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Severe Intracranial Hemorrhage and Intracranial Infection Caused by Ureaplasma parvum Infection in an Extremely Preterm Infant: A Case Report and Literature Review

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Case Report

Keywords: Ureaplasma parvum, Extremely preterm infant, Intracranial hemorrhage, Meningitis, Metagenomic next-generation sequencing

Posted Date: November 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11177595/v1

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Additional Declarations: No competing interests reported.

Abstract

Background:Ureaplasma parvum (Up) is an under-recognized pathogen in neonatal central nervous system infections. We retrospectively analyzed the clinical data of one extremely preterm infant presenting with severe intracranial hemorrhage (ICH) and intracranial infection attributed to Up infection, and systematically reviewed the relevant literature. The analysis covered perinatal history, neurological manifestations, serial cerebrospinal fluid (CSF) and imaging changes, metagenomic next-generation sequencing (mNGS) results, and treatment course.

Case presentation:A male infant was born at 26^{+1} weeks of gestation with a birth weight of 920 g. Intracranial hemorrhage, initially grade I on day 1 of life, progressed to grade IV by day 4. CSF examination showed typical features of intracranial infection: the nucleated cell count was markedly elevated, glucose was profoundly decreased (0.07 mmol/L), and protein reached 7,443 mg/L. Conventional bacterial cultures were repeatedly negative; however, mNGS of CSF identified Up (115 sequence reads; relative abundance 87.19%). Following targeted treatment with azithromycin, CSF inflammatory markers improved. Nevertheless, given the severity of the intracranial lesions, the family ultimately chose to withdraw care.

Conclusion:This case suggests that Up infection may act as a synergistic factor in the development or progression of severe ICH in extremely preterm infants. Potential mechanisms include direct injury to the cerebral vascular endothelium and fragile germinal matrix vessels, as well as blood-brain barrier disruption secondary to inflammatory cytokine release. In extremely preterm infants with unusually rapid progression of ICH and poor response to conventional treatment, Up infection should be considered early, and mNGS testing should be arranged without delay. As this is a single case report, the causal relationship warrants confirmation in future studies.

1. Introduction

Intracranial hemorrhage (ICH), particularly germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH), is one of the most serious neurological complications in extremely preterm infants. The reported incidence of intraventricular hemorrhage (IVH) in very low birth

weight (VLBW) infants is as high as 20% [1]. Severe intracranial hemorrhage (grades III–IV) often

leads to post-hemorrhagic hydrocephalus, white matter injury, and long-term neurodevelopmental impairment, with substantially increased mortality and morbidity [2]. Established risk factors include immature cerebral autoregulation, heightened fragility of the germinal matrix vasculature, hemodynamic instability, coagulopathy, and mechanical ventilation [3].

Perinatal infection has drawn increasing attention as a contributor to intracranial hemorrhage in preterm infants. Chorioamnionitis, an important trigger of preterm birth, has been shown to increase the risk of neonatal intracranial hemorrhage [4,5]. Nevertheless, the role of specific pathogens—particularly

Ureaplasma spp.—in the initiation and progression of intracranial hemorrhage remains underappreciated.

We report the case of an extremely preterm infant who developed severe intracranial hemorrhage and intracranial infection attributed to Ureaplasma parvum (Up) infection. In this infant, the hemorrhage progressed from grade I to grade IV by day 4 of life. Based on serial imaging, cerebrospinal fluid (CSF) findings, and metagenomic next-generation sequencing (mNGS) results, we believe that Up infection likely played a significant synergistic role in the rapid deterioration of the intracranial pathology.

2. Case Presentation

A male infant, was the first pregnancy and first delivery, conceived by in vitro fertilization (IVF), and born at 26^{+1} weeks of gestation by spontaneous vaginal delivery, with a birth weight of 920 g. His mother had a history of first-trimester vaginal bleeding treated with tocolytic therapy; she denied premature rupture of membranes or fever. The amniotic fluid, placenta, and umbilical cord appeared grossly normal at delivery. The infant experienced birth asphyxia, with Apgar scores of 6, 5, and 5 at 1, 5, and 10 minutes, respectively. Shortly after birth, he developed grunting and progressive respiratory distress, requiring endotracheal intubation, invasive mechanical ventilation, pulmonary surfactant administration, and vitamin K1. Empirical antimicrobial therapy with ceftazidime and ampicillin sodium was initiated. He was transferred to our hospital at 9 hours of age.

