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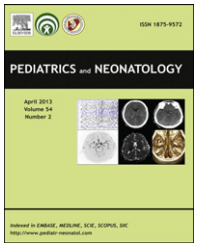

CASE REPORT

Citrobacter freundii Brain Abscess in a Preterm Infant: A Case Report and Literature Review

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Intracranial abscesses are serious conditions but uncommon in preterm neonates. *Citrobacter* species are an uncommon cause of bacterial meningitis in neonates, but are associated with brain abscesses in a majority of cases. We report a preterm infant who developed *Citrobacter freundii* meningitis with brain abscess, who was successfully treated with antibiotics and surgical drainage. The infant had normal neurological outcome at follow-up. We report this case to highlight the importance of serial neuroimaging in the diagnosis of cerebral abscess in infants with *Citrobacter* meningitis.

1. Introduction

Citrobacter species are facultative anaerobic Gram-negative bacteria found infrequently as normal inhabitants of the intestinal tract of humans. *Citrobacter* infection is uncommon among neonates but is often associated with meningitis and intracranial abscesses. Meningitis caused by *Citrobacter* in infants was first reported in 1960.[1] *Citrobacter* species account for about 4% of all Gram-negative meningitis cases in infants.[2] Unlike other Gram-negative organisms causing meningitis, *Citrobacter* species have a propensity for invading the central nervous system, causing brain abscess in 75% of patients with meningitis, and resulting in high mortality (~30%) and morbidity.[3,4] We report a preterm female neonate who developed *Citrobacter freundii* meningitis and brain abscess who was successfully treated with antibiotics and surgical drainage. We also review the literature and highlight the importance of serial neuroimaging in infants with *Citrobacter* meningitis.

2. Case Report

A female neonate was born at 27 weeks of gestation and weighed 1230 g. Apart from preterm labor, the mother had no symptoms or signs of infection. The infant's initial clinical course was complicated by respiratory distress

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syndrome treated with surfactant, jaundice, apnea, and a small patent ductus arteriosus. She received ampicillin and gentamicin for 7 days for suspected sepsis. Blood and cerebrospinal fluid (CSF) cultures were negative. A head ultrasound done at 7 days of life showed a small left germinal matrix hemorrhage. A sepsis workup was done during the second week of life, and the patient was treated with 48 hours of antibiotics. Blood culture was again negative, and CSF analysis was normal. By the third week of life, the patient was on full feeds and required oxygen via nasal prongs.

On Day 31, she was noted to be tachycardic and was having an increasing number of apneas that required intubation and ventilation. Full sepsis evaluation was performed, and treatment with cloxacillin and gentamicin was initiated. CSF analysis showed 681 white blood cells/L with 54% neutrophils, glucose $<$0.5 mmol/L, and protein 5.74 g/L. CSF culture later grew *Citrobacter freundii* sensitive to gentamicin, meropenem, ciprofloxacin and trimethoprim—sulfamethoxazole, but resistant to ampicillin. No organism was isolated from blood cultures. On Day 34, an ultrasound scan of the brain showed diffuse extensive areas of increased echogenicity within the deep and superficial white matter of the posterior occipito-parietal region in the right hemisphere, without any midline shift. Magnetic resonance imaging (MRI) of the brain revealed a right occipito-parietal brain abscess measuring 3.5×3.2 cm (Figure 1A and B) and ventriculitis without midline shift. An electroencephalogram showed seizure activity, which was treated with phenobarbitone. Antibiotics were changed to meropenem and gentamicin, given for 1 week, followed by 5 weeks of meropenem and ciprofloxacin. Serial weekly cranial ultrasound scans were performed to assess the extent of the abscess, along with brain MRI. Over the subsequent 2 weeks, brain MRI showed an increase in the size of the abscess, with midline shift to the left (Figure 1C), right uncal herniation, and a dilated right temporal horn suggesting entrapment (Figure 1D). The abscess was surgically drained, and subsequently diminished in size before disappearing. Culture of the surgically drained abscess fluid was sterile. A follow-up brain MRI scan obtained prior to discharge showed right-sided cortical thinning and atrophy with temporoparietal gliosis and *ex vacuo* dilatation of the temporal horn (Figure 2A and B). The infant was discharged home at 41 weeks' corrected age. At follow-up, she had normal clinical neurologic examination along with normal ophthalmology and hearing evaluations.

