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Analysis of Eight Cases of Neonatal Meningitis and Sepsis Due to *Enterobacter sakazakii*

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Eight cases of neonatal meningitis due to *Enterobacter sakazakii* (formerly known as yellow-pigmented *Enterobacter cloacae*) which occurred in The Netherlands during the last 6 years were investigated retrospectively. Two patients had necrotizing enterocolitis and meningitis simultaneously. Despite treatment (in most cases with ampicillin and gentamicin), the fatality rate was 75%. Strains were much more susceptible to some of the new β-lactam antibiotics than to ampicillin. A mode of transmission other than passage through the birth canal was likely, at least for some patients. A cluster of four patient strains in one hospital had almost identical plasmid DNA profiles. However, two strains isolated from formula at the same hospital 2 days after the onset of one case had different profiles, as did the strains from patients in other hospitals.

The most common causes of bacterial meningitis during the neonatal period are *Escherichia coli* and beta-hemolytic group B streptococci (*Streptococcus agalactiae*), which together constitute 50 to 75% of the strains isolated at many medical centers. In the remaining cases, a wide spectrum of bacteria, including *Enterobacter* spp. and other members of the *Enterobacteriaceae*, have been isolated.

Enterobacter sakazakii was described in 1980 as a new member of the *Enterobacteriaceae* (3) and has been reported as a cause of neonatal meningitis (1, 3, 7, 8, 11, 20). The natural habitat of *E. sakazakii* is unknown, but it has been isolated from a number of hospital sources (3). Most of these reports describe single cases. Because pigment production, a distinguishing characteristic of *E. sakazakii*, is greatly diminished at the usual incubation temperature of 36°C, it seemed likely that a number of *E. sakazakii* isolates were not recognized as atypical *E. cloacae* in the past. Therefore, we decided to reanalyze a number of *Enterobacter* strains isolated from cerebrospinal fluid (CSF) and blood to investigate more cases of *E. sakazakii* infection.

CASE REPORTS

Patient 2. A girl, small for gestational age (39 weeks, 2,400 g), was referred for confirmation and management of a meningomyelocele situated on the lower part of the sacrum, on day 3 of life. On admission, she had a temperature of 36.6°C and a leukocyte count of 10,300/mm^3, with 13% band neutrophils in the differential count. Other findings were normal except for jaundice (total bilirubin, 9.5 mg/100 ml) and some grunting. During the next 12 h, her skin became yellow-grey and she grunted more often. Repeated examination showed a full anterior fontanel. Her arms and legs were hypotonic. A lumbar puncture yielded cloudy CSF with a leukocyte count of 37,200/mm^3, 80% of which were neutrophils. No microorganisms were seen when the CSF was Gram stained after centrifugation. Chloramphenicol treatment (50 mg/kg every 24 h) was started. *E. sakazakii* was cultured from the blood and CSF. The next day, apnoeic and bradycardiac attacks occurred. She was incubated and mechanically ventilated. A repeated lumbar puncture yielded clear xanthochromic fluid with a leukocyte count of 4,900/mm^3, 95% of which were neutrophils. No organisms were found by Gram staining or culturing. Because of the discrepancy between the CSF findings and the deteriorating condition of the patient, a ventricular tap was done. Bloody pus was obtained. Gram-negative rods were easily seen by Gram staining. *E. sakazakii* was cultured. Chloramphenicol was stopped and gentamicin was given both systemically (5 mg/kg every 24 h) and by direct administration into a lateral ventricle via a Rickham reservoir (5 mg every 24 h). Nevertheless, the condition of the patient continued to deteriorate, and she died the next day. At autopsy, the brain was very soft, swollen, and necrotic. *E. sakazakii* was cultured from the brain. An inflamed meningomyelocele was confirmed.