At admission, the infant was slightly tachypneic with mild respiratory distress under invasive ventilation. The anterior fontanelle was flat and soft, and no petechiae or ecchymoses were noted. Breath sounds were slightly diminished bilaterally. Muscle tone was reduced in the extremities, and primitive reflexes were absent. On the day of admission, C-reactive protein (CRP) was 6.1 mg/L and procalcitonin was 15.37 ng/mL; the following day, CRP rose to 16.8 mg/L, with a peak white blood cell count of 22.55 $\times 10^9$/L and 77.9% neutrophils. Blood cultures remained sterile for 5 days. Intermittent fever occurred on days 1, 5, and 10 of life, with a maximum temperature of 38.2°C. On day 3, in the context of rising CRP and leukocytosis complicated by pulmonary hemorrhage, antimicrobial therapy was escalated to meropenem and ampicillin sodium.

Cranial ultrasound on day 1 of life revealed grade I intracranial hemorrhage; a repeat examination on day 4 showed progression to grade IV hemorrhage. Periventricular leukomalacia subsequently developed. The infant began having seizures, and amplitude-integrated electroencephalography (aEEG) demonstrated an abnormal pattern for a preterm infant, with depressed background voltage, scattered dysmorphic sharp waves in the central regions, and prolonged interburst intervals. Management during this period included hemostatic agents, transfusion of plasma, platelets, and red blood cells, and phenobarbital for seizure control.

On day 7, a throat swab was positive for Ureaplasma urealyticum (Uu) DNA by polymerase chain reaction (PCR). Considering the possibility of ureaplasma colonization or mixed infection, oral azithromycin (10 mg/kg once daily) was added. On day 10, CSF examination revealed a grossly bloody, turbid fluid without

clot formation: the corrected white blood cell count was 17,946 × 10⁶/L, protein 7,443 mg/L, glucose 0.07 mmol/L, and chloride 132.1 mmol/L, consistent with typical intracranial infection. CSF mNGS identified Up with 115 sequence reads and a relative abundance of 87.19%, while ruling out other common and uncommon pathogens, including Escherichia coli, Group B Streptococcus, Listeria monocytogenes, cytomegalovirus, and herpes simplex virus. Conventional CSF culture was negative. After confirmation, azithromycin was immediately switched to intravenous administration at 20 mg/kg once daily.

Following the initiation of intravenous azithromycin, no further significant progression was observed on serial cranial imaging. On day 15, repeated CSF examination showed a white blood cell count of 3,791 × 10⁶/L with 77.4% segmented neutrophils, glucose 0.38 mmol/L, protein 3,946 mg/L, and chloride 111.2 mmol/L, indicating improvement. On day 21, CSF showed a white blood cell count of 80 × 10⁶/L, glucose 1.44 mmol/L, and protein 8,640 mg/L. Although the white blood cell count and glucose level improved markedly, the persistently elevated protein was thought to reflect resolving hemorrhage or ongoing ventriculitis. Given the established grade IV hemorrhage with extensive white matter injury and ventriculomegaly, the neurological prognosis was deemed extremely poor, and the family ultimately chose to withdraw care. The infant's mother declined cervical swab and placental pathological examination.

3. Discussion

To date, only two species of the genus Ureaplasma are recognized as human pathogens: Up and Uu [6]. Although both commonly colonize the genitourinary tract, Up has been reported more frequently in neonatal invasive infections [7-10]. In this case, the throat swab detected Uu while CSF detected Up, consistent with the possibility of mixed involvement.

Because Ureaplasma does not stain with Gram staining and may not grow on conventional culture media, diagnosis depends heavily on molecular techniques such as PCR and mNGS [11]. A consistently reported CSF finding in Ureaplasma central nervous system infection is a markedly decreased glucose concentration [10], often accompanied by IVH, ventriculitis, and/or hydrocephalus [12,13]. The present case exhibited these classic features.