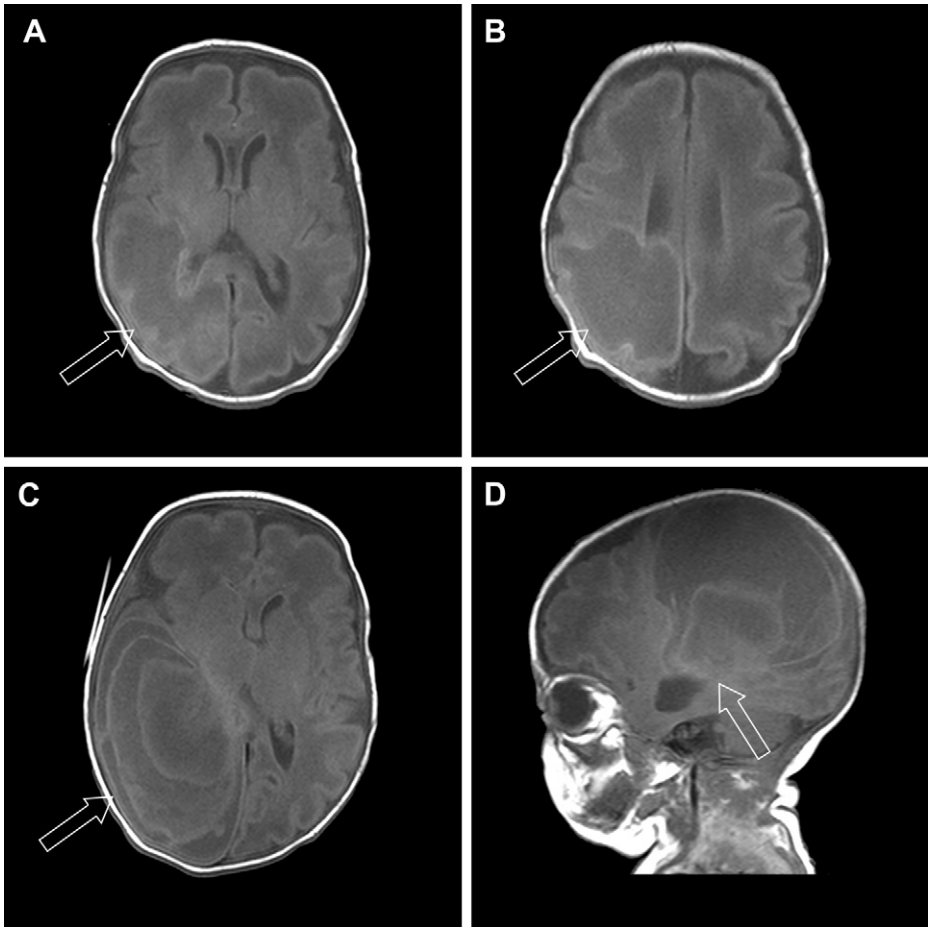

Figure 1 Preoperative magnetic resonance imaging of the brain showing: (A and B) right occipito-parietal brain abscess without midline shift; (C) increase in the size of the abscess with midline shift to the left; (D) right uncal herniation and a dilated right temporal horn suggesting entrapment.

