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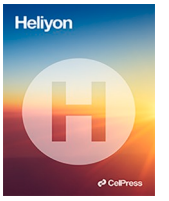

Meningitis in neonate caused by *Mycoplasma hominis*: A case report

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ABSTRACT

Background: Mycoplasma hominis (*M. hominis*) commonly colonizes the genitourinary tract of adult women and may result in neonatal meningitis through vertical transmission. Although there are few case reports, if the treatment is not conducted timely, the disease progresses rapidly, which may lead to serious complications and a poor prognosis.

Case presentation: In the present study, a 10-day-old full-term neonate who presented with fever as the initial symptom and was eventually diagnosed with meningitis caused by *M. hominis* was reported. In the present case, the pathogen was not detected during the initial routine investigations, and the therapeutic effects of empiric antibiotic therapy were poor. Metagenomic next-generation sequencing (mNGS) in the cerebrospinal fluid (CSF) was conducted with the detection of *M. hominis*, and the antibiotics were adjusted to moxifloxacin combined with doxycycline. The clinical symptoms of the pediatric patient disappeared with an improvement in related laboratory results.

Conclusion: It was difficult to detect *M. hominis* by routine bacterial culture. Therefore, *M. hominis* infection should be checked for in children with meningitis who had a negative result in CSF culture and poor therapeutic effects of empirical medication. mNGS in CSF should be conducted as soon as possible, and sensitive antibiotics should be administered in time to reduce the incidence of complications and improve the prognosis.

1. Background

Neonatal meningitis is a common infectious disease during the neonatal period. If not treated in time, complications such as ependymitis and subdural effusion may occur, and some children are left with serious sequelae such as cerebral palsy. However, we must acknowledge that complications can occur even with early diagnosis, and early diagnosis and timely treatment can indeed reduce the risk of certain infections, such as pneumococcus, HSV. Neonatal meningitis is mainly caused by bacterial infection. There are many methods for species identification of bacteria, among which 16s PCR technique is more commonly used and can quickly obtain

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bacterial species information. However, its functional prediction accuracy is relatively low, which can only achieve the third level of KEGG [1]. In recent years, with the rapid development of metagenomic next-generation sequencing (mNGS), more and more pathogens, including mycobacteria, RNA and DNA viruses, mycoplasma, and fungi, have been detected in cerebrospinal fluid (CSF), in addition to common bacteria, providing more laboratory basis for the clinical diagnosis and management of neonatal meningitis [2]. In the present study, a case of neonatal meningitis caused by *Mycoplasma hominis* (*M. hominis*) admitted to our hospital was reported to raise the awareness of the disease among clinicians.

2. Case presentation

2.1. General material

A 10-day-old female pediatric patient was admitted to the neonatal unit of our hospital with the complaint of "fever for 3 h" The pediatric patient was G1P1 with a gestational age of 39^{+2} weeks. The patient was delivered by natural delivery with a birth mass of 3300 g and premature rupture of membranes for 10 hours. The parents denied that the patient had a history of scalp damage at birth or maternal perinatal fever. Three hours before admission, the pediatric patient developed a fever without obvious cause. The peak body temperature was 38.7 °C. Before the onset of the disease, the pediatric patient had a good mental response, with normal breastfeeding, as well as normal bowel movements and urination. Physical examination at admission: T 38.0 °C, HR 150 beats/min, RR42 times/min. The anterior fontanelle was flat and soft with a head circumference of 35 cm. The pediatric patient had clear consciousness. The pupils were equal in size and round with normal light reflex. There was no abnormality in the physical examination of the heart, lungs, and abdomen. The muscle tones of the four extremities were normal with normal primitive reflexes.

