Medical and neurosurgical management of *Citrobacter koseri*, a rare cause of neonatal meningitis

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Introduction

*Citrobacter* are Gram-negative bacilli from the *Enterobacteriaceae* family that colonize the human gastrointestinal and urogenital tract. They produce sepsis, focal infections and less frequently affect the central nervous system, where they are responsible for 1.3% of cases of neonatal meningitis (Agrawal & Mahapatra, 2005). The most common complication is brain abscess, which is seen in 76% of *Citrobacter*-related meningitis cases, compared with 1% of neonatal meningitis cases of other aetiologies. The most common *Citrobacter* species is *Citrobacter koseri* (CK).

The cases of three patients diagnosed with neonatal meningitis with brain abscesses caused by CK between 2006 and 2010 are presented below.

Case 1

A male infant, 7 days old, was admitted after a prolonged episode of apnoea, fever, hypotonia and feeble crying. He showed irritability, generalized hypertonia and jaundice. A haemogram test and C-reactive protein levels were both normal. Proteinuria and bacteriuria were isolated in the urine sediment. The cerebrospinal fluid (CSF) was compatible with bacterial meningitis (Table 1) and Gram-negative bacteria were present. Despite treatment with ampicillin and cefotaxime, the fever persisted and focal seizures, myoclonus and apnoea pauses appeared. Anticonvulsants and mechanical ventilation were both started.

After CK was identified in the blood, urine and CSF samples, the treatment was changed to meropenem and gentamicin, with chloramphenicol added after a further 2 weeks. Ultrasonography of the brain carried out 24 h after admission identified a left-sided temporo-occipital infarction. Magnetic resonance (MR) imaging later confirmed the presence of three similar lesions associated with ventriculitis (Fig. 1a). All of the lesions evolved into abscesses, which required ultrasound-guided aspiration. After 6 weeks, the infant developed porencephaly and secondary hydrocephalus that required external ventricular drainage (EVD) (Fig. 1b) and the placement of a ventriculoperitoneal shunt (VPS). Because of the persistent presence of positive cultures in the CSF, gentamicin was administered intrathecally resulting in a clinical and biochemical improvement of the CSF. The boy was discharged after 9 weeks’ hospitalization.

Case 2

An 8-day-old boy presented with jaundice and vomiting. Low fever, jaundice and mild dehydration were confirmed on admission. The boy was diagnosed with hyperbilirubinaemia within the range for phototherapy; negative acute-phase reactants and a urine infection were also detected (Table 1). Treatment was initiated with gentamicin and ampicillin. The boy presented with fever and irritability during the first 48 h of admission and a lumbar puncture therefore was carried out. CK was identified in the CSF culture, as well as in the urine sample. The antibiotics were switched to meropenem. Brain ultrasonography showed three lesions compatible with brain abscesses (Fig. 2a). The abscesses continued to grow (Fig. 2b, c), and neurosurgical drainage was therefore performed and cefotaxime was added to the treatment for 20 days. The CSF and material drained demonstrated positive cultures for CK. The boy developed hydrocephalus (Fig. 2d) and an EVD was
placed on day 28 of his admission; the patient remained neurologically asymptomatic. The boy was discharged after 6 weeks of therapy with meropenem, although he later needed VPS placement.

**Case 3**

An 18-day-old boy presented with a temperature of 38 °C, irritability and vomiting. Blood tests showed leukopenia and a raised level of procalcitonin, and the CSF sample indicated bacterial meningitis (Table 1). Treatment was initiated with ampicillin and cefotaxime. Two days later the patient suffered generalized seizures, which were brought under control with phenobarbital. Brain ultrasonography and a subsequent MR scan showed a left-sided fronto-temporal infarction with perilesional oedema, midline deviation and collapse of the periventricular system (Fig. 3a). After isolating CK in the blood and CSF samples, antibiotic therapy was modified to meropenem and chloramphenicol. The latter was maintained for 19 days. The lesion evolved into an abscess and an EVD was placed on day 28 of admission (Fig. 3b). Because of cytochemical deterioration, amikacin was administered intravenously and puncture and drainage were repeated. The boy was discharged after 9 weeks of hospitalization and the placement of a VPS (Fig. 3c).