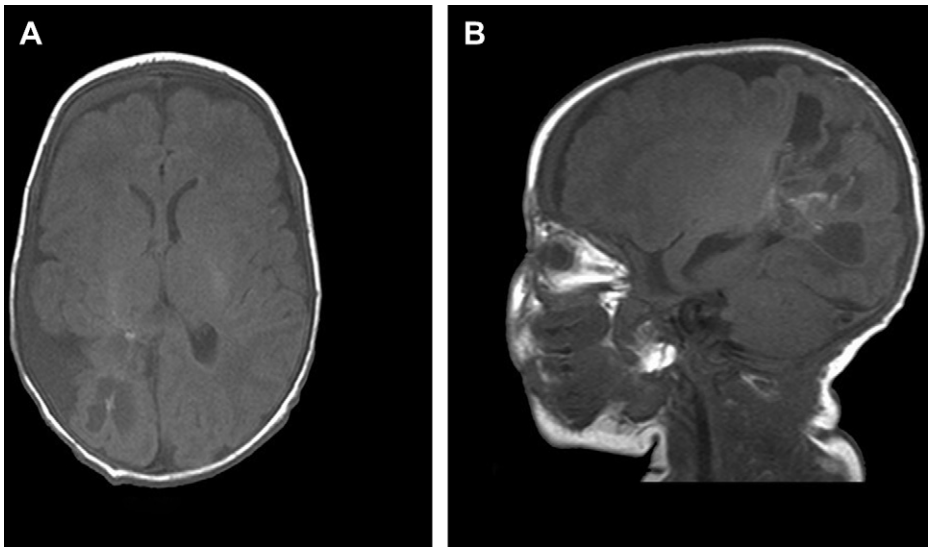

Figure 2 Postoperative magnetic resonance imaging of the brain showing (A) right-sided cortical thinning and atrophy with temporo-parietal gliosis and (B) *ex vacuo* dilatation of the temporal horn.

3. Discussion

Citrobacter species are facultative anaerobic Gram-negative bacilli of the family *Enterobacteriaceae* that infrequently cause neonatal infections. Infection in the neonatal period predominantly involves the central nervous system (CNS).[1] *Citrobacter koseri* (formerly *Citrobacter diversus*) is the most common (>90%) species, followed by *Citrobacter freundii*, accounting for about 6.4% of *Citrobacter* meningitis.[3,4] Unlike other Gram-negative bacterial meningitis, *Citrobacter* meningitis is often associated with brain abscess (in 75% of affected children). The unusual predilection for CNS invasion and brain abscess formation in neonates has not been fully explained. Studies in infant rats have shown that the infection is hematogenous in origin. The CNS involvement by *Citrobacter diversus* begins with bacteremia and leptomeningitis, followed by ventriculitis, disruption of ventricular ependymal lining, and direct extension of the infection into adjacent brain tissue.[5] *Citrobacter freundii* can invade and replicate in human brain microvascular endothelial cells.[6] An outer membrane protein in *Citrobacter* species may also act as a neurovirulence factor, producing ventriculitis and brain abscess in the infant.[7]

Both vertical transmission from the mother and horizontal transmission as nosocomial infection have been described.[3,4] Mother-to-child transmission is suspected when the onset of symptoms is early, and proven maternal infection or colonization is corroborative. Nosocomial infections occur later and are more likely to result in brain abscesses. Outbreaks in neonatal intensive care units (NICUs) have been linked to colonized hospital personnel and contaminated infant formula.[8] Recently, Etuwewe et al reported brain abscess caused by *Citrobacter koseri* in dizygotic twins, one of whom was asymptomatic, highlighting the increased risk of infection in the asymptomatic twin of an affected infant.[9] None of the infants admitted to the NICU during this time had similar infections.

Given the high incidence of abscess formation, brain imaging should be performed in all infants with proven *Citrobacter* meningitis. Ultrasound of the brain may be useful as a bedside screening tool, especially in clinically unstable infants. This can be followed by MRI (or computed tomography (CT) where MRI is not available or feasible). Serial imaging, as in the index case, is useful to determine progression of the disease and to assess response to therapy. Early and effective antibiotic therapy is important, but many cases also require surgical intervention. Third-generation cephalosporins, imipenem, chloramphenicol, trimethoprim—sulfamethoxazole and gentamicin are all effective against *Citrobacter species*.[1] Recently, it has been suggested that combination of ciprofloxacin and meropenem is the most appropriate therapy for *Citrobacter* brain infection, because of good penetration into the CNS and neutrophils, low toxicity, and favorable sensitivity data.[10] However, the use of quinolones should be restricted in neonates and young children because of the increased risk of arthropathy in weight-bearing joints.[11] The duration of antibiotic therapy is typically for a minimum of 21 days (or 14 days after negative cultures) for meningitis and for 4—6 weeks in brain abscess.[4]