2.2. Diagnostic, therapeutic process, and medication

After examinations were conducted, including routine blood tests, C-reactive protein (CRP), CSF routine test, and biochemistry after admission, the results showed that in the blood routine, the white blood cells count was 24.63×10^9/L, which significantly increased, and neutrophils accounted for 67.7 %, while in the cerebrospinal fluid, the white blood cells count was 666×10^6/L, which also significantly increased, and monocytes 93.7 %, glucose decreased by 1.72 mmol/L, protein slightly increased by 0.56 g/L. Brain MRI plain scan + DWI imaging indicated abnormal diffusion limited signal imaging in the vermis, right tentorial region of the cerebellum, posterior margin of the cerebellar hemisphere, and the edge of the great venous cistern of the brain, possibly with inflammatory changes. Amplitude integrated electroencephalogram (aEEG) monitoring indicated multiple seizures, all of which were full seizures. The pediatric patient was initially diagnosed with neonatal bacterial meningitis. Ampicillin combined with meropenem was administered as empiric antibiotic therapy, but the therapeutic effects were poor. The pediatric patient had a repeated occurrence of fever and convulsions. The antibiotics were adjusted to vancomycin combined with meropenem together with oral administration of levetiracetam for anticonvulsant therapy. The convulsions improved, but the fluctuations in body temperature persisted. On the 14th day of admission, after multidisciplinary consultation, the mNGS of CSF was performed, and *M. hominis* was detected (serial number 1885), the mapping and distribution of *M. hominis* reads was shown as a supplementary material. Moreover, *M. hominis* and *Ureaplasma urealyticum* were also detected in the vaginal secretions of the mother at the same time. Therefore, the pediatric patient was diagnosed with meningitis caused by *M. hominis*. Medication was changed to doxycycline 4 mg/(kg-d) q12h combined with moxifloxacin 5 mg/(kg-d) QD for anti-infection and discontinued after six weeks of treatment (four weeks with intravenous administration and two weeks with oral administration). The trends of white blood cell (WBC) count (Fig. 1A), blood glucose (Fig. 1B), and protein (Fig. 1C) in CSF during treatment are shown in Fig. 1. The results of cranial plain MRI + DWI at admission (Fig. 2A), before the change to the sensitive antibiotics (Fig. 2B), and one month after discharge (Fig. 2C) are demonstrated in Fig. 2. The results of an amplitude-integrated electroencephalogram (aEEG) are shown in Fig. 3.

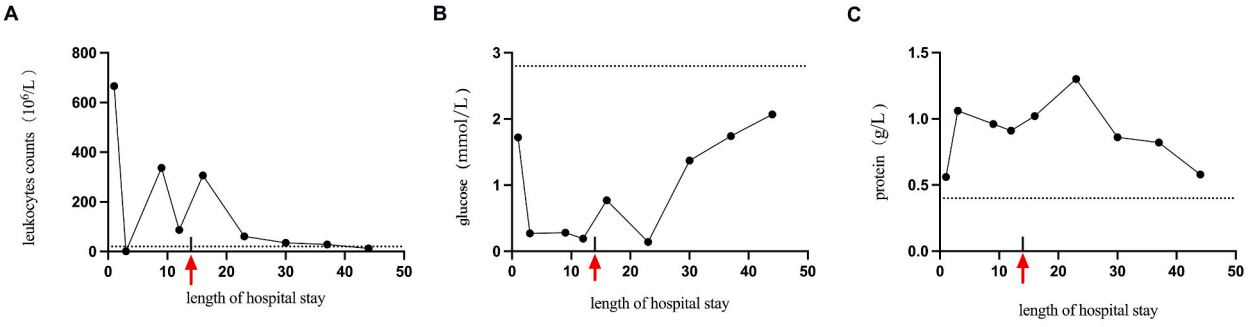

Fig. 1. The trends of white blood cell count (A), blood glucose (B), and protein (C) in CSF during treatment. The arrow indicated moxifloxacin combined with doxycycline on day 14 after admission, and the dotted line indicated the normal reference range.