Patient 6. A boy (2,085 g), one of twins, was delivered by cesarian section after 38 weeks of gestation. The infants were born within 45 min after the

membranes were ruptured artificially. Both were in good condition and orally fed. Cesarian section was chosen because of the abnormal breech presentation of the patient's brother (1,970 g), which was an uneventful development. On day 5 of life, the patient became ill. His skin became grey, and he showed abdominal distention with erythema of the umbilical region. No bowel sounds could be heard. The boy grunted. The anterior fontanel was tense. Sometimes the eyes had a "setting sun" appearance. Laboratory examination revealed leukopenia (1,500/mm^3) with 10% band neutrophils and thrombocytopenia (56,000/mm^3). A radiograph of the abdomen showed free air and signs associated with ascites. The CSF was turbid and had a leukocyte count of 1,000/mm^3, most of which were neutrophils. The protein concentration was 480 mg/100 ml, the glucose concentration in CSF was 68.4 mg/100 ml, and the simultaneous blood glucose was 215.1 mg/100 ml. *E. sakazakii* was isolated from the blood and CSF. Gentamicin and chloramphenicol were started, and exchange transfusion was performed twice during the next 48 h. Despite these measures, apnoeic and bradycardiac attacks occurred during day 2 of illness, and artificial ventilation was required. A second radiograph of the abdomen showed intestinal pneumatosis intestinalis. The boy's condition deteriorated, and progressive bradycardia occurred. The boy died the next day. At autopsy, meningoencephalitis, signs of disseminated intravascular coagulation, and necrotizing enterocolitis were verified.

Patient 1. A boy (2,830 g) was born after 36 weeks of gestation. During the first postnatal examination, some grunting was noted. He reacted slowly to stimuli but was otherwise in good condition. His temperature rose to 38.2°C and twitching was noticed during day 5 of life. The leukocyte count was 5,500/mm^3, with 10% band neutrophils in the differential count. Blood and CSF mixed with blood were cultured. *E. sakazakii* was isolated from the bloody CSF only. Ampicillin and kanamycin were started. *E. sakazakii* was also isolated from a second CSF sample taken some days later. The CSF had a leukocyte count of 3,300/mm^3. The protein concentration was 223 mg/100 ml, and the glucose concentration was 1.8 mg/100 ml. As the boy's temperature rose to 39°C, ampicillin and kanamycin were stopped and gentamicin was given for 15 days. The patient's temperature declined to normal. After therapy, the leukocyte count in the CSF was 100/mm^3, and the protein concentration was 420 mg/100 ml. No *E. sakazakii* was isolated. The patient recovered.

MATERIALS AND METHODS

A total of 20 *Enterobacter* strains isolated from CSF in The Netherlands during the last 6 years were reanalyzed. Most of the strains were in the bacterial meningitis culture collection of the Laboratory of Hygiene, University of Amsterdam, to which most Dutch CSF isolates are referred. We also reanalyzed 25 *Enterobacter* strains isolated from the blood of patients (all ages) in St. Radboud Hospital during the last 2 years. Identification of all strains was redone in the Department of Medical Microbiology, St. Radboud Hospital. The strains were identified with the API 20E system and by observing DNase reactions (after 2 and 7 days of incubation at 36°C) and growth on Trypticase soy agar at 25°C for 48 h to detect yellow pigment production (3). Identification of all *E. sakazakii* strains was confirmed at the Centers for Disease Control. Antimicrobial susceptibilities were tested by the Kirby-Bauer agar disk diffusion procedure. Zone diameters were recorded. The minimal inhibitory concentrations (MIC) of some antibiotics were determined by an agar dilution technique described previously (12). The clinical data for patients in which *E. sakazakii* was identified were analyzed retrospectively. Biotyping (3) and determination of plasmid DNA (by agarose gel electrophoresis) (18) to fingerprint the strains were done at the Centers for Disease Control.

RESULTS

Five *E. sakazakii* strains were identified from among the 20 *Enterobacter* strains isolated from CSF. The other 15 *Enterobacter* strains were identified as *E. cloacae* (13), *E. agglomerans* (1), and *E. aerogenes* (1). In the course of the study, three more cases were identified: two in St. Radboud Hospital and one in the Pathologisch Laboratorium. Therefore, a total of eight cases of neonatal meningitis due to *E. sakazakii* were studied. Among the *Enterobacter* strains isolated from the blood of patients with bacteremia, no *E. sakazakii* could be identified.

