilus influenzae* b, and *N. meningitidis* serogroups A, C, Y, and W135. CSF parameters were as follows: glucose level of 2.6 mmol/liter, with serum glucose level of 16.6 mmol/liter and protein level of 1.14 g/liter. Based on these first results, and given the possibility of decreased susceptibility to penicillin of the presumed microorganism, empirical therapy, consisting of intravenous cefotaxime (300 mg/kg of body weight/day) and vancomycin (60 mg/kg/day), was started. The CSF sample was cultured on Trypticase soy agar, Trypticase soy broth, Schaedler broth with vitamin K3 and 0.2% agar (bioMérieux, Marcy l'Etoile, France), and blood-chocolate agar incubated at 37°C in a 5% CO₂ atmosphere. Detection of microorganisms by PCR was not performed on this CSF sample. After 24 h of incubation, cultures of CSF yielded mixed growth of catalase-negative, gram-positive cocci and oxidase-positive, gram-negative diplococci. The two organisms were further identified as *S. pneumoniae* and *N. meningi-*

tidis, respectively. The *S. pneumoniae* isolate was presumptively identified on the basis of the observation of an 18-mm-diameter inhibition zone around a 5-μg optochin disk (Becton Dickinson, Sparks, Mass.) after incubation in an atmosphere of increased CO₂. This identification was confirmed by using a DNA probe, the Accuprobe *Streptococcus pneumoniae* culture identification test (Gen-Probe; bioMérieux), according to the manufacturer's instructions. *S. pneumoniae* was shown to belong to serotype 9N by specific agglutinations. The identification of *N. meningitidis* was performed by API NH (bioMérieux). The *N. meningitidis* strain was further shown to belong to serogroup B and to serotype 14; its subtype specificity was P1.4. The antibiotic MICs were determined by using the E-test method (AB Biodisk, Solna, Sweden). The *N. meningitidis* strain displayed decreased susceptibility to penicillin G, of which the MIC was 0.094 μg/ml; others MICs were as follows: amoxicillin, 0.125 μg/ml; cefotaxime, 0.008 μg/ml; and rifampin, 0.016 μg/ml. In contrast, the *S. pneumoniae* strain was considered fully susceptible to β-lactam antibiotics according to MICs of penicillin G (0.032 μg/ml), amoxicillin (0.094 μg/ml), and cefotaxime (0.012 μg/ml). A second CSF puncture performed after 48 h remained negative. After 72 h of therapy with cefotaxime and vancomycin, the treatment was changed to intravenous amoxicillin (300 mg/kg/day) for 10 days. Two blood cultures remained negative. Nasal and throat swabs were not taken to investigate the carriage of the two causative microorganisms. Serodiagnosis for human immunodeficiency virus types 1 and 2, human T-cell leukemia virus types 1 and 2, and hepatitis B and C virus infections were all negative. The terminal components of the complement pathway, as well as AP50 and CH50 concentrations, were all within the normal range. Immunoglobulin G (IgG), IgA, and IgM were detected at normal concentrations of 6.43, 0.30, and 1.22 g/liter, respectively. Lymphocyte phenotyping was considered to be normal despite slightly decreased levels of CD2⁺ (66%) and CD3⁺ (63%) T lymphocytes, an increased ratio of CD4/CD8 (at 3.4), and B-lymphocyte and natural killer lymphocyte percentages of 28 and 7%, respectively. Abdominal ultrasonography showed no spleen abnormality in structure or size. Coronal and axial cranial computed tomography scans with and without contrast enhancement failed to show any CSF leak; particularly, high-resolution computed tomography of paranasal sinuses and temporal bones was negative. The patient had no history of im-

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TABLE 1. Cases of MBM involving common pathogens reported since the study of Herweg et al. in 1963 (8)

Organisms isolated	Age, sex of patient ^a	Outcome	Predisposing condition	Reference or source
<i>H. influenzae</i> and <i>S. pneumoniae</i>	26, F	Favorable	None	10
<i>H. influenzae</i> and <i>S. pneumoniae</i>	4, F	Favorable	Pansinusitis	4
<i>H. influenzae</i> and <i>N. meningitidis</i>	47, F	Favorable	None	12
<i>S. pneumoniae</i> and <i>S. pneumoniae</i>	60, M	Favorable	Otitis	3
<i>S. pneumoniae</i> and <i>N. meningitidis</i>	1.5, F	Favorable	Rhinitis	This report

^a Patient ages are reported in years. F, female; M, male.

munization with heptavalent pneumococcal conjugate vaccine or immunization against *N. meningitidis* A and C. Other routine infant vaccines had been correctly completed. The child's parents and siblings were given prophylaxis with rifampin for 48 h. Finally, the patient had an uneventful hospital stay and was discharged on day 13, after completely recovering. Given the family's poor living conditions, she was referred to a mother-and-child welfare center. Follow-up at 6 months was favorable, with no neurological and auditory sequelae.

