Ureaplasma-Driven Neuroinflammation in Neonates: Assembling the Puzzle Pieces

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Abstract
Ureaplasma species (spp.) are commonly regarded as low-virulence colonizers of the genitourinary tract. Intrauterine Ureaplasma infection, however, has been associated with chorioamnionitis and preterm birth. The overall impact of a neonatal Ureaplasma colonization is yet to be understood. High pathogen prevalence and frequent neurological morbidities particularly in immature preterm infants call for an assessment of the significance of Ureaplasma spp. in neonatal neuroinflammation. This narrative review summarizes clinical data, animal studies, and in vitro results to elucidate potential Ureaplasma-associated neurological morbidities as well as underlying mechanisms. Increasing evidence indicates an involvement of Ureaplasma spp. in invasive central nervous system infections, suggesting a meticulous ability of Ureaplasma spp. to interfere with immune defense mechanisms. Ultimately, Ureaplasma spp. should be considered as relevant pathogens in neonatal neuroinflammation.

Introduction
Ureaplasma species (spp.) are some of the smallest self-replicating organisms [1]. Their cultivation can be challenging, and molecular techniques helped improving diagnostic sensitivity and detection rate only recently [2, 3]. The 2 human spp. Ureaplasma urealyticum (serovar 2, 4, 5, 7–13) and Ureaplasma parvum (serovar 1, 3, 6, 14) are common colonizers of the adult urogenital tract and often considered of low virulence [1]. In neonates, however, Ureaplasma spp. appear to be clinically relevant pathogens with often underestimated impacts on morbidity and mortality [3].

As many as 80% of pregnant women can be considered colonized with Ureaplasma spp. in their lower urogenital tract, and vertical transmission during pregnancy occurs frequently [4, 5]. Ureaplasma spp. were detected in up to 23% of the umbilical cord blood samples taken from infants born prematurely between 23 and 32 weeks of gestation [6–8]. Prenatal amniotic infection with Ureaplasma spp. has been associated with chorioamnionitis and can contribute to preterm birth [6, 9, 10]. Pre-, peri-, or postnatal transmissions may result in neonatal Ureaplasma infection. This can become apparent either as an acute
invasive infection such as pneumonia and sepsis or may present as long-term inflammation and contribute to chronic morbidities like bronchopulmonary dysplasia [11–14].

Furthermore, *Ureaplasma* spp. are increasingly considered relevant in neonatal neuroinflammation. The latter may accompany systemic inflammation, for example in the event of *Ureaplasma*-induced chorioamnionitis [3], but may also be caused by direct *Ureaplasma* invasion of the central nervous system (CNS): *Ureaplasma* spp. were detected within the cerebrospinal fluid (CSF) in up to 19% of the preterm infants ≤1,500 g [8]. This review gathers clinical data as well as evidence from animal and *in vitro* studies to elucidate the neuroinflammatory potential of *Ureaplasma* spp.

**Ureaplasma*-Driven Neonatal Neuroinflammation: *In vivo* Data**

Within the past 45 years, 35 cases of meningitis caused by *Ureaplasma* spp. or the related pathogen *Mycoplasma hominis* were described in neonates, indicating that *Ureaplasma* spp. are causal pathogens in neonatal CNS infection [15–17]. The most immature preterm infants appear to be at highest risk; however, term neonates can also be affected, and even a first description of *Ureaplasma* meningitis in an immunocompetent adult patient has recently been published [16, 18]. Typical clinical symptoms in neonatal *Ureaplasma* meningitis include sepsis-like conditions, apnea, and seizures, as well as development of internal hydrocephalus, often followed by long-term neurodevelopmental impairment [16]. Chronic courses were described, such as the unique case of an 8-month history of chronic *Ureaplasma* meningitis in a former preterm infant [17].

Other typical neurological morbidities of prematurity are intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL). Since inflammation may relevantly contribute to both conditions, a potential causal relationship between *Ureaplasma* exposure and development of IVH or PVL in preterm infants has been discussed [1, 3, 16, 19–21]. Only few and often small clinical studies have addressed this subject so far (Table 1). Two elaborate and comparatively large studies reported a higher risk for development of preterm IVH upon *Ureaplasma* exposure [8, 22] (Table 1). One study, however, did not confirm such a correlation [6, 7, 23–28] (Table 1). Similarly, a significant association between prenatal and postnatal *Ureaplasma* infection and PVL has not been verified so far [6–8, 22, 23, 25, 26] (Table 1). A study addressing long-term neurodevelopmental outcome in preterm infants, however, found intrauterine *Ureaplasma* infection to be associated with cerebral palsy and psychomotor delay at the age of 24 months [26].

