Neonatal Meningitis and Subdural Empyema Caused by an Unusual Pathogen

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Abstract: We report a case of neonatal meningitis with subdural empyema, caused by *Ureaplasma parvum.* In this case, diagnosis was made by genus-specific polymerase chain reaction, after regularly used diagnostic techniques failed. This unusual pathogen should be considered in cases that do not respond to therapy and/or where cultures for typical pathogens in neonatal sepsis and meningitis remain negative.

Key Words: Ureaplasma, meningitis, empyema, neonate

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Central nervous system (CNS) infections in newborns are an important cause of morbidity and mortality. *Ureaplasma* species are unusual causative pathogens but are possibly underdiagnosed because standard diagnostic methods to detect typical pathogens in neonatal meningitis do not reveal *Ureaplasma* spp.[1] We report a case of neonatal meningitis with subdural empyema caused by *Ureaplasma parvum* in which regular diagnostic methods failed and an additional genus-specific *Ureaplasma* polymerase chain reaction (PCR) revealed the diagnosis.

CASE REPORT

A 6-days-old male infant was seen at the emergency department with increasing irritability and temperature between 37.8°C and 38.6°C over the last 2 days. Pregnancy had been uneventful. He was born full term, and no maternal risk factors for infection had been present. Laboratory tests showed a slightly elevated C-reactive protein (6 mg/L) and white blood cell count (WBC) (19.2×10^9/L; absolute neutrophil count 9.2×10^9/L). The WBC in cerebrospinal fluid (CSF) was markedly elevated (901×10^6/L; 567×10^6/L mononuclear cells). Intravenous empiric treatment for meningitis with cefotaxime, amoxicillin and aciclovir was initiated. Regular diagnostic methods using Gram stained smears, cultures and PCR of blood, urine and nasopharyngeal swab revealed no common pathogens; CSF tested by culture and by genus-specific PCR for *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, herpes simplex virus, varicella zoster virus, enterovirus, parechovirus and *Mycobacterium tuberculosis* complex, were all negative. Aciclovir was discontinued after viral PCR results came back negative. Clinically, the infant remained slightly agitated with a temperature between 37.1°C and 38.3°C, while C-reactive protein increased to 26 mg/L. After 4 days of antibiotic treatment, WBC in CSF decreased to 498×10^6/L and repeated Gram stain and CSF cultures remained negative, as was maternal serology for HIV, syphilis, toxoplasmosis and lymphocytic choriomeningitis virus. Cranial ultrasound showed no abnormalities. After 14 days of treatment, antibiotics were discontinued. However, several hours later, the infant developed seizures and was treated with phenobarbital and levetiracetam. CSF collected at that moment showed a marked increase in WBC (1387×10^6/L). Because of the recurrence of symptoms, treatment with meropenem and erythromycin was started, considering multidrug-resistant Gram-negative rods and atypical pathogens like mycoplasmas and ureaplasmas. Cultures of CSF again remained negative. CSF cultures were incubated for 5 days on blood agar plates, chocolate agar plates with polyvitex, Tryptone Soya Broth plus factor X & V and thioglycolate medium with resazurin. No specialized culture techniques were available at our lab to culture *Ureaplasma* spp. In search for a causative agent, a genus-specific Ureaplasma PCR was performed (real time PCR detection kit Venorr GeN-qEP of Minerva Biolabs and subsequently with an in-house multiplex PCR to distinguish between species) which showed *Ureaplasma parvum*. Cranial ultrasound revealed mild ventricular dilatation and echogenic ventricular lining suggesting ventriculitis. Consecutive MRIs displayed subdural collections with contrast enhancement suggesting empyema (Fig. 1). Neurosurgical aspiration of one of the subdural collections showed hemoserous fluid. Although *Ureaplasma parvum* could not be detected in the aspirated fluid using PCR, the pathogen was considered as the causative agent because in retrospect also the CSF obtained at admission proved to be positive using the genus-specific Ureaplasma PCR. Intravenous erythromycin was continued and ciprofloxacin was added because of poor CSF penetration of erythromycin. Meropenem was discontinued. The child improved clinically and a normalization of CSF WBC was seen. Treatment was continued until CSF PCR was negative for 3 consecutive weeks, hence for a total of 6 weeks. During the last week of treatment, medication was given orally (Fig. 2). At discontinuation of treatment, MRI demonstrated resolution of subdural collections, normal brain development and no parenchymal abnormalities. The infant has achieved a normal age-related development during neonatal follow-up at the age of 30 months. Since *Ureaplasma parvum* meningitis with subdural empyema was considered an unusual pathogen and an unusually severe complication, immunologic screening was done. This revealed no abnormalities.

