# Mechanisms and consequences of neuroinflammation following *Streptococcus pneumoniae* infection: implications for synaptic function

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**Abstract:** *Streptococcus pneumoniae* (*S. pneumoniae*) is the leading cause of bacterial meningitis, a disease associated with significant morbidity and mortality. Beyond direct neuronal injury, *S. pneumoniae* induces profound neuroinflammation, contributing to synaptic dysfunction and long-term cognitive impairment. One of the key pneumococcal virulence factors, pneumolysin (Ply), plays a critical role in neuroinflammation and synaptic pathology by disrupting the blood-brain barrier (BBB), inducing glutamate excitotoxicity and promoting synaptic loss. This review explores the molecular mechanisms underlying neuroinflammation in pneumococcal meningitis and its impact on synaptic function, highlighting potential therapeutic targets to mitigate neurological sequelae.

**Keywords:** *Streptococcus pneumoniae,* neuroinflammation, synaptic dysfunction

## 1. Introduction

Bacterial meningitis is an infection of central nervous system (CNS) sheaths, with *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* being the main causative agents. Though the relative importance of the latter has been reduced in the recent years due to the vaccination programme, it still remains relevant for low-income health systems. Despite advances in antibiotic therapy, mortality remains high and approximately 50% of survivors suffer from long-term consequences (focal neurological deficits, hearing loss, cognitive impairment and epilepsy) (van de Beek *et al.* 2016; Lucas *et al.* 2016; Wahl *et al.* 2018). These neurological complications arise from a combination of direct bacterial toxicity and neuroinflammatory responses, leading to synaptic loss and dysfunction. Understanding the mechanisms underlying this neuroinflammation is crucial for developing targeted therapies to improve patient outcomes.

## 2. *Streptococcus pneumoniae* in central nervous system infections

### 2.1. Pathway toward the central nervous system

The steps necessary for bacteria to cause the meningitis involve colonising the upper respiratory tract mucosa (typically as an asymptomatic event (Mook-Kanamori *et al.* 2011)), being transferred and surviving in the blood vessels (while proliferating to reach a sufficiently high bacteraemia load), eventually penetrating the blood-brain barrier (BBB) and resulting in the structural and functional changes in the brain tissue itself (Xu *et al.* 2024). In order to reach and invade the CNS, bacteria need to survive and replicate in the blood, achieving the appropriate load sufficient to cause brain infection. The strategy utilised by *S. pneumoniae* to this purpose involves a virulence factor capsular polysaccharide (CPS), which prevents the binding of both IgG and CRP to *S. pneumoniae* and thereby inhibits classical complement pathway activity (Hyams *et al.* 2010). In addition, pneumococcal surface proteins A and C sequester the C4 binding protein, limiting complement C4b deposition on the bacterial surface and preventing the destruction of bacteria (Haleem *et al.* 2019).

The next step is the adhesion of *S. pneumoniae* to endothelial cells of the brain microvasculature. This is achieved by the binding of the major adhesin

of the pneumococcal pilus-1, RrgA, to both polymeric immunoglobulin receptor (pIgR) and platelet endothelial cell adhesion molecule (PECAM-1). In addition, the choline binding protein pneumococcal surface protein C (PspC) contributes to the process, but binding only to the former target protein. Pneumococcal CbpA, meningococcal PilQ and PorA, and OmpP2 of *H. influenzae* were shown to bind to laminin receptor on endothelial cells (Orihuela *et al.* 2009; Iovino *et al.* 2017). The pneumococcal adherence and virulence factor A (PavA) has been identified as a pneumococcal adhesin for fibronectin and is also relevant for the adhesion to the endothelial cells (Pracht *et al.* 2005). Another pneumococcal virulence factor is neuraminidase A (NanA), a surface-anchored sialidase that facilitates colonisation by cleaving terminal sialic acid residues from oligosaccharide receptors of the host epithelial cells (Sharapova *et al.* 2018). It, however, also promotes the adhesion of *S. pneumoniae* to brain endothelial cells. This involves both its adhesin function and sialidase activity, believed to modify host cell receptors to reveal higher affinity ligands (Uchiyama *et al.* 2009). Finally, a similar role has been described for the teichoic acid (Heß *et al.* 2017).