The clinical profiles of the eight newborns are summarized in Table 1. There was a clear-cut geographical clustering in The Netherlands: Five of the eight newborns were born and hospitalized in the same general hospital, in which about 800 deliveries a year are performed. The other three patients were born and nursed until the day 1 of illness in three hospitals in the same city in another part of the country. There was also some clustering in time: three of the five patients in the general hospital, including a twin, became ill within 3 months, and two of the patients in other hospitals became ill within 2 months. Frequently associated with the development of *E. sakazakii* meningitis were a birth weight of 2,500 g or less (75%) and nursing in an incubator (88%). In 63% of the patients, bacteremia was demonstrated. Two patients had necrotizing enterocolitis and meningitis simultaneously. The most frequent early signs were grunting (7/8); pallor, cyanosis, and collapse (7/8); bulging fontanel (6/8); and convulsions, twitching, and hypertonia (6/8). No neck stiffness or head retraction was recorded. These early signs are similar to those of neonatal coliform meningitis (5, 21).

Although all strains were inhibited in vitro by ampicillin, gentamicin, chloramphenicol, and kanamycin, as measured by an agar disk diffusion procedure, all but two of the infants died. The MIC of the newer β-lactam antibiotics tested were extremely low, compared with the MIC of ampicillin (Table 2). Since five of the eight infants were nursed in the same hospital, envi-

TABLE 1. Clinical data for patients with *E. sakazakii* meningitis

Patient no.	Sex	Hospital	Onset		Birth wt (g)	Gestational age (wk)[a]	Complication(s)	Other medical condition(s)	Antibiotics[b]	Outcome
			Day of life	Mo/yr						
1	M	A	5	9/77	2,830	36	Incubator		Ampicillin + kanamycin (5), gentamicin (15)	Recovered (retarded)[c]
2	F	A	3	4/79	2,400	39	Meningomyelocele, incubator	Bacteremia	Chloramphenicol (3), gentamicin (1)[d]	Died
3[e]	F	A	3	4/81	1,670	32	Membranes ruptured (6d),[f] incubator		Ampicillin + gentamicin (7)	Died
4[g]	M	A	4	4/81	1,900	32	Membranes ruptured (6d), incubator		Ampicillin + gentamicin (10)	Died
5	F	A	5	7/81	2,690	Full term		Bacteremia	Ampicillin + gentamicin (1.5)	Died
6	M	B and D	5	2/78	2,085	38	Cesarian, twin, incubator	Bacteremia, necrotizing enterocolitis	Chloramphenicol + gentamicin (2)	Died
7	F	C and D	5	7/79	1,370	Premature	Cesarian, placenta previa, incubator	Bacteremia, necrotizing enterocolitis, intraventricular bleeding, hemorrhage	Ampicillin + gentamicin (4), chloramphenicol + gentamicin (1)	Died
8	F	E	9	9/79	850	30	Incubator	Bacteremia	Ampicillin (10), gentamicin (5)	Recovered (retarded)[h]

[a] Normal gestational age at birth, 40 weeks.
[b] Number in parentheses indicates day of life on which antibiotics were started.
[c] Patient had hydrocephalus and severe physical and mental retardation; he died of a malfunction of the Spitz-Holter drain after 2.5 years.
[d] Gentamicin was administered intravenously and intraventricularly.
[e] Twin of patient 4.
[f] 6d, Membranes ruptured 6 days before delivery.
[g] Twin of patient 3.
[h] Patient had hydrocephalus and died of aspiration pneumonia after 16 months.

TABLE 2. Antimicrobial susceptibilities of *E. sakazakii* strains isolated from patients 1 through 8

Antibiotic	No. of strains susceptible to MIC (mg/liter) of:									
	0.06	0.125	0.25	0.5	1	2	4	8	16	32
Ampicillin						2	5	1		
Gentamicin			3	5						
Chloramphenicol								6	1	1
Cefuroxime							4	3		1
Cefotaxime	3	3	1	1						
Moxalactam	6	1	1							

ronmental sampling was done in the pediatric department of that hospital. *E. sakazakii* was isolated several times from prepared formula. The formula powder, as well as the water used in preparing the formula, were negative by culturing. *E. sakazakii* was cultured from samples taken from a dish brush and a stirring spoon. No differences in pigment production, morphology, biochemical reactions (biogroup), and susceptibilities to 21 antibiotics could be demonstrated between the isolates from the environment and those from the CSF of all patients, except for one difference in biogroup (the isolate from patient 6 was of biogroup 2; all other isolates were of biogroup 1) (Table 3). Plasmid profiles indicated that three or four of the five isolates from the patients at the general hospital were probably the same strain. The plasmid profiles of the remaining patient and environmental isolates were different, indicating that the environmental strains did not cause the infections.