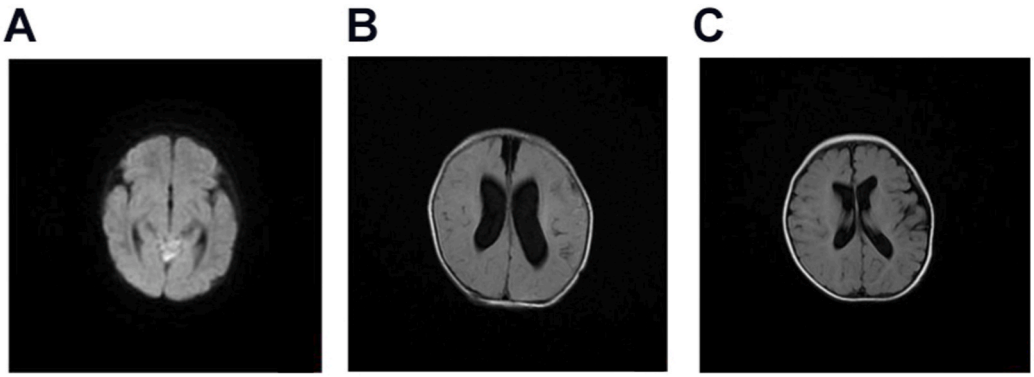

Fig. 2. The results of cranial plain MRI + DWI.
A: At admission, with the suggestions of abnormal diffusion-restricted signal in the cerebellar vermis, right tentorium cerebelli, posterior margin of cerebellar hemisphere, and the edge of the Vein of Galen; B: Before the change to the sensitive antibiotics, it was suggested with bilateral enlargement of the lateral ventricles with slight fullness of the third ventricle; C: One month after discharge, it was suggested that the lateral ventricles were full bilaterally with slightly deepened sulci, and bilaterally widened extratemporal spaces.

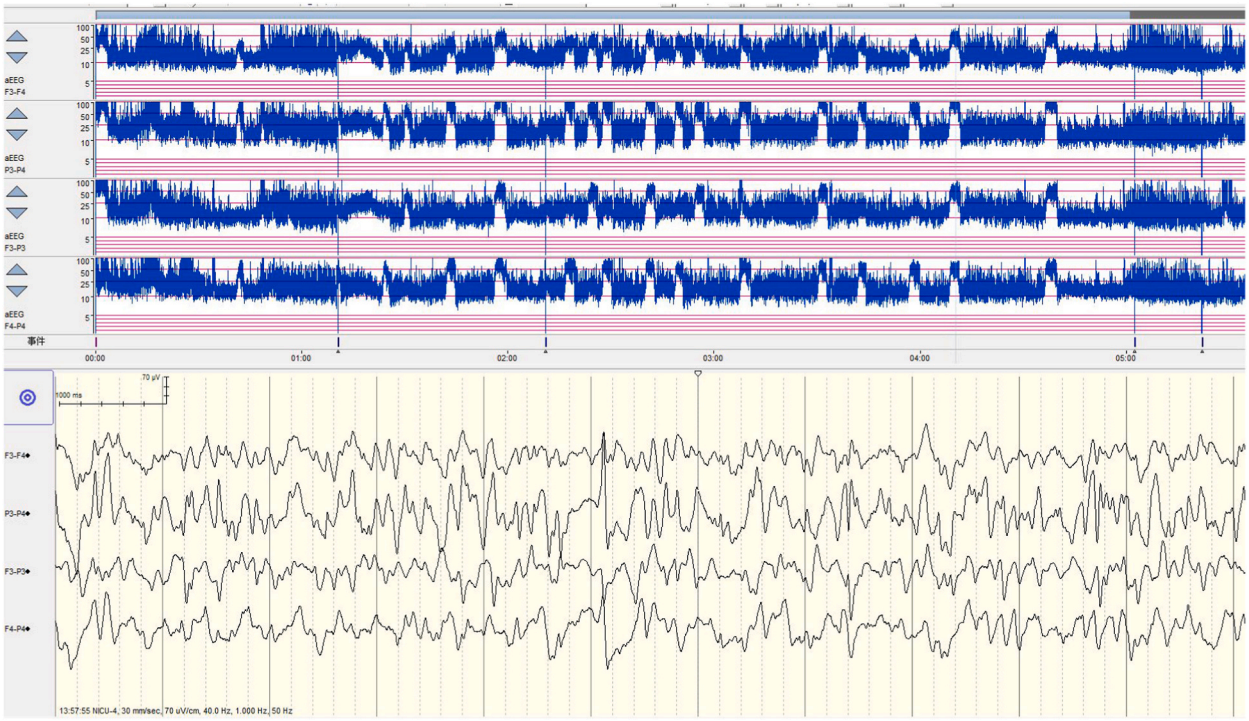

Fig. 3. Monitoring of the amplitude-integrated electroencephalogram with the observation of multiple convulsive episodes.