The presence of *Ureaplasma* spp. within the CSF is not necessarily accompanied by local inflammation. Single studies reported on *Ureaplasma* detection within the CSF without an elevation of typical biomarkers of inflammation, such as interleukins (ILs) or tumor necrosis factor-α [8, 29]. Clinically symptomatic *Ureaplasma* meningitis, however, is usually accompanied by characteristic CSF findings including pleocytosis, elevated protein, and, typically, decreased glucose levels [16, 17].

**Ureaplasma*-Driven Neonatal Neuroinflammation: Animal Studies**

Animal models addressing *Ureaplasma*-driven neuroinflammation are scarce. In a mouse model, prenatal *Ureaplasma* infection provoked abnormal neuronal development with retarded myelination and microglia activation [30]. MRI data suggested disturbed brain growth and maturation upon intra-amniotic *Ureaplasma* infection in rhesus macaques [31]. Of note, the same primate model found no association between intra-amniotic *Ureaplasma* exposure and intracerebral elevation of pro-inflammatory cytokines, including IL-1β and tumor necrosis factor-α [32]. In sheep, chronic intrauterine *Ureaplasma* exposure resulted in cerebral injury, comprising decreased astrocyte numbers and increased oligodendrocytes [33]. Interestingly, however, this was accompanied by protective preconditioning effects against secondary inflammatory hits [33].

All 3 available animal models described CNS inflammation subsequent to prenatal *Ureaplasma* infection. However, despite the ability of *Ureaplasma* spp. to cross the blood-brain barrier (BBB), no *Ureaplasma* growth was detected in the ovine CSF, and *Ureaplasma* mRNA was found in only 1 of the 10 primate brains [32, 33]. To date, there are no animal models representing invasive CNS infection caused by *Ureaplasma* spp.

**Ureaplasma*-Driven Neonatal Neuroinflammation: *In vitro* Data**

Available *in vitro* data on *Ureaplasma*-driven neuroinflammation derive from our own cell culture model of *Ureaplasma* meningitis, using human brain microvascu-
lar endothelial cells (HBMEC), main components of the BBB. *Ureaplasma* spp. did not evoke classic inflammatory responses in HBMEC [34, 35]. Some pro-inflammatory mediators were even suppressed upon pathogen exposure, namely, monocyte chemoattractant protein (MCP)-3 and granulocyte colony-stimulating factor (G-CSF), as well as important agents in inflammatory cell death, including caspases 1 and 4 [34–36].

Several pro-apoptotic agents, such as caspases 3, 7, and 9, were upregulated in HBMEC upon *Ureaplasma* exposure, and, ultimately, the rate of cell death increased in cells with pathogen contact [36]. Moreover, *Ureaplasma* spp. were shown to influence receptors and mediators constituting BBB permeability. Atypical chemokine receptor (ACKR) 3 was elevated in *Ureaplasma*-exposed HBMEC [37]. Similarly, *Ureaplasma* spp. increased C-X-C chemokine receptor (CXCR) 4 and vascular endothelial growth factor (VEGF) expression in HBMEC [34, 35]. ACKR3, CXCR4, and VEGF enhancements have all been associated with BBB leakage [38–42]. A negative impact of *Ureaplasma* spp. on endothelial barrier function was confirmed by continuous monitoring of cell adhesion properties [36].

In HBMEC primed with bacterial LPS, *Ureaplasma* spp. modulated several LPS-induced immune reactions. LPS-evoked pro-inflammatory cytokine and chemokine

### Table 1. Clinical studies addressing neonatal *Ureaplasma* exposure and potentially associated neurological morbidities

