CASE REPORT

Mycoplasma hominis Meningitis in a 24 Week Premature Neonate: Case Report and Short Literature Review

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Over the last 20-year period there have been fewer than 10 reported cases of *Mycoplasma hominis* central nervous system infection in either premature or full term infants. The optimum management of *M hominis* infection in premature infants is still unclear. We report the case of a premature infant with persistent central nervous system infection caused by *M hominis* treated successfully with intravenous chloramphenicol. Previous reports of *M hominis* central nervous infection and its management are reviewed.

KEYWORDS chloramphenicol, meningitis, mycoplasma, neonatal

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CASE REPORT

A 19-year-old primigravida presented with preterm labor at 24 weeks gestation with a history of spontaneous rupture of the membranes for 4 days. A male infant was delivered in poor condition, but his heart rate, color and overall tone responded well to intubation and surfactant administration. Apgar scores were 1 at 1 minute and 6 at 5 minutes. The birth weight was 623 g.

Blood cultures were taken and the infant commenced empirically on benzyl penicillin (25mg/kg per dose every 12 hours) and gentamicin (2.5 mg/kg per dose every 24 hours) according to local protocols. Benzylpenicillin was changed to cefotaxime (25 mg/kg per dose every 12 hours) along with gentamicin after 48 hours due to a sustained increase in serum C-reactive protein with no clinical improvement. *Neiserria gonorrhea* and anaerobes were isolated from a maternal high vaginal swab. Blood cultures from the neonate remained negative, there were no signs of conjunctival infection and antibiotics were stopped on day seven of life. The clinical course was otherwise complicated by severe surfactant-deficient lung disease progressing to chronic lung disease, and he suffered bilateral intraventricular hemorrhages with subsequent post-hemorrhagic ventricular dilatation.

The neonate underwent further evaluation for sepsis on day 13 following increased ventilatory requirements and a tonic clonic seizure. *Candida guilliermondii* species were

ABBREVIATIONS ACV, acyclovir; AMK, amikacin; AMP, ampicillin; AMX, amoxicillin; CHL, chloramphenicol; CIP, ciprofloxacin; CLI, clindamycin; CRO, ceftriaxone; CTX, cefotaxime; CXM, cefuroxime; DOX, doxycycline; ERY, erythromycin; GEN, gentamicin; GA, gestational age; MEM, meropenem; PCN, penicillin; RBC, red blood cells; WBC, white blood cells

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isolated from peripheral blood cultures and echocardiography demonstrated the presence of fungal vegetation within the left atrium. Treatment was commenced with liposomal amphotericin (250 micrograms/kg per dose every 24 hours) and flucytosine (50 mg/kg per dose every 12 hours).

A lumbar puncture was performed at this time. Cerebrospinal fluid microscopy showed $1,142 \times 10^6$/L white cells (50% neutrophils, 50% lymphocytes) and $64,980 \times 10^6$/L red blood cells. After three days of incubation at 37°C in an atmosphere containing 5% carbon dioxide the culture yielded a pure growth pinpoint colonies of *Mycoplasma* species from the chocolate agar plate. The organism was subsequently confirmed as *M hominis* at the Respiratory and Systemic Infections Laboratory, Health Protection Agency Centre for Infections, London, UK.

A further cerebrospinal fluid sample was sent after 24 hours. This showed 513×10^6/L white blood cells (50% neutrophils and 50% lymphocytes) and $3,330 \times 10^6$/L red blood cells with no organisms seen on Gram stain. The protein concentration was 0.59 g/dL and the glucose was 21.6 mg/dL. After three days of incubation this second culture yielded a pure growth pinpoint colonies of *Mycoplasma hominis*. *M hominis* had also been previously isolated from a placental swab taken at the time of delivery. Treatment was commenced with intravenous chloramphenicol sodium succinate, at 12.5 mg/kg per dose every 12 hours for *M hominis* meningitis and was subsequently increased to 15 mg/kg per dose every 12 hours, in response to low serum concentrations.

Serum chloramphenicol concentrations were monitored during treatment. Following 48 hours of therapy, pre-dose and post-dose concentrations were 5.7 mg/L (target range <5 mg/L) and 13.3 mg/L (target range 15-25 mg/L), respectively. Target ranges were based on therapeutic concentrations for adults. Despite an increase in the dose of chloramphenicol, peak and trough serum concentrations continued to be sub-therapeutics. Blood cell counts and liver function tests were monitored and remained normal for age.

An improvement in seizures and ventilation represented a good clinical response and the infant completed a 21-day course of chloramphenicol without any complications. Serial cerebrospinal fluid samples taken during treatment showed an improving trend. On day 10 of treatment, they showed white blood cells count was 98×10^6/L with 372×10^6/L red blood cells and no growth of any organisms. On day 15, the cerebrospinal fluid showed white blood cells 20×10^6/L with red blood cells $17,970 \times 10^6$/L. An alpha-hemolytic streptococcus species was isolated from enrichment after 3 days and likely represented a contamination. The infant subsequently made good clinical progress and was transferred back to the referring hospital at 60 days of age. He is undergoing local follow up.

DISCUSSION

The pathogenic role of Mycoplasma species transmitted from the genital tract in perinatal mortality and morbidity has been disputed for sometime.[1] *Mycoplasma hominis* colonization of the female urogenital tract is common with reported prevalence of 10% to 20%.[2] Despite this, clinical infection due to Mycoplasma species in extremely premature infants is rare. Vertical transmission to both premature and full term infants may occur at the time of birth. We found only a few reported cases of *M hominis* central nervous infections in either premature or full term infants in a review of the literature (Table).