**Table 1.** Clinical, diagnostic and therapeutic characteristics of three patients with neonatal meningitis with brain abscesses caused by CK

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (days)/gender</td>
<td>7/male</td>
<td>8/male</td>
<td>18/male</td>
</tr>
<tr>
<td>Obstetrical history</td>
<td>Vaginal delivery at 37 weeks</td>
<td>Vaginal delivery at 38 weeks</td>
<td>Vaginal delivery at 40 weeks</td>
</tr>
<tr>
<td>Initial clinical manifestations</td>
<td>Fever, jaundice, hypotonia, central apnoea</td>
<td>Low fever, jaundice (phototherapy range), refusing feeding</td>
<td>Fever, jaundice, irritability, vomiting</td>
</tr>
<tr>
<td>CK isolation</td>
<td>Blood, CSF, abscess aspiration</td>
<td>Urine, CSF (after 3 days of admission), abscess aspiration</td>
<td>CSF, abscess aspiration</td>
</tr>
<tr>
<td>Empirical treatment</td>
<td>Ampicillin + cefotaxime</td>
<td>Ampicillin + gentamicin</td>
<td>Ampicillin + cefotaxime</td>
</tr>
<tr>
<td>Specific antibiotics</td>
<td>Meropenem + chloramphenicol, intraventricular gentamicin</td>
<td>Meropenem + cefotaxime</td>
<td>Meropenem + chloramphenicol, intraventricular amikacin</td>
</tr>
<tr>
<td>Duration treatment (weeks)</td>
<td>9</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Complications</td>
<td>Left cerebral ictus, multiple cerebral abscesses, hydrocephalus, seizures</td>
<td>Three cerebral abscesses, hydrocephalus</td>
<td>Left cerebral ictus, two cerebral abscesses, hydrocephalus, seizures</td>
</tr>
<tr>
<td>Neurosurgical treatment</td>
<td>Abscesses requiring aspiration, EVD, VPS placement</td>
<td>Abscess aspiration, EVD, VPS placement</td>
<td>Abscesses requiring aspiration, EVD, VPS placement</td>
</tr>
<tr>
<td>Neuropsychological sequelae</td>
<td>5 years: symptomatic epilepsy, language disorders, hyperactivity</td>
<td>3 months: lost to follow-up</td>
<td>8 months: axial hypotony, mild sensorineural hearing loss</td>
</tr>
</tbody>
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**Fig. 1.** Patient 1. (a) MR scan taken 10 days after admission showing three brain abscesses in the left temporoparietal, parietal and frontal regions associated with ventriculitis. (b) Hydrocephalus (day 30 after admission) before placement of an external drain. (c) Current situation: brain atrophy with severe white matter loss in the left cerebral hemisphere, basal ganglia, corpus callosum and left pyramidal tract. Areas of porencephaly are seen in the left cerebral hemisphere and right frontal encephalomalacia.
Discussion

Two transmission mechanisms for *Citrobacter* species have been described in the neonatal period: vertical and horizontal (mainly nosocomial infection). The onset of symptoms in the first days of life suggests vertical transmission, although it is often difficult to isolate the pathogen in the mother (Martínez-Lage *et al*., 2010). The risk factors and symptoms of CK infection in the nervous system during the neonatal period are similar to those of other pathogens (Agrawal & Mahapatra, 2005; Azrak *et al*., 2009). None of the patients described presented any infection risk factors in their maternal–obstetrical history.

The mechanisms that explain the predilection of CK for infecting the central nervous system have not been clarified, although bacterial resistance to phagocytosis has been observed (Azrak *et al*., 2009). In addition, a particular 32 kDa protein in the external membrane of the bacteria has been identified; this seems to have meningeal tropism, as well as a tendency to produce abscesses and ventriculitis (Martínez-Lage *et al*., 2010).

In animals, CK takes a haematogenous route of infection, spreading to the brain parenchyma and leading to meningeal infiltration and dilatation of the ventricular system. It induces vasculitis, which explains the perivascular location of abscesses, and intraventricular fibrous septa, which cause hydrocephalus (Martínez-Lage *et al*., 2010). The patients in the first two cases described developed multiple abscesses, while the third patient developed a single infarct that subsequently evolved into an abscess.

Given that 80% of children infected with CK develop brain abscesses, it is important to carry out an early neuroimaging test (cranial ultrasound or computed tomography scan) once the pathogen has been isolated. Regular tests are

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**Fig. 2.** Patient 2. (a) Ultrasonography showing brain abscesses in the frontal side. (b) MR scan showing frontal and right occipital side abscesses (day 7 day after admission). (c) Computed tomography scan showing the increased size of the abscesses and ventriculomegaly. (d) MR scan showing porencephalic cavities and perilesional oedema. Hydrocephalus can also be seen.