DISCUSSION

In this case report, we present a newborn infant with meningitis and subdural empyema caused by an unusual pathogen: *Ureaplasma parvum.* Most antibiotics commonly used for neonatal meningitis have proven to be ineffective in case of an ureaplasmal

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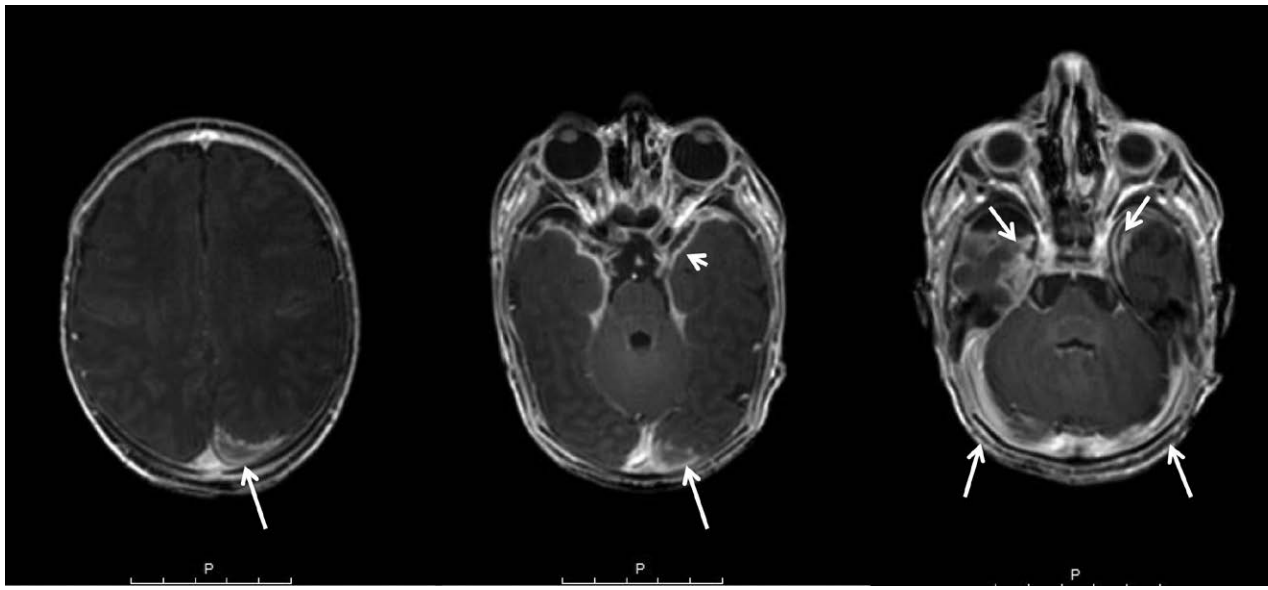

FIGURE 1. Contrast-enhanced T1-weighted MR images, performed 3 weeks postnatally, showing enhancement of subdural collections left parieto-occipital, bilateral temporal and pericerebellar (arrows), suspect for empyema. Also, leptomeningeal enhancement (short arrows).

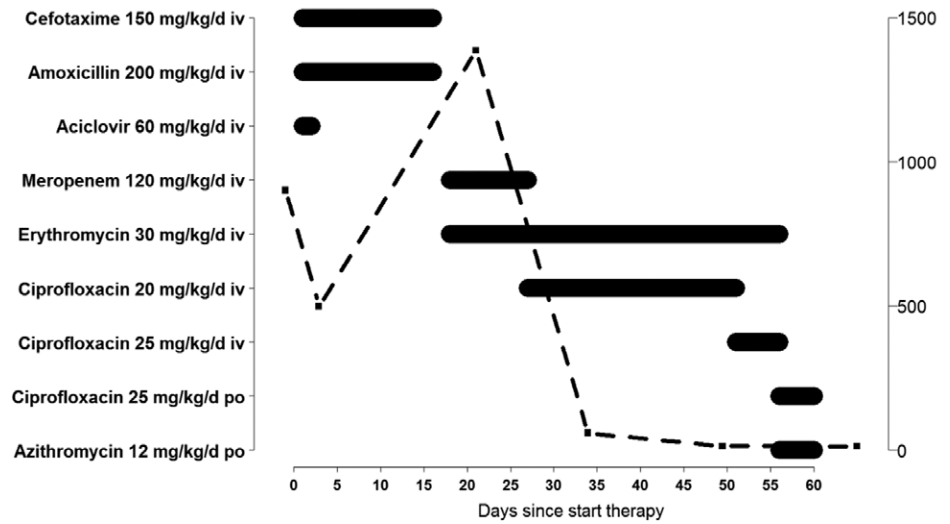

FIGURE 2. Timeline stating antibiotics doses and routes.