| Study (year) | Study type | Infants total, n | GA, weeks | Patients Ureaplasma POS, n | Sample | Methods | Clinical characteristics (Ureaplasma NEG vs. Ureaplasma POS) (significance) |
|--------------|------------|------------------|-----------|---------------------------|--------|---------|---------------------------------------------------------------|
| Kirchner et al. [28] (2007) | Single center, retrospective cohort | 48 | 24–32 | 12 | Amniotic fluid | Culture | IVH °III–IV: 3.4 vs. 12.5 (ns) |
| Goldenberg et al. [6] (2008) | Single center, retrospective cohort | 351 | 23–32 | 61 | Cord blood | Culture | IVH °III–IV: 6.6 vs. 8.8 (ns) PVL: 2.3 vs. 3.8 (ns) |
| Viscardi et al. [8] (2008) | Single center, prospective cohort | 313 | <33 | 74 | Blood | PCR | IVH all: 42 vs. 54 (p = 0.092) IVH °III–IV: 12 vs. 24 (p = 0.039) PVL: 7 vs. 9 (ns) |
| Berger et al. [26] (2009) | Single center, prospective cohort | 114 | 23–33 | 32 | Amniotic fluid | Culture | IVH: 22.4 vs. 25 (ns) PVL: 1.5 vs. 12.5 (ns) Abnormal 2YNDO: 9.7 vs. 37.9 (p = 0.003) |
| Fonseca et al. [27] (2011) | Single center, prospective cohort | 95 | ≤32 | 12 | Blood | PCR | IVH °III–IV: 15.7 vs. 16.7 (ns) |
| Kasper et al. [22] (2011) | Single center, prospective cohort | 257 | <34 | 85 | Amniotic fluid | Placenta Amniotic membranes | PCR Culture | IVH: 8.9 vs. 18.5 (p = 0.032) IVH °III–IV: 0.0 vs. 4.9 (p = 0.013) PVL: 5.1 vs. 7.4 (ns) |
| Rodriguez-Trujillo et al. [23] (2016) | Single center, prospective cohort | 190 | >24 | 37 | Amniotic fluid | Culture | IVH °III–IV: 9 vs. 8 (ns) PVL: 0 vs. 0% (ns) |
| Cobo et al. [24] (2017) | Single center, prospective cohort | 228 | 22–36 | 22 | Amniotic fluid | Culture | IVH °III–IV: 3 vs. 4 (ns) |
| Glaser et al. [7] (2019) | Single center, prospective cohort | 103 | <30 | 40 | Cord blood Nasopharyngeal swabs | PCR Culture | IVH °III–IV: 27 vs. 28 (ns) PVL: 18 vs. 14 (ns) |
| Takakura et al. [25] (2019) | Single center, retrospective cohort | 38 | 22–33 | 5 | Amniotic fluid | Culture | IVH °III–IV: 8 vs. 0 (ns) PVL: 8 vs. 0 (ns) |

Studies with maternal *Ureaplasma* therapy or without direct comparison between exposed and nonexposed infants were not included. CSF, cerebrospinal fluid; GA, gestational age; IVH, intraventricular hemorrhage; NEG, negative; ns, not significant; POS, positive; PVL, periventricular leukomalacia; 2YNDO, neurodevelopmental outcome after 2 years.
responses for C-X-C chemokine ligand 5, MCP-1, MCP-3, IL-1α, IL-8, G-CSF, and vascular cell adhesion molecule 1 were mitigated upon Ureaplasma exposure [34, 35]. Vice versa, Ureaplasma spp. and LPS showed additive effects regarding mediators increasing BBB permeability, resulting in an intensified elevation of VEGF, intercellular adhesion molecule 1, ACKR3, and CXCR4 [34, 35, 37].

Discussion

The neonatal CNS is regarded as an immune-privileged site. Its immune privilege, however, can be undermined once inflammation has been established [43]. In this context, data from clinical and animal studies as well as in vitro results suggest certain key aspects in Ureaplasma-driven neuroinflammation. Ureaplasma exposure distinctly mediates pathways in the CNS that may (i) impair BBB integrity, (ii) mitigate pro-inflammatory immune responses, and (iii) bear an immunomodulatory capacity (Fig. 1).

By employing different mediators and receptors responsible for endothelial barrier function [38–42], Ureaplasma spp. appear to increase BBB permeability [34, 35, 37] (Fig. 1). Ureaplasma-driven apoptosis of HBMEC, as integral components of the BBB, may further compromise BBB integrity [36] (Fig. 1). A similar ability to induce apoptosis in HBMEC has been described for other neuroinvasive pathogens [44, 45]. BBB breakdown is a key finding in several neuroinflammatory morbidities. It may facilitate pathogen entry into the CNS as well as inflammatory cell influx and thus promote neuroinflammation [46] (Fig. 1). Ureaplasma-driven BBB impairment may therefore represent an important mechanism allowing invasive CNS infection both with Ureaplasma spp. and other pathogens (Fig. 1).