There have been 7 detailed reports of *M hominis* central nervous system infection over the last 20 years. Two were premature infants and five were full term neonates.[3-9] Each presented with clinical deterioration during treatment with broad spectrum antibiotics that are used routinely for meningitis. Antibiotics available for the treatment of invasive *M hominis* are variable, and range from doxycycline, clindamycin, ciprofloxacin and chloramphenicol. Six of the reported neonates recovered when treatment was started for *M hominis* meningitis, with only one reported fatality.

Susceptibility testing of Mycoplasma species in general is non-standardized and difficult to interpret. *M hominis* lacks a peptidoglycan cell wall; it is not affected by beta-lactams and cephalosporins, which are commonly used empirically to treat central nervous infection. Antimicrobial agents which inhibit *Mycoplasma species* in vitro include tetracycline, doxycycline, clindamycin and fluoroquinolones.[10] Making

Table. Summary of cases of *M hominis* central nervous system infection in newborn

References (Infection)	GA (Weight)	Initial CSF	Treatment for *M.hominis* (Duration)	Comments	Outcome
Kirk 1987[3] (Meningitis)	30 wks (1080 g)	WBC 1.6×10^5/L RBC 5.5×10^4/L protein 0.48 g/dL glucose 86.48 mg/dL (+) blood cultures after 3 days	Dose of CHL and DOX were not provided. (14 days of CHL; 10 days of DOX)	Clinical condition continued to deteriorate despite change from CXM to PCN plus CHL; hence, PNC was stopped and DOX added	Resolved
McDonald 1988[4] (Meningitis)	26 wks (920 g)	WBC 73 mm^3 WBC (all neutrophils) RBC 217 mm^3 Protein 0.358 g/dL Glucose 16 mg/dL (blood glucose 124mg/dL)	25 mg/kg/day of CHL (10 days). Changed to DOX 4mg/kg/day following CHL toxicity (16 days)	Progressive neurological deterioration with decreased spontaneous activity and increasing episodes of apnea and bradycardia	Resolved
Waites 1990[5] (Meningitis)	37 wks (2950 g)	WBC 2 mm^3 RBC 3 mm^3 Protein 0.10 g/dL	Dose of CLI not provided. (not provided)	None	Resolved
Alonso-Vega 1997[6] (Meningo-encepha-litis)	37 wks (4020 g)	WBC 650 mm^3 (9% neutrophils, 91% lymphocytes) RBC 915 mm^3 Protein 0.175 g /dL Glucose 9 mg/dL (blood glucose 112 mg/dL) (–) Gram stain (+) culture after 5 days	Although M..*hominis* meningitis was not suspected, 30 mg/kg/day DOX begun empirically on day 8. (15 days)	Generalized seizures despite AMP and AMK. Changed to AMP, CTX, and ACV	Died
Rao 2002[7] (Brain ab-scess)	Full term (3070 g)	WBC 32000 mm^3 (79% polymorphs) RBC 19700 mm^3 Protein 1.156 g/dL Glucose was undetectable (–) Gram stain Culture positive from pus material aspirated from cerebral abscess cavity. Identified as *M.hominis* according to 16s ribosomal RNA sequencing. Urea plasma was isolated when suitable culture was used.	19 mg loading dose and 4 mg/kg/day DOX intravenous. 40 mg/kg/day CLI (45 mg Q DS) and ERY (6 wks)	New parietal lobe abscess and dilatation of ventricular systems despite intravenous AMP and GEN	Resolved
Knausz 2002[8] (Meningo-encepha-litis)	41 wks (4340 g)	WBC 216/μL (predominantly polymorphs) glucose was undetectable (blood glucose 154.9 mg/dL) Protein 0.52 g/dL (–) Gram stain (+) cultures after 3 days	50 mg q 6 hr CHL Intravenous (3 wks)	Seizures on day 8 despite intravenous AMP. Changed to CRO	Resolved
Wolthers 2003[9] (Meningitis)	37 wks (2990 g)	200×10^6/L mononuclear cells 1122×10^6/L polynuclear cells Glucose 19.8 mg/dL (serum glucose 72.0 mg/dL) Protein 0.2397 g/dL (–) Gram stain (+) Cultures after 7 days	20 mg/kg/day CIP intravenous (3 wks)	Clinical deterioration and increase in inflammatory markers despite intravenous MEM, AMX, and ACV	Resolved

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specific recommendations for treating invasive infections in neonates is particularly difficult as choices are limited due to associated toxic side effects. For example, tetracycline is associated with dental discolorations and abnormal skeletal developments, chloramphenicol with 'grey baby syndrome' and ciprofloxacin with its arthropathogenic effect.

We used chloramphenicol due to its good CSF penetration. However, it is known to have a narrow therapeutic index with variable pharmacokinetics; hence, serum concentration monitoring is essential.[11] Various dosing regimens have been recommended with some reports using up to 40 mg/kg for neonates.[12] We believe this is the first report of the effective use of chloramphenicol to treat *Mycoplasma hominis* meningitis in a premature neonate. The chloramphenicol dose of 15 mg/kg per dose every 12 hours used in our case resulted in successful eradication of the organism from the CSF and clinical resolution of infection.

CONCLUSIONS

M hominis may result in invasive meningitis in neonates. It should be considered in the differential diagnosis when *M hominis* is isolated in the cerebrospinal fluid of sick neonates who remain clinically septic despite empiric antibiotics for central nervous system infection. This is particularly true if the Gram stain is negative, conventional cultures yield no growth and there is a history of maternal infection. Our experience demonstrated that chloramphenicol is an effective and safe antimicrobial for the treatment and eradication of M*ycoplasma hominis* infection, including meningitis in premature neonates.

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