2.3. Therapeutic outcome and prognosis

After multi-department consultation, combined with the opinions of the pharmacy department, and full communication with the patient's family to inform the possible adverse drug reactions, the medication schedule was adjusted. After changing to doxycycline combined with moxifloxacin, the body temperature in the pediatric patient gradually normalized with cessation of convulsions and improvement of the mental status and reactions. On the review, the laboratory test results showed that the CSF's WBC count, CRP, and WBC count decreased to normal. The mNGS of the CSF showed no detection of *M. hominis* after four weeks of treatment, and the long-range video EEG showed only emissions of scattered spikes. Cranial MRI suggested absorption of the abnormal signals and improvement of lateral ventricular enlargement.

The pediatric patient was discharged from the hospital after six weeks of treatment and was followed up at one, two, and four weeks after discharge as planned. After discharge, the body temperature was normal with no convulsive episodes. The increase in the body

weight and head circumference was normal. At two months of age, the outpatient assessment in the rehabilitation department showed that the pediatric patient had poor wrist pulling and head erection, with good hand touch and fist clench, as well as a good response to sounds. She could make small guttural sounds and look face to face well. The muscle tones of the four extremities during movement were unstable and sometimes low. Levetiracetam for anti-convulsion was discontinued one month after discharge. The pediatric patient was still under rehabilitation.

3. Discussion

M. hominis has a worldwide colonization rate of between 21 % and 53 % and often adheres to the mucosal surface of the genitourinary tract in adult women, where it may develop into a pathogenic microorganism in the presence of low immunity or damaged mucosa [3]. Neonates may be infected with *M. hominis* through intrauterine infection or contact via the birth canal, causing pneumonia, meningitis, abscesses, and bacteremia, among which prematurity and low birth weight are considered to be the most common risk factors for *M. hominis* infection in the neonatal period [4]. However, full-term infants are rarely reported to have the disease. In this case, the infant developed symptoms 10 days after birth with a history of premature rupture of membranes. However, the mother did not exhibit any clinical symptoms of mycoplasma infection during pregnancy. After the onset of illness in the infant, *M. hominis* was detected in the vaginal secretions of the mother by culture, and the pathogen was found to be consistent with that identified in the infant's cerebrospinal fluid by second-generation sequencing. Therefore, it is considered that the infant's disease was vertically transmitted from the mother, who was colonized by the pathogen. The onset of meningitis caused by *M. hominis* had no clear pattern, and some cases might manifest within the first three weeks of life and act as the acute onset. The clinical manifestations might include fever, refusal of breast milk, convulsions, apnea, and tachycardia. The results of laboratory tests might show increased WBC and elevated CRP in the peripheral blood, as well as increased WBC in the CSF [5–7]. However, these clinical manifestations and test results are similar to those of neonatal suppurative meningitis, and lack of specificity, so the etiological diagnosis cannot be made. At the same time, the routine blood culture and cerebrospinal fluid culture are mostly negative, so it is easy to misdiagnose in the early stage, resulting in poor routine treatment effect for some infected children. The present case belonged to this type, during the early stage of the disease, only fever is present without other symptoms and signs of central nervous system infection, such as alterations in consciousness, bulging fontanelle, and abnormal muscle tone. As a result, it may be underdiagnosed or misdiagnosed. After multidisciplinary consultation, mNGS testing of the CSF was conducted on the 14th day after admission. The results suggested the presence of *M. hominis* infection. Therefore, for pediatric patients in whom the pathogens failed to be identified by routine pathogenic tests and those who had poor therapeutic effects with the empirical anti-infection and no improvement in symptoms, mNGS testing in the CSF should be conducted as early as possible to provide sufficient laboratory basis for clinical diagnosis. On the other hand, there is no doubt that 16sPCR, as a basic sequencing method, has been widely used in current clinical research and applications because of its fast and cheap characteristics [8]. The sequencing principle, research purpose and species identification depth of this method are different from mNGS technology. Specifically, 16s PCR focuses on the species composition of communities, the evolutionary relationships between species, and the diversity of communities. While mNGS can also conduct in-depth studies at the gene and functional level (GO, Pathway, etc.) on the basis of 16s PCR sequencing analysis. In addition, many of the sequences obtained by 16s PCR are less than the species level, which meas the functional prediction accuracy of this method is relatively low, while mNGS can identify microorganisms to the species level or even the strain level. The detection range of mNGS technology includes common bacteria, mycobacteria, mycoplasma, chlamydia, rickettsia, fungi, various DNA and RNA viruses, and parasites with known genomic sequences. Therefore, clinicians increasingly value it in diagnosing unexplained intracranial infections, and it has good application value [9,10]. In the present case, moxifloxacin combined with doxycycline was administered for anti-infection with a definite diagnosis, and the clinical symptoms and results of related laboratory tests gradually improved. Since quinolones and tetracyclines have obvious side effects, these drugs should be applied only with a definite diagnosis, and adverse drug reactions and serum drug concentrations should be closely monitored during the medication. Quinolone and tetracycline antibiotics are first-line treatments for adult Mycoplasma pneumoniae infection, but their use in children is limited due to significant risks such as hepatorenal toxicity, bone marrow suppression, coagulation dysfunction, cartilage injury, and permanent tooth damage. Zhang Tao et al. pointed out that theoretically, tetracycline drugs should not be used in children under 8 years old, but they can be used as off-label drugs for children with mycoplasma encephalitis who are clinically life-threatening or have a high probability of serious central nervous system sequelae [11]. At present, there are domestic reports on the application of moxifloxacin in the treatment of refractory mycoplasma infection in children, and the prognosis of the children is good without drug-related adverse reactions, indicating that short-term use is safe [12]. Levofloxacin has also been reported in foreign countries to treat mycoplasma-associated encephalitis and meningitis, and its clinical efficacy is significant, with neurological symptoms and signs disappearing in a short period of time and no adverse reactions [13,14]. In this case, the child had repeated fever, significant increases in white blood cells and CRP, accompanied by convulsive attacks, and abnormal brain imaging results in the course of the disease, which had a high probability of life-threatening or severe central nervous system sequelae. Therefore, the combination of doxycycline and moxifloxacin was chosen for anti-infection. In addition, the child was only treated with moxifloxacin and doxycycline after the diagnosis was confirmed and considering the mother's vaginal secretion culture and antibiotic sensitivity test results, and when other antibiotics had been ineffective. The parents were fully informed and agreed to the treatment. During hospitalization, the child's blood routine, blood biochemistry, coagulation function, and other indicators were monitored once a week until one month after discharge, and no abnormality was found. However, it is still necessary to continue to follow up and monitor whether there is cartilage injury or permanent tooth damage during the child's growth and development process. According to the literature, some newborns with meningitis caused by *M. hominis* might be prone to serious complications such as hydrocephalus, cerebral hemorrhage, hemiparesis, and even death [15]. Therefore, early diagnosis and effective