Even if present within the CNS, Ureaplasma spp. do not necessarily evoke classic cytokine and chemokine responses in vivo [29]. In vitro findings similarly indicate absent or even suppressed pro-inflammation [34–36]. In case of infections, cytokines, chemokines, and cell death usually interact to achieve pathogen eradication [47, 48]. Absent local inflammatory responses in Ureaplasma-driven neuroinflammation may thus impede bacterial elimination, reduce the ability to resolve infections, and promote sustained inflammation [34–36] (Fig. 1). Interestingly, this phenomenon may be limited to Ureaplasma-induced CNS infection. In other (non-immune-privileged) compartments, such as lung, chorioamnion, or blood, Ureaplasma spp. were shown to evoke marked pro-inflammatory immune responses [49–55].

Ureaplasma-driven immunomodulation may be another aspect facilitating secondary infections. In vitro findings of mitigated pro-inflammatory responses in co-stimulated HBMEC may indicate reduced immune responses in the event of coinfection in vivo [34, 35]. Clinical and animal studies revealed mitigated LPS-induced inflammation in Ureaplasma-colonized fetal sheep and a higher sepsis incidence in Ureaplasma-exposed preterm infants, respectively [7, 56]. A potentiated enhancement of mediators allowing BBB passage, as seen in co-stimulated cells, may contrarily aggravate barrier impairment and facilitate invasive CNS infections in vivo [34, 35, 37].

As polymicrobial colonization is common in preterm infants, Ureaplasma-driven immunomodulation in the event of coinfection may be of particular clinical relevance.

Some inflammatory mediators appear to exert additional neuroprotective and neuroregenerative effects. In animal models, MCP-1 increased brain ischemia tolerance and G-CSF proved beneficial in neonatal hypoxemia-ischemia [57, 58]. Ureaplasma-induced attenuation of these mediators in vitro may therefore indicate impaired brain resilience and increased CNS vulnerability to secondary injurious events in vivo. Altogether, this may not only aggravate the sequelae of Ureaplasma CNS infection, but may also facilitate other neurological morbidities of prematurity (Fig. 1).

Only few clinical studies address the potential association between Ureaplasma exposure and development of IVH and PVL. Results are contradictory, and several studies are limited by small numbers (Table 1). Moreover, a certain selection bias has to be presumed, since invasive diagnostic measures are primarily applied to sicker patients. Most authors furthermore did not distinguish between Ureaplasma urealyticum and Ureaplasma parvum, although no difference in outcome was found in the 1 study comparing both spp. [8]. IVH and PVL are both commonly associated with severe long-term sequelae and are therefore of considerable clinical relevance. Scarce data call for large clinical studies to elucidate the role of Ureaplasma spp. in these morbidities.

Apart from a direct impact of local Ureaplasma CNS infection, brain injury may also be generated by Ureaplasma-driven systemic inflammation initiated elsewhere (Fig. 1). Animal models demonstrated brain-derived inflammatory responses upon peripheral cytokine exposure and profound neurodegeneration caused by systemic inflammation [59, 60]. Increased levels of pro-inflamm-
Fig. 1. Presumed cascades and pathomechanisms in *Ureaplasma*-driven neuroinflammation. a *In vitro* results indicate that *Ureaplasma* spp. may increase BBB permeability via employment of ACKR3, CXCR4, and VEGF. Apoptosis of HBMEC may additionally impair barrier function. Mitigation of the inflammatory mediators MCP-3 and G-CSF as well as downregulation of inflammatory caspases may hamper pathogen elimination. All factors may ultimately facilitate influx of inflammatory cells, *Ureaplasma* spp., and other pathogens into the CNS. b Animal data confirm *Ureaplasma*-associated neuronal impairment and cerebral injury. c Ultimate consequence may be acute and chronic neuroinflammation, as seen in clinical studies. d *Ureaplasma*-driven systemic inflammation may contribute to CNS affection. Illustrations: https://smart.servier.com/. spp., species; BBB, blood-brain barrier; ACKR, atypical chemokine receptor; CXCR, C-X-C chemokine receptor; VEGF, vascular endothelial growth factor; HBMEC, human brain microvascular endothelial cells; MCP, monocyte chemoattractant protein; G-CSF, granulocyte colony-stimulating factor; CNS, central nervous system.
Inflammationary cytokines were furthermore able to evoke BBB leakage in vitro [61]. In preterm infants, development of IVH or white matter disease have been associated with chorioamnionitis or elevated amniotic fluid ILs [19–21]. Elevated amniotic fluid IL levels in chronic Ureaplasma infected sheep, distinct pro-inflammatory responses in human monocytes, and the association between Ureaplasma spp. and chorioamnionitis may therefore indicate additional indirect pathways of Ureaplasma-driven neuroinflammation [6, 8–10, 52–55, 62, 63]. Pre-, peri-, or postnatal Ureaplasma exposure may activate fetal and neonatal inflammatory cascades, leading to systemic inflammation. This may, ultimately, cause CNS inflammation and brain injury in the affected infant even without the presence of Ureaplasma spp. within the CNS (Fig. 1). This hypothesis is underlined by an ovine model of chronic intrauterine Ureaplasma infection, where cerebral inflammatory responses were registered, but not accompanied by cultural detection of Ureaplasma spp. in CSF [33]. In fact, studies found IVH development in preterm infants associated with in utero Ureaplasma exposure [22] as well as with Ureaplasma detection in serum, but not in CSF [8].