### 2.2. Entry into the CNS

Once *S. pneumoniae* reaches the BBB, it can cross it by three main mechanisms, including transcellular migration, paracellular penetration and a "Trojan horse" mechanism via immune cells (Barichello *et al.* 2013), the relative importance of which is still not clearly established.

The transcellular pathway occurs via clathrin- and dynamin-dependent endocytosis (Radin *et al.* 2005; Asmat *et al.* 2014). In this process, pneumolysin (Ply), a cytolysin produced by *S. pneumoniae*, plays a critical role (Kalin *et al.* 1987).

Ply creates pores in eukaryotic cell membranes by binding membrane cholesterol and forming the pores in the target cell membrane (van Pee *et al.* 2017). It also binds the mannose receptor C type 1 (MRC-1) which leads to an anti-inflammatory response (Subramanian *et al.* 2019). Importantly, it has been shown that even within the isogenic *S. pneumoniae* population there is a stochastic heterogeneity in Ply expression, which gives rise to a variable fate and the ability of bacteria to cross the BBB (Surve *et al.* 2019). Namely, a low Ply-producing subset halts autophagosomal maturation and evades all intracellular defence mechanisms, promoting its prolonged survival and successful transcytosis across BBB. Conversely, high Ply expression extensively damages autophagosomes leading to pneumococcal escape into cytosol and efficient clearance by host ubiquitination machinery (Surve *et al.* 2018).

Hematogenous infection by *S. pneumoniae* led to massive transcriptional changes in the BBB microvessels. Among downregulated molecules were the important constituents of tight junctions, including occludin, claudin-5 and zonula occludens –1 (ZO-1). Conversely, it led to the upregulation of hypoxia-inducible factor 1 (HIF-1) with consequent increase in vascular endothelial growth factor expression (VEGF), a phenomenon known to occur in other forms of infection (Werth *et al.* 2010). VEGF is known to induce the change in tight junction organisation and increased BBB permeability in conditions such as ischemia or brain tumours (Engelhardt *et al.* 2014; Machein *et al.* 1999). Indeed, bacterial transfer via paracellular route has been visualised. It is inhibited by echinomycin, a potent HIF-1α inhibitor (Devraj *et al.* 2020), indicating its important role in the ensuing brain oedema.

Upon bacterial invasion, the host immune response is evoked, initially mediated by the activation of toll-like receptors 2 (Schröder 2003, Tomlinson 2014) and activation of the various signalling mechanisms. As a result of this, resident microglia become activated, releasing pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 (Coutinho *et al.* 2013). These cytokines attract neutrophils and other immune cells, leading to further BBB breakdown and increased intracranial pressure.

### 2.3. Structural and functional CNS damage

While this immune response is necessary for bacterial clearance, excessive inflammation exacerbates neuronal injury and synaptic dysfunction. In the animal experimental model, the rise in the levels of TNF-α has been correlated with the sensorineural loss in the cochlea (Perny *et al.* 2016). *S. pneumoniae* meningitis frequently results in auditory deficits due to cochlear damage and synaptic ribbon loss in the auditory system (Baronti *et al.* 2022). The inflammatory response and cytotoxic effects of Ply contribute to spiral ganglion neuron loss and irreversible hearing impairment. All these events are progressing in a matter of hours, underlining the importance of the prompt recognition of the condition and the institution of antibiotic therapy. This is reflected in the finding that both severity of disease and late arrival for treatment act as predictors for profound hearing impairment in children with bacterial meningitis (Roine *et al.* 2013). Damage to the auditory pathway can lead to central auditory processing disorders, further complicating rehabilitation efforts in survivors.

Structurally, the post-synaptic part of cortical synapses is located on dendritic spines, which are the protrusions of dendritic membranes. Morphologically, dendritic spines start as filopodia-like immature forms, progressing into mature ones (mushroom, stubby, or thin) (Segal *et al.* 2017). Functional maturation

of dendritic spines is manifested by the expression of postsynaptic density 95 (PSD95) and other postsynaptic scaffold proteins, followed by the insertion of the appropriate set of neurotransmitter receptors. This process is reversible and determines the stability of the synapses (Runge *et al.* 2020). Importantly, in various neurological conditions (including dementias), it is the level of synaptic loss, rather than the actual neuronal loss (death) that correlates better with the level of cognitive impairment (Colom-Cadena *et al.* 2020).

