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Mini Review

Diagnosis and antimicrobial therapy of *Mycoplasma hominis* meningitis in adults

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ABSTRACT

Meningitis in adults due to infection with *Mycoplasma hominis* is rarely reported. Here, we document the third case of *M. hominis* meningitis in an adult individual, developed upon neurosurgery following a subarachnoid haemorrhage. Our findings are noteworthy, because the presence of *M. hominis* in cerebrospinal fluid cannot be identified by standard culturing, Gram-staining, or matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Importantly, however, 16S rDNA sequencing did lead to an unambiguous diagnosis and guided successful antimicrobial therapy. Based on our present findings and a review of the respective literature, we conclude that *M. hominis* should be considered as a candidate causative agent of infections of the central nervous system following neurosurgical procedures, especially if there is no response to standard antimicrobial therapy, and routine culturing yields negative results.

Introduction

Urogenital colonization with *Mycoplasma hominis* is common in sexually active adolescent females. The presence of this bacterium has been most frequently linked to genito-urinary tract infections and reproductive diseases. Extra-genito-urinary tract infections caused by this species have also been described (Madoff and Hooper, 1988; McMahon et al., 1990). These include sporadic cases of *M. hominis* infection of the central nervous system (CNS) of young infants and adults. To date, only 2 cases of meningitis caused by *M. hominis* have been reported in adults. Here, we report a third case of an adult patient with meningitis due to infection with *M. hominis* following a neurosurgical intervention, and we review the relevant literature of this topic.

Case report

A 48-year-old woman was admitted to the University Medical Center Groningen because of a subarachnoid haemorrhage. The haematoma was removed and an aneurysm in the left middle cerebral artery was clipped. Furthermore, an external ventricular drain was inserted. On day 3 of her hospitalization, the bone flap was removed because of an oedema of the left hemisphere of the brain. On day 6, the patient developed a fever of 39 °C. On days 7 and 9, blood cultures were tested positive for *Staphylococcus epidermidis* and *Staphylococcus aureus*, using routine diagnostic techniques. On the 10th day, growth of *S. epidermidis* was identified in the culture of a cerebrospinal fluid (CSF) sample, which had been obtained on the 7th day. Accordingly, flucloxacillin was administered intravenously (12 g daily divided in 6 doses) in combination with vancomycin which was administered both intravenously and intrathecally (1 g every 12 h and 20 mg daily, respectively). Although the infection responded, the patient developed a high fever (39.5 °C) after 3 days despite the antibiotic therapy. Laboratory results showed a C-reactive protein level of 49 mg/l (normal level is <5 mg/l) and a white blood cell count of 19.6×10^9/l (normal is $<10 \times 10^9$/l). A follow-up head-computed tomography was performed, but no abscess was detected. Therefore, the ventricular shunt was substituted. Cultures of subsequent CSF samples and blood remained negative for bacteria and fungi in routine diagnostic tests. However, after incubating CSF samples from days 9 and 11–18 for 6 days on blood agar with 5% sheep blood (BA, Oxoid; 37 °C, 5% CO_2), pin point colonies were detected. No such growth was detected upon plating of 7 CSF samples taken before day 9 except for the aforementioned sample taken on day 7 that was tested positive for *S. epidermidis*. Gram-staining of colony samples showed no bacteria, and a Ziehl–Neelsen stain for acid-fast bacilli was negative. Furthermore, the analysis of colony samples by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) with the microflex LT (Bruker Daltonics, Germany), following the

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Table 1
Literature reports of CNS infection caused by *M. hominis* in adults (1950–2011).

No.	Literature/year	Age/sex	Mode of acquisition	Specimen that yielded *M. ominis*	Diagnostic technique	Diagnosis	Management	Outcome
1.	Paine et al. (1950)	20 years/M	Trauma	Pus	Culture	Post-traumatic brain abscess	ND + STR	Survived
2.	Payan et al. (1981)	29 years/M	MVA	Pus	Culture	Post-operative	ND + CHL + TC	Survived
3.	McMahon et al. (1990)	76 years/M	VT after CVA	CSF	Culture	Post-operative meningitis	None	Death
4.	Cohen and Kubak (1997)	18 years/F	MVA	CSF	Culture	Post-operative meningitis	CHL	Survived
5.	Zheng et al. (1997)	22 years/F	Delivery	Pus	ELISA	Post-partum brain abscess	ND	Survived
6.	House et al. (2003)	40 years/F	An infected CA	Pus	Culture + 16S rDNA	Brain abscess	ND + CIP	Survived
7.	Douglas et al. (2003)	17 years/F	Delivery	CSF, blood	Culture	Post-partum brain abscess	ND + Dox + CLI	Survived
8.	Kupila et al. (2006)	40 years/M	Head trauma GUT manipulation	Pus	16S rDNA	Post-traumatic brain abscess	ND + TC	Survived
9.	McCarthy and Looke (2008)	48 years/M	Colloid cyst resection	CSF and bone graft	Culture + 16S rDNA	Post-operative brain abscess	ND + GTX + CLI	Survived
10.	McCarthy and Looke (2008)	17 years/F	MVA	Soft tissue + pus aspirates	Culture	Post-operative brain abscess	ND + GTX MFX[a]	Survived
11.	Al Masalma et al. (2011)	41 years/F	Uterine curettage	Pus	16S rDNA	Postabortal brain abscess	ND + Dox	Survived
12.	Present case	48 years/F	Craniotomy after CVA	CSF	16S rDNA	Post-operative meningitis	MFX	Survived