Of note, animal data demonstrated not only injurious but also protective effects of systemic fetal Ureaplasma exposure, preventing brain injury upon a second inflammatory hit [33]. This “preconditioning” could be explained by a phenomenon similar to a condition called “endotoxin tolerance,” describing a transiently refractory immune state following inflammation [64]. Assuming such Ureaplasma-driven endotoxin tolerance, systemic Ureaplasma infection may therefore prevent local CNS inflammation to some extent: systemic inflammation initiated by Ureaplasma spp. might cause a subsequent refractory immune state. Even in case of inflammation-induced BBB impairment, allowing influx of Ureaplasma and inflammatory cells into the CNS, local interactions between Ureaplasma spp. and preexposed immune cells would be mitigated. In fact, this phenomenon might explain cases of Ureaplasma presence within the CNS without relevant inflammatory responses [8, 29]. Dual effects exerted by Ureaplasma spp. may furthermore contribute to discrepant clinical data regarding an association with, for example, IVH and PVL (Table 1). Pathogen virulence, host immune response, and contributing risk factors such as polymicrobial interaction and the duration of infection might be critical determinants shaping Ureaplasma effects [3].

Increasing evidence for Ureaplasma-driven neonatal neuroinflammation raises the consecutive question of potential therapeutic approaches. Treatment standards of neonatal Ureaplasma infection in general are poorly defined, and therapy of Ureaplasma-driven CNS inflammation in particular is hampered by poor CNS penetration of well-established antibiotics like macrolides and clindamycin. Chloramphenicol as well as tetracyclines and quinolones have successfully been used for treatment of Ureaplasma meningitis in neonates, although contraindications and side effects have to be considered [16, 17]. In general, however, a postnatal therapy cannot fully intercept inflammatory processes deriving from intratertiary Ureaplasma exposure and might therefore not sufficiently prevent associated neonatal morbidities. In fact, a significantly increased rate of IVH was described in Ureaplasma-colonized preterm infants despite neonatal macrolide therapy [65]. Questions remaining to be determined therefore include the appropriate timing of antimicrobial therapy, the choice of antibiotics, duration and dosage of treatment, and the differentiation between colonization and infection [3]. Furthermore, antibiotic resistances as well as potential adverse effects have to be taken into account. Maternal erythromycin therapy, for example, has been associated with higher rates of infantile cerebral palsy, indicating potential long-term risks of treatment during pregnancy [66].

**Conclusion**

In vivo and in vitro data indicate a neuroinflammatory capacity of Ureaplasma spp. By employing a variety of mechanisms, Ureaplasma spp. appear to weaken different host immune defense strategies. Ureaplasma-driven BBB breakdown may facilitate CNS invasion, and attenuated immune reactions may impede pathogen eradication and allow chronic infections. Immunomodulation may aggravate these effects in the event of coinfections. Brain injury may furthermore derive from neonatal systemic Ureaplasma infection and sustained systemic inflammatory response.

Against the background of high prevalence of Ureaplasma spp. particularly in very immature preterm infants and persistently high rates of CNS morbidity in this cohort, the complex interplay of mechanisms exerted or induced by Ureaplasma spp. ought to attract notice to a considerable clinical relevance of Ureaplasma-driven neuroinflammation in neonates. Its full impact is likely to still be underestimated.
Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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