antibiotic treatment would play a key role in the prognosis of meningitis caused by *M. hominis*.

4. Conclusion

In summary, for neonates diagnosed with meningitis, if the therapeutic effects of the empirical medication were poor with a negative result in the routine CSF bacterial culture, as well as the existence of significant inflammatory changes on imaging or with hydrocephalus, the possibility of specific pathogens such as *M. hominis* infection should be examined. mNGS testing in the CSF should be conducted as early as possible and reasonable treatment should be given promptly to avoid delaying the optimal time for treatment.

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Ethics declarations

Informed consent was obtained from the guardian of the patient for the publication of all images, clinical data and other data included in the main manuscript.

Data availability statement

Data associated with the study has not been deposited into a publicly available repository, and data will be made available on request.

CRediT authorship contribution statement

Min Xi: Writing – review & editing, Writing – original draft, Conceptualization. **Shan Cui:** Writing – review & editing, Writing – original draft, Conceptualization. **Yu-Li Zhong:** Writing – review & editing, Writing – original draft, Conceptualization. **Ling Liu:** Writing – review & editing, Writing – original draft, Conceptualization. **Yan Zhang:** Writing – review & editing, Writing – original draft, Conceptualization. **Shuang-Yan Zhu:** Resources, Investigation, Conceptualization. **Can-Lin He:** Visualization, Resources, Investigation. **Fei Xiong:** Resources, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23489.

Abbreviations

mNGS	metagenomic next-generation sequencing
RNA	ribonucleic acid
DNA	deoxyribonucleic acid
T	temperature
HR	heart rate
RR	respiratory rate
cm	centimeter
mg	milligram
kg	kilogram
d	day
h	hour
qd	quaque die
MRI	magnetic resonance imaging
DWI	diffusion weigthed imaging

CRP C-reactive protein

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