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SPECIAL ARTICLE

Pathophysiology of bacterial infection of the central nervous system and its putative role in the pathogenesis of behavioral changes

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Abstract
Invasion of the central nervous system (CNS) by microorganisms is a severe and frequently fatal event during the course of many infectious diseases. It may lead to deafness, blindness, cerebral palsy, hydrocephalus, cognitive impairment or permanent neurological dysfunction in survivors. Pathogens can cross the blood-brain barrier by transcellular migration, paracellular migration and in infected macrophages. Pathogens may breach the blood-brain barrier and be recognized by antigen-presenting cells through the binding of Toll-like receptors. This induces the activation of nuclear factor kappa B or mitogen-activated protein kinase pathways and subsequently induces leukocyte infiltration and proliferation and the expression of numerous proteins involved in inflammation and the immune response. Many brain cells can produce cytokines, chemokines and other pro-inflammatory molecules in response to bacteria stimuli; as a consequence, polymorphonuclear cells are attracted and activated, and release large amounts of superoxide anion and nitric oxide, leading to peroxynitrite formation and oxidative stress. This cascade leads to lipid peroxidation, mitochondrial damage and blood-brain barrier breakdown, contributing to cellular injury during neuronal infection. Current evidence suggests that bacterial CNS infections can play a role in the etiopathogenesis of behavioral disorders by increasing pro-inflammatory cytokines and bacterial virulence factors. The aim of this review is to summarize the current knowledge of the relevant pathophysiologic steps in CNS infections.

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Introduction

Bacterial infection of the central nervous system (CNS) is a life-threatening condition with a high rate of mortality. Even with protective barriers, pathogens can reach the CNS.[1] The replication of these microorganisms within the CNS occurs in association with the release of compounds such as peptidoglycans, cell wall fragments, lipoteichoic acids (from Gram positive bacteria)[2], lipopolysaccharides (from Gram negative bacteria) and exotoxins, which are highly immunogenic and may elicit an increased inflammatory response in the host.[1-4] The host's inflammatory response against the infection has been increasingly recognized as playing a central role in neurological morbidity and mortality. CNS infections may present clinically as meningitis, meningoencephalitis and, more rarely, myelitis.[5]

Cognitive outcomes after bacterial meningitis include impairment of memory, decreased psychomotor performance and impairment of attention/executive functions.[6] In neonatal meningitis, the main pathogens are *Streptococcus agalactiae* and *Escherichia coli* K1, which together are responsible for at least two thirds of all meningitis deaths in Europe.[7,8] *Listeria monocytogenes*,[9] also causes meningitis, usually in immunocompromised individuals and in pregnant women.[10] *E. coli* K1 infection includes cognitive involvement in 50% of patients.[11] The main bacterial agents causing meningitis in young children and adults are *Streptococcus pneumoniae* and *Neisseria meningitidis*, with the former being responsible for two-thirds of cases in Europe and the United States.[2,12-14] Pneumococcal meningitis leads to cognitive impairment in 30 to 52% of surviving patients,[2] including learning difficulties, cognitive slowness, short-term memory deficits and poor academic performance.[15] The aim of this review is to summarize the current knowledge of the relevant pathophysiologic steps of CNS infections: (a) bacterial crossing through the blood-brain barrier; (b) bacterial survival and growth within the CNS; (c) bacterial induction of CNS inflammation; and (d) the role of bacterial infection in the development of behavioral disorders.

Microbial traversal of the blood-brain barrier

The CNS is protected by a bony skull, the leptomeninges, the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier.[1] The BBB is composed of brain microvascular endothelial cells, astrocytes and pericytes. It maintains the neural microenvironment by regulating the flux of molecules into and out of the brain, and protects the brain from microorganisms and toxins that come from the blood.[3] Pathogens can cross the BBB by transcellular migration, paracellular migration and by "hitch-hiking" inside infected macrophages. Using transcellular migration, pathogens can cross the BBB without any evidence of intercellular tight-junction disruption or detection of microorganisms between endothelial cells.[16] *S. agalactiae*, *S. pneumoniae*, *E. coli* and *N. meningitidis* reach the CNS through this mechanism[3] (Figure 1a). The paracellular traversal mechanism involves the penetration of the pathogen between barrier cells, with or without evidence of tight-junction disruption. *Borrelia sp* and *Treponema pallidum* cross the BBB through this mechanism (Figure 1b). Other pathogens can cross the BBB inside infected macrophages. *L. monocytogenes* enters host cells during internalization of phagosomal vacuoles, and produces phospholipase C and the pore-forming cytolysin listeriolysin O to escape the phagosome and replicate within the host cytosol.[17] *Mycobacterium tuberculosis* also crosses the BBB while residing in the phagosomes of macrophages[3,18] (Figure 1c).

Mechanisms of innate immunity in the CNS

The innate immune response represents the first line of defense against invading microorganisms. Bacterial compounds such as peptidoglycans, cell wall fragments, lipopolysaccharides and lipoteichoic acid, collectively known