Although extreme prematurity itself is a major risk factor for IVH, progression from grade I to grade IV within 4 days is unusual. While detection of Up in CSF does not establish it as the direct cause of acute cerebral injury, this rapid deterioration cannot be readily explained by conventional risk factors alone. Up infection likely acted as an important synergistic factor.

A prospective cohort study of 313 VLBW infants showed that infants with Ureaplasma detected by serum PCR had a 2.32 times higher risk of severe IVH (≥ grade III) than those who tested negative (adjusted OR 2.50, 95% CI 1.06–5.89, P = 0.036) [14]. Of note, all PCR-positive infants with severe IVH in that study had Up, consistent with our case. The germinal matrix vasculature in extremely preterm

infants is structurally immature and characterized by a thin basement membrane. Up can adhere to and invade endothelial cells, and the ammonia generated by its urease activity may directly damage the endothelium [15,16]. Such endothelial insult may act additively with the intrinsic fragility of germinal matrix vessels, thereby increasing the risk of hemorrhage [15,17]. In this case, vascular fragility served as the underlying substrate, while Up-induced endothelial injury may have been the precipitating factor; their combined effects likely contributed to the rapid hemorrhagic progression. The stabilization of hemorrhage after azithromycin treatment offers indirect therapeutic support for this relationship.

Beyond these direct vascular effects, Up upregulates inflammatory cytokines [15,18] and may increase blood-brain barrier permeability [19,20]. The striking CSF findings in this infant—protein > 7 g/L and marked leukocytosis—point to substantial intracranial inflammation, which can disrupt CSF secretion and absorption and aggravate post-hemorrhagic hydrocephalus.

In extremely preterm infants with intracranial hemorrhage that progresses unusually rapidly or exceeds the expected severity, a high index of suspicion for occult pathogens such as Ureaplasma is warranted when the following clues are present: rapid escalation from low-grade to high-grade hemorrhage; CSF pleocytosis with extremely low glucose; purulent CSF that is negative on conventional culture; maternal chorioamnionitis or unexplained preterm birth; and failure of empirical broad-spectrum antibiotics accompanied by leukocytosis without a corresponding CRP elevation.

Ureaplasma species are intrinsically resistant to β-lactam antibiotics [21]. The lack of response to initial ceftazidime and meropenem in this case is consistent with this resistance profile, and both hemorrhage and infection continued to deteriorate despite these agents. Although subsequent azithromycin (initially 10 mg/kg orally, then 20 mg/kg/day intravenously after the diagnosis was confirmed) improved CSF inflammatory markers, the hemorrhage had already progressed to grade IV, leaving limited room for neurological recovery. Early diagnosis and treatment are therefore paramount. mNGS, which is unaffected by prior antibiotic exposure [22-24], should be performed at the point of first high clinical suspicion rather than after waiting for conventional culture results.

This case has several limitations. First, a single case report cannot establish a causal relationship between Up infection and intracranial hemorrhage; it can only provide clinical clues. Second, the detection of Uu in the throat swab and Up in the CSF precludes distinction of their independent contributions to the intracranial pathology. Third, the mother declined cervical swab and placental pathological examination, so the route of infection could not be fully clarified.

4. Conclusion

Here we report an extremely preterm infant with Up infection who developed severe intracranial hemorrhage and ultimately experienced withdrawal of care due to the poor neurological prognosis. Reviewing the relevant literature, Up infection may serve as an important synergistic factor in the rapid

progression of intracranial hemorrhage in preterm infants, through mechanisms involving endothelial injury and inflammatory cascades.

For extremely preterm infants with rapidly progressive intracranial hemorrhage, markedly decreased CSF glucose, and negative conventional cultures, Up infection should be included in the core differential diagnosis, and early CSF mNGS should be obtained to identify the pathogen. Well-designed prospective cohort studies are warranted to further validate the independent association between Up infection and adverse neurodevelopmental outcomes in preterm infants.

Declarations

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.This study was approved by the Ethics Committee of Bazhong Central Hospital (Sichuan Provincial People's Hospital Bazhong Hospital). Written informed consent to participate was obtained from the patient's legal guardians.

Consent for publication

Written informed consent for publication of this case report and any accompanying images was obtained from the patient's legal guardians. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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