CA, cavernous angioma; CHL, chloramphenicol; CIP, ciprofloxacin; CLI, clindamycin; CSF, cerebrospinal fluid; CVA, cerebrovascular accident; Dox, doxycycline; GTX, gatifloxacin; GUT, genito-urinary tract; MFX, moxifloxacin; ND, neurosurgical debridement; MVA, motor vehicle accident; STR, streptomycin; TC, tetracycline; and VT, ventriculostomy tube.

[a] Oral for outpatient therapy.

manufacturer's recommendations, yielded no identifying profile. Finally, DNA of the bacteria was extracted, and the 16S rDNA was amplified by PCR with universal primers and sequenced as previously described (Möller et al., 1999). The obtained sequences were compared to the sequences present in the GenBank database using BLASTn (www.ncbi.nlm.nih.gov/blast), which identified the colonies as *M. hominis*.

Antibiotic susceptibility testing using the E-test method was performed on Mueller–Hinton agar plates, which were supplemented with 5% sheep blood (MHB, Oxoid). These plates were inoculated with 0.5 McFarland units of a suspension of bacterial cells grown overnight on BA. The E-test strips (AB Biodisk, Solna, Sweden) were then placed on the MHB plates. After 48–72 h of incubation at 35 °C in an atmosphere with 5% CO_2, the minimal inhibitory concentrations (MICs) were read according to the MIC value EUCAST breakpoints for *S. aureus*, because no EUCAST breakpoints have been defined for *M. hominis*. This indicated susceptibility to doxycycline (MIC 0.38 μg/ml), clindamycin (MIC < 0.016 μg/ml) and moxifloxacin (MIC 0.023 μg/ml). Therefore, the treatment with flucloxacillin and vancomycin was discontinued on day 18, and the patient was intravenously treated with moxifloxacin at a daily dose of 400 mg. Within 24 h, the patient responded to this therapy. Antibiotic therapy was continued for 14 days. The patient's clinical conditions improved, and all CSF cultures from day 19 onward tested negative for *M. hominis*.

Discussion

The first human mycoplasma species was recovered from an abscess of Bartolin's gland by Dienes and Edsall (1937). At that time, it was referred to as pleuropneumonia-like organism (PPLO). Since then, mycoplasmas have become known as normal components of the microbiota in the human genital tract. Robinson and Wichelhausen (1956) reported the first mycoplasma infection in cell cultures. Subsequently, the role of *M. hominis* in various human diseases has been revealed. For example, *M. hominis* can play an important role in urinary tract infections, postpartum and postabortal fevers, and pelvic inflammatory disease. This bacterium is also capable of causing extragenital infections, such as joint and surgical wound infections and the infection of the CNS.

Most cases of CNS infections with *M. hominis* have been reported for neonates (Hata et al., 2008), and these are probably associated with the genital colonization of pregnant women. Only 11 cases of CNS infections with *M. hominis* in adult patients have been reported so far, and Table 1 provides an overview of these 11 cases and the present case (Al Masalma et al., 2011; Cohen and Kubak, 1997; Douglas et al., 2003; House et al., 2003; Kupila et al., 2006; McCarthy and Looke, 2008; McMahon et al., 1990; Paine et al., 1950; Payan et al., 1981; Zheng et al., 1997). The majority of these patients had a brain abscess (75%), and there were only 2 patients with meningitis. Ten CNS infections with *M. hominis* occurred in patients with pre-existing comorbidities including neurosurgical interventions, trauma, an infected cavernous hemangioma, genito-urinary manipulation, and uterus curettage, whereas the 2 remaining CNS infections related to vaginal delivery by immunocompetent women. Clinical outcomes were positive in all but one case where an untreated patient passed away (Table 1).

As shown in Table 1, most of the previous *M. hominis* infection isolates have been identified by conventional methods. Nevertheless, it has turned out difficult to diagnose the *M. hominis* CNS infections at an early stage, resulting in delayed initiation of appropriate therapy. Due to its minute size and the absence of a cell wall consisting of peptidoglycan, *M. hominis* is not detectable by Gram staining. Analysis of the CSF gives only a profile of lymphocytic pleocytosis or a minimal or absent inflammatory response (Waites et al., 1990). In effect, longer periods of time are required for the detection of *M. hominis* by culturing methods due to its fastidious slow-growing nature. When viewed by microscopy at a132-fold magnification, *M. hominis* produces typical fried egg-shaped microcolonies on blood agar plates that are composed of a dense central zone and a less dense peripheral zone (Waites and Robinson-Taylor, 2007). In our case, this characteristic appearance of colonies was not recognisable. Possibly, the use of direct immunofluorescence techniques could have facilitated the identification of the mycoplasmal colonies on culture plates (Waites and Robinson-Taylor, 2007), but this technique