DISCUSSION

The incidence of neonatal meningitis is many times higher in newborns of low birth weight. Of the eight newborns in the present study, six had birth weights of less than 2,500 g. It may be significant that one of the two patients who survived had the highest birth weight (2,830 g). In another study, 11 of 12 babies with meningitis due to *E. cloacae* died (15). All but one were premature. Their progress in the first few days of life was normal, as was true for the *E. sakazakii* patients. The first signs of sepsis appeared suddenly between days 4 and 8 of life. After the first signs appeared, death occurred within a few hours to several days. Eight of the patients showed a distinctive form of hemorrhagic encephalitis.

Although the short incubation period is in accordance with the view that the source of the infection is the birth canal, three patients were delivered by cesarian section and thus did not have intensive contact with the birth canal, which suggests another source. When the membranes are ruptured, the clock of infection starts to tick (Shubeck), as is illustrated by the observation that in one study, 94% of the newborns were infected with herpes from maternal genitals when cesarian section was done more than 4 h after membrane rupture, but only 7% were infected when cesarian section was performed within 4 h (13). An ascending infection was unlikely in the two patients delivered by cesarian section in our study: patient 6 was born within 45 min after rupture of the membranes, and the membranes were not ruptured before case no. 7 was delivered (a diagnosis of placenta previa was made by echoscopy) (20). It should be noted that the twin of patient 6 made good progress, despite a much lower birth weight (1,200 g). It is not known if *E. sakazakii* can form part of the vaginal flora. Cervical, vaginal, and fecal samples from the mother of patients 3 and 4 were obtained and cultured 4 weeks after delivery; coliform bacilli grew, but not *E. sakazakii* (11). Patients 3 and 4 were not colonized either: *E. sakazakii* was not cultured from samples from the skin, nose, external ear, umbilicus, or anus

TABLE 3. Plasmid DNA profiles of *E. sakazakii* strains

Source	Hospital	Plasmid size(s) (Mdal)[a]
Patient 1	A	34
Patient 2	A	70, 39
Patient 3	A	70, 37
Patient 4	A	70, 37
Patient 5	A	70, 37
Patient 6	B and D	98
Patient 7	C and D	100, 24
Patient 8	E	98, 40
Prepared formula 1[b]	A	98, 40, 6.8
Prepared formula 2	A	98, 40, 6.8
Prepared formula 3	A	98, 40, 6.8
Dish brush[c]	A	61, 34

[a] Mdal, Megadalton.

[b] Formula samples 1 and 2 were cultured on day 2 of the illness of patient 5, and sample 3 was cultured 3 months later.

[c] Cultured 2 weeks after formula sample 3 was cultured.

on the day of delivery. Cultures of samples from the nose, external ear, gastric aspirate, and umbilicus were negative for *E. sakazakii* on the day of delivery for patient 6 and on the day after delivery for patient 7.

Urmenyi and White-Franklin suggested that the two patients they studied died of aerosol infection because the patients were nursed in the same incubator and postmortem cultures of the bronchi of both patients were positive (20). In another report, a positive culture from a sample taken from an inner edge of an incubator was obtained; however, this could have been secondary to the infected patient (11). *E. cloacae* was repeatedly cultured from samples taken from incubators used in the nursery involved in the *E. cloacae* meningitis outbreak that affected 12 babies (15). No new cases were detected since a technique for exhaustively cleaning the incubators was instituted in this nursery. In our study, the isolations of *E. sakazakii* from the dish brush, stirring spoon, and prepared formula suggested a mode of transmission. However, because the plasmid DNA profiles were different (Table 3), the source and mode of transmission remain unknown. The profiles of strains isolated from patients 2 through 5 might point to an epidemiological relationship (transmission or common source) or a local prevalence of the strain. The dissimilar profiles of strains from patients 1 and 6 through 8 reflect the geographical and temporal variations in isolation.