In both human post-mortem brain samples and animal models, it has been demonstrated that pneumococcal meningitis leads to significant synaptic loss in the neocortex. Immunostaining for synaptic markers such as synapsin I and PSD95 revealed reductions in pre- and post-synaptic densities, respectively, particularly in cortical layers 1 and 2 (Baronti *et al.* 2022). As a result of the early insult, Ply causes delayed changes eventually resulting in the spine loss, as manifested by the reduction of PSD95 expression (Wippel *et al.* 2013).

Pneumococcal infection is accompanied by the actual destruction of neurons, as well. This process is related to the release of glutamate, the major excitatory neurotransmitter in the cortex, from the astrocytes. It has previously been shown that the level of glutamate released correlates with the severity of the disease (Spranger *et al.* 1996). The uncontrolled release of glutamate leads to a phenomenon of excitotoxicity (Yu *et al.* 2023) in which the overactivation of NMDA receptors leads to massive $Ca^{2+}$ inflow into the neurons, triggering the death mechanisms. Importantly, in pneumococcal meningitis, a similar mechanism seems to be at play, because the use of NMDA receptor blockers acts in a protective manner against Ply-induced cell loss (Wippel *et al.* 2013).

The specificity of CNS as the site of infection is manifested by the fact that Ply can also stimulate functional elements of neurons, leading to diverse consequences. For example, Ply can activated voltage-gated sodium channels Nav1.8 on nociceptors to release calcitonin gene-related peptide (CGRP), which is stored in dense core vesicles at nerve endings (Pinho-Ribeiro *et al.* 2023). Upon release, CGRP acts via receptor activity modifying protein 1 (RAMP1) on meningeal macrophages to polarise their transcriptional responses, suppressing macrophage chemokine expression, neutrophil recruitment and dural antimicrobial defences. The activation of receptors on nociceptory neurons, which serve as a detector of tissue damage and whose signalling is critical for nociception (Staurengo-Ferrari *et al.* 2022) is associated with the pain in the disease.

This is not to say that *S. pneumoniae* affects only neurons. Astrocytes are much more abundant than neurons and are involved in BBB formation and maintenance (Cohen-Salmon *et al.* 2021). They are interconnected by connexin channels (Lei *et al.* 2023), each creating a hexameric pore in the membrane of the neighbouring cells, which, when apposed, form gap junctions that serve to facilitate the transfer of various small signalling molecules. It has been proposed that during the early stages of pneumococcal meningitis, Ply induces the release of ATP from astrocytes, which then, acting back via purinergic receptors, results in $Ca^{2+}$ overload, the destruction of astrocytic processes, plasma membrane permeabilization and eventually astrocytic death. This causes a breach in the BBB allowing for the passage of bacteria into the brain tissue (Bello *et al.* 2020).

An important understanding that follows from the previous discussion is that a simple administration of antibiotics if far from sufficient for the successful treatment and prevention of consequences in pneumococcal meningitis. In this regard, among numerous options tested, complement inhibition, specifically of C5 component emerges as the most viable one (Koning *et al.* 2024). It has been shown that a common nonsynonymous complement component 5 (C5) SNP (rs17611) is associated with unfavourable disease outcome and that C5 fragment levels in cerebrospinal fluid (CSF) of patients with bacterial meningitis correlated with several clinical indicators of poor prognosis. In line with data from humans, C5a receptor-deficient mice with pneumococcal meningitis had lower CSF white blood cell counts and decreased brain damage compared with WT mice (Woehrl *et al.* 2011).

The potential issue of targeting C5 directly (i.e. prior to its split into C5a and C5b) would be that it could prevent the formation of membrane attack complex (MAC), which serves as an executive arm of innate immunity in actually killing the bacteria. Recently, C5a inhibitors such as eculizumab and avacopan have been developed (Ricklin *et al.* 2024), presenting a potential opportunity to bypass this problem.

## 3. Conclusion

Neuroinflammation and excitotoxicity are central mechanisms driving synaptic dysfunction in pneumococcal meningitis. While antibiotic therapy is essential for bacterial clearance, additional interventions targeting neuroinflammatory pathways and synaptic protection are needed to improve neurological outcomes. Future research should focus on understanding long-term synaptic alterations and developing targeted therapies to mitigate the cognitive and sensory deficits observed in survivors. Advances in precision medicine, including biomarker-guided therapeutic strategies, hold promise for optimising treatment outcomes and minimising long-term neurological sequelae.

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