Simultaneous mixed meningitis has been reported since the early 1900s and implies that two or more bacterial species are isolated on culture of the patient's initial CSF specimen (8). Two main categories of mixed bacterial meningitis (MBM) could be distinguished: community-acquired MBM involving common pathogens (like *S. pneumoniae*, *N. meningitidis*, *H. influenzae* and *Branhamella catarrhalis*) that are mainly observed in infants and were more frequently reported before 1950 (13) and hospital-acquired MBM involving mainly gram-negative bacilli. The latter form represents the majority of MBM cases reported since 1950 and is more frequently observed in adults (2, 6). In addition, polymicrobial meningitis involving anaerobic bacteria, mainly associated with gastrointestinal or gynecological disorders (7), and unusual MBM involving mycobacteria have been described. Predisposing factors clearly differ from one form to another, with otitis or sore throat for the first form and malignancies, shunts, immunodepression, cranial trauma or neurosurgical procedures, splenectomy, complement deficiency, and intracranial abnormalities leading to CSF leak for the second (6). In the present report, none of the previously reported predisposing factors for MBM were found. Only rhinitis was observed 2 days before the onset of meningitis, but asymptomatic rhino- and oropharyngeal carriage of *N. meningitidis* and *S. pneumoniae*, which could precede invasive disease, was not investigated. *N. meningitidis* and *S. pneumoniae* are two leading causes of bacterial meningitis all over the world. In France, more than 1,000 cases of bacterial meningitis were recorded in 1999. Among them, the more common pathogens were *S. pneumoniae* (46% of cases) and *N. meningitidis* (32%) (11). Serogroup B was shown to be the major serogroup in invasive infections due to *N. meningitidis* in France (1), and serotype 9 was the major *S. pneumoniae* serotype implicated in invasive infections in children in the south of France. Some MBM cases implicated *S. pneumoniae* or *N. meningitidis* (Table 1), but the association of these two common meningitis agents has rarely been reported for simultaneous infection of the meninges. The last case of MBM involving simultaneous culture of *S. pneumoniae*, formerly *Diplococcus*

pneumoniae, and *N. meningitidis* from a CSF sample was reported in 1963 (8). In the case of MBM, the identification of one microorganism may well jeopardize diagnosis of the second, particularly when the mixed culture includes both a gram-positive and a gram-negative bacterium. In the present case, only the gram-positive diplococcus was detected by microscopic examination of the Gram-stained CSF preparation. Misdiagnosis or ignorance of MBM may lead to inadequate therapy, reported in 67% of cases of MBM (6), and to deleterious outcomes, especially if the undetected pathogen is resistant to the antibiotics used to treat the detected one. The incidence of MBM remains to be established precisely. In 1987, Downs et al., in an extensive review, estimated that MBM represents about 1% of the total cases of bacterial meningitis (6). Few data and fewer recent data on MBM in children are available. In 1963, Herweg et al. reported a 3.75% rate of MBM in reviewing 534 cases of acute bacterial meningitis (8), suggesting that MBM is not so uncommon in children. In this series ($n = 20$), MBM was associated with poor diagnosis, as only 35% of the patients recovered completely without sequelae. Recent studies based on molecular-based detection of pathogens in CSF and blood samples suggested that mixed bacterial infections could be underestimated. Indeed, Corless et al., developing a multiplex real-time PCR for the simultaneous detection of *N. meningitidis*, *H. influenzae*, and *S. pneumoniae* to improve bacteriological diagnosis for culture-negative CSF and blood samples, showed that 3 out of 4,113 samples were PCR positive for *N. meningitidis* and *S. pneumoniae*. Among them, two cultures yielded growth of *N. meningitidis* only. These results suggested that in the case of MBM, one of the microorganisms could remain undetected by conventional laboratory methods (5). The development of multiplex molecular tools with increased sensitivity could lead to a more precise estimation of the frequency of MBM, improve case findings, and ultimately optimize therapy. However, the pathophysiology of such mixed invasive infections remains completely unknown. The role for cofactors of bacterial meningitis, such as respiratory viruses or other underlying immunosuppressive conditions leading to the invasion of subarachnoid spaces by respiratory pathogens, is highly suspected but remains to be investigated (9).

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