The plasmid profiles of strains from patients 2 through 5 are interesting: patients 3 through 5 were infected within 3 months of one another and thus are closely related in both time and location. Each of the three strains from these patients contained two plasmids, 70 and 37 megadaltons (Table 3). The strain from patient 2 had a similar but not identical profile. It contained a 70-megadalton plasmid, but its second plasmid was 39 megadaltons, rather than 37. This strain was isolated 2 years before the strains from patients 3 through 5 were. It is interesting to speculate on what happened. One explanation is that in April 1979, the strain existed with the 70- and 39-megadalton plasmids, but over a 2-year period, one of the plasmids evolved by losing a transposable DNA element of about 2 megadaltons (2). This explanation postulates a continuous reservoir for the evolving strain for at least 2 years or a local prevalence. The other explanation is that the cluster of cases in 1981 was caused by a different strain whose plasmid profile resembled that of the strain isolated in 1979 by chance alone. We favor the first explanation.

Patients 6 and 7 are remarkable because both developed necrotizing enterocolitis and bacteremia, as well as meningitis, at the same time. The cause of neonatal enterocolitis in unknown (9). Patient 6 showed erythema of the umbilical region, so the umbilicus could have been the port of entry, as has been suggested by Kliegman et al. (9). However, patient 7 had no omphalitis or other infection from which the bacteria could have been seeded into the bloodstream. This is in agreement with most published reports of neonatal necrotizing enterocolitis. Because oral gentamicin therapy is effective in the prevention of this disease (4), the bacterial flora of the intestinal tract may play a role in its etiology. It is interesting that a causal relationship between *E. cloacae* and an epidemic of necrotizing enterocolitis in a neonatal intensive-care unit was suggested, as pure *E. cloacae* stool cultures were obtained either before necrotizing enterocolitis developed or early in the course of the disease. The same biotype was also recovered from the blood of some patients (14). Although no feces were examined for the presence of *E. sakazakii*, it is possible that in patient 7, the origin was the intestinal tract and the bacteria reached the meninges via the bloodstream. There is only one study in which stool from an infant with *E. sakazakii* meningitis was cultured, and the culture was negative for *E. sakazakii* (7). *E. sakazakii* is typically associated with neonatal meningitis: of 13 patients with meningitis due to *E. sakazakii*, 11 were 10 days old or less. *E. sakazakii* bacteremia without meningitis seems to be uncommon: two such patients have been described (6, 10), but we identified no *E. sakazakii* isolates among *Enterobacter* strains isolated from the blood of 25 children and adults with bacteremia. No clinically significant isolations of *E. sakazakii* in materials other than CSF or blood are known to us.

Newborns with meningitis due to *E. sakazakii* have a poor prognosis. The fatality rate in the present study was 80%; previous studies have reported 40% (1, 7, 8, 20).

Taking this poor prognosis into account, one might consider treatment with one of the newer β-lactam antibiotics, such as moxalactam (latamoxef, World Health Organization-approved generic name) or cefotaxime, as a first choice instead of the usual ampicillin-gentamicin combination. The MIC of the β-lactam drugs were much lower than that of ampicillin for the strains tested (Table 2). Clinical experience in moxalactam treatment of neonatal meningitis due to coliform bacteria is encouraging (17; D. A. Olson, Clin. Res. **29**:92A, 1981; J. K. Todd, Program Abstr. Int. Congr. Chemother. 12th, Florence, Italy, abstr. no. 229, p. 95, 1981). If no clinical improvement is observed, a ventricular tap to exclude the possibility of persisting ventriculitis is indicated. When ventriculitis is demonstrated, intraventricular treatment with gentami-

cin or amikacin can be considered as a last resort (16, 19, 22). Environmental sampling (including milk and incubator), as well as culturing of samples from patients and mothers (especially stool and vagina), could be of value to elucidate the pathogenesis of this intriguing disease and, possibly, prevent further cases.

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