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**Fig. 3.** Patient 3. (a) Large haemorrhagic infarction in the left frontotemporal side. (b) An area of encephalomalacia in the left frontotemporoparietal area and right frontal abscessified cavity. A VPS can be seen in the right hemisphere. (c) Multicystic postinfectious hydrocephalus with a cystic cavity in the left hemisphere and frontal volume loss.
necessary to evaluate the evolution of the infection (Martínez-Lage et al., 2010). In our experience, both ultrasonography and MR scans are useful for tracking progress, particularly during the initial phases.

Therapy is based on prolonged antibiotics, but neurosurgery is often necessary (Agrawal & Mahapatra, 2005). Once initiated, spinal puncture should be repeated within 24–72 h and periodically to confirm sterilization of the CSF. The persistence of altered CSF biochemistry or the lack of clinical improvement requires a review of the treatment and repeated scans in order to rule out possible complications. Administration of combined antibiotics with different mechanisms of action – intracellular or extracellular (Agrawal & Mahapatra, 2005) – is recommended. Citrobacter is resistant to ampicillin in 97% of cases, but is susceptible to third-generation cephalosporins. Its susceptibility to aminoglycosides varies; it is especially susceptible to gentamicin. Intravenous chloramphenicol can be an alternative because of its good capacity for penetrating brain tissue (Doran, 1999), although its haematological toxicity can be serious. None of the patients described experienced secondary effects associated with the use of chloramphenicol. Citrobacter is also sensitive to carbapenems, piperacillin–tazobactam and trimethoprim with or without sulfamethoxazole (Doran, 1999; Martínez-Lage et al., 2010). However, the initial administration of cefotaxime and aminoglycosides is reportedly associated with disappointing results, partly explained by the poor pharmacokinetics of the aminoglycosides and the emergence of resistance to cephalosporins because of the induction of β-lactamases. The infection usually has an initial intracellular phase that does not respond effectively to any of these antibiotics (Martínez-Lage et al., 2010).

In the cases described, Columbia agar and chocolate agar were used for cultures. Antibiotic susceptibility testing was carried out in MIC/ID panel for Gram-negative. Strains isolated in the three patients were the natural strain of CK, with resistance to ampicillin. In cases 1 and 3, the patients were initially suspected to have bacterial meningitis and treatment was therefore started with ampicillin and cefotaxime. In case 2, ampicillin and gentamicin were administered because of a suspected urinary tract infection. This therapy was modified to meropenem in all three patients after the pathogen was isolated. Cefotaxime was added in the case of the second patient and chloramphenicol in the other two patients (after gentamicin in the case of the first patient).

Intrathecally administered aminoglycosides do not appear to have any advantages over isolated intravenous therapy (Agrawal & Mahapatra, 2005); in fact, an increase in mortality has been reported (Doran, 1999). However, they are used in the most serious cases and this may explain their apparently poor results (Shah et al., 2004). Intraventricularly administered gentamicin and amikacin, respectively, were added to the treatment for the patients described in cases 1 and 3 because of cytochemical deterioration in the CSF, despite prolonged intravenous treatment.

The high morbidity and mortality rates associated with bacterial meningitis mean that a long-lasting antibiotic regimen is required (3–8 weeks) (Agrawal & Mahapatra, 2005; Doran, 1999). The patients described in cases 1 and 3 received treatment for 9 weeks, while the patient described in case 2 received treatment for 6 weeks. In addition, all three patients needed abscess puncture and drainage; the third patient underwent this procedure on several occasions.

Neurosurgical treatment is recommended when the infection cannot be brought under control satisfactorily, abscesses exceed 2.5 cm or cranial hypertension is present. Abscess drainage can help to confirm the diagnosis, and reduces the mass effect and bacteriological load and improves the efficacy of systemic treatment (Doran, 1999).

Multilocus hydrocephalus is a frequent complication that requires the use of complex drainage techniques; intraventricular urokinase (Azrak et al., 2009) can also be used. EVD and VPS were necessary in the three patients described here, bilateral in the case of the third patient.

The mortality rate for a central nervous system (CNS) infection with CK is 30%. Of those who survive, 80% of individuals present with serious neurological damage requiring long-term monitoring (Doran, 1999). The patient described in the first case is currently 5 years old and has partial symptomatic epilepsy, language and psychomotor development delay, attention deficit and hyperactivity disorder and decreased visual acuity. He has been hospitalized on numerous occasions with VPS complications. It was not possible to keep track of the second patient’s progress, although he did not present any symptoms at the age of 3 months. The third patient is currently 42 months old. He underwent multiple septostomy at 11 months as a result of growing hydrocephalus (Fig. 3). He exhibits developmental delay, symptomatic epilepsy, right hemiparesis and alterations in acoustic evoked potentials.

References