Neurosurgical consultation for surgical aspiration or drainage of the abscess is recommended. The goals of abscess aspiration include removal of the mass effect, and reduction of the bacterial load, thereby improving the local environment for systemic antibiotics to have their effect. Aspiration may not be feasible in infants with multiple or inaccessible abscesses. There have been cases which are successfully managed with antibiotics alone.[12,13] There is no evidence that intrathecal administration or intra-abscess instillation of antibiotics improves the outcome.[4] Because of the propensity to form brain abscesses, about 30% of infants with *Citrobacter* meningitis die during the course of illness and nearly two-thirds of survivors are neurologically abnormal.[4]

4. Conclusion

Citrobacter meningitis in the neonate is an uncommon but devastating illness, as a result of the high incidence of brain abscess formation. Serial neuroimaging (ultrasound/MRI/CT scanning) of the head should be performed in any patient with proven *Citrobacter* meningitis. Early diagnosis and prompt treatment with antibiotics and surgical drainage may improve the outcome. All surviving infants should be followed for neurodevelopmental assessments.

References

1. Harris D, Cone Jr TE. *Escherichia freundii* meningitis: report of two cases. *J Pediatr* 1960;**56**:774—7.
2. McCracken Jr GH, Mize SG. A controlled study of intrathecal antibiotic therapy in gram-negative enteric meningitis of infancy: Report of the Neonatal Meningitis Cooperative Study Group. *J Pediatr* 1976;**89**:66—72.
3. Graham DR, Band JD. *Citrobacter diversus* brain abscess and meningitis in neonates. *J Am Med Assoc* 1981;**245**:1923—5.
4. Doran TI. The role of *Citrobacter* in clinical disease of children: review. *Clin Infect Dis* 1999;**28**:384—94.
5. Kline MW, Kaplan SL, Hawkins EP, Mason Jr EO. Pathogenesis of brain abscess formation in an infant rat model of *Citrobacter diversus* bacteremia and meningitis. *J Infect Dis* 1988;**157**: 106—12.
6. Badger JL, Stins MF, Kim KS. *Citrobacter freundii* invades and replicates in human brain microvascular endothelial cells. *Infect Immun* 1999;**67**:4208—15.
7. Li J, Musser JM, Beltran P, Kline MW, Selander RK. Genotypic heterogeneity of strains of *Citrobacter diversus* expressing a 32-kilodalton outer membrane protein associated with neonatal meningitis. *J Clin Microbiol* 1990;**28**:1760—5.
8. Thurm V, Gericke B. Identification of infant food as a vehicle in a nosocomial outbreak of Citrobacter freundii: epidemiological subtyping by allozyme, whole-cell protein and antibiotic resistance. *J Appl Bacteriol* 1994;**76**:553—8.
9. Etuwewe O, Kulshrestha R, Sangra M, Riordan A. Brain abscesses due to *Citrobacter koseri* in a pair of twins. *Pediatr Infect Dis J* 2009;**28**:1035.
10. McPherson C, Gal P, Ransom JL. Treatment of *Citrobacter koseri* infection with ciprofloxacin and cefotaxime in a preterm infant. *Ann Pharmacother* 2008;**42**:1134—8.
11. Adefurin A, Sammons H, Jacqz-Aigrain E, Choonara I. Ciprofloxacin safety in paediatrics: a systematic review. *Arch Dis Child* 2011;**96**:874—80.
12. Levy RL, Saunders RL. *Citrobacter* meningitis and cerebral abscess in early infancy: cure by moxalactam. *Neurology* 1981; **31**:1575—7.
13. Marcus MG, Atluru VL, Epstein NE, Leggiadro RJ. Conservative management of *Citrobacter diversus* meningitis with brain abscess. *N Y State J Med* 1984;**84**:252—4.