infection and as the detection of *Ureaplasma* spp. requires specific culture media and PCR techniques, microbiologic diagnosis is often delayed, which might contribute to an increased risk of neonatal brain injury. This case stresses the importance of considering *Ureaplasma* species in newborns with culture-negative meningitis without clinical improvement.

The genus *Ureaplasma* belongs to the family *Mycoplasmataceae* and are among the smallest organisms that are self-replicating. They are distinguished from *Mycoplasma*, the other genus in this family, by their ability to hydrolyze urea to ammonia to generate metabolic energy, hence its name. *Ureaplasma* spp. are difficult to culture. The organism cannot be stained by Gram stain because it lacks a cell wall. Therefore, detection of *Ureaplasma* spp. mainly depends on molecular techniques like PCR.[2,3]

Ureaplasma spp. are primarily mucosa-associated organisms, estimated to colonize the urogenital mucosa in about 40%–80% of sexually active women. Vertical transmission is estimated at 8%–88% depending on the population studied and can occur by 3 different routes: ascending intrauterine into the amniotic sac causing chorioamnionitis, hematogenous transmission, or by colonization of the skin after passage through the birth canal.[4,5]

In adults, *Ureaplasma* spp. are considered to be of low virulence and their pathogenic role continues to be subject of debate. However, multiple case reports and studies report that *Ureaplasma* spp. are associated with a spectrum of perinatal infections. Particularly in premature infants, *Ureaplasma* spp. can cause congenital pneumonia and secondary bacteremia.[4–6] However, the development of cerebral empyema, as in our case, is extremely rare and was previously only reported once.[7]

The incidence of neonatal ureaplasmal CNS infections is unknown and based on small clinical studies. Prematurity is an important risk factor for developing an infection with *Ureaplasma* spp., particularly infections affecting the CNS. Clinical studies, however, showed that only 25% of the neonates with bacterial-negative but *Ureaplasma* spp.-positive CSF samples had an elevated WBC compared with 16% of the ones with also *Ureaplasma*

spp.-negative samples, suggesting that ureaplasmal infections are common in neonates, but often asymptomatic.[8]

Ureaplasmas possess relevant immunomodulatory properties, such as stimulation of the inflammatory cytokine response. Both invasion of *Ureaplasma* spp. itself as well as secondary inflammation may play an important role in causing symptoms. These properties are thought to enhance the pathogenesis of bronchopulmonary dysplasia in preterm infants.[4,9] It is unknown to what extent the neurologic sequelae are a direct consequence of invasion by the microorganism itself or due to the inflammation caused by the infection. In cases with symptomatic CNS infections, early diagnosis and treatment seem essential to prevent adverse sequelae.[5] In our case, appropriate treatment was only started after 14 days. Earlier diagnosis and treatment might have prevented the complicated course.

There is little evidence on the optimal treatment of cerebral ureaplasmal infections. Macrolides and quinolones in particular, have been used as either monotherapy or combination therapy.[10] Doxycycline is contra-indicated in neonates for toxicity reasons. In our opinion, quinolones are the therapy of choice and may be preferable over macrolides, because of better CSF penetration. However, quinolones may be contra-indicated in neonates with epileptic seizures. In this case, complicated by cerebral empyema, we decided that prolonged therapy (6 weeks) was warranted. We argued that in the later course of the treatment, when meningeal inflammation was no longer an issue, but the collections still persisted, macrolides would not have reached adequate CSF concentrations.

In conclusion, neonatal CNS infections with subdural empyema are rare. To prevent adverse sequelae in infants who do not respond well to common therapy and in whom all other cultures remain negative, unusual pathogens such as *Ureaplasma* spp. should be considered. Because regularly used diagnostic techniques usually fail in these cases, specific PCR techniques, such as used in our case, can play a significant role in revealing the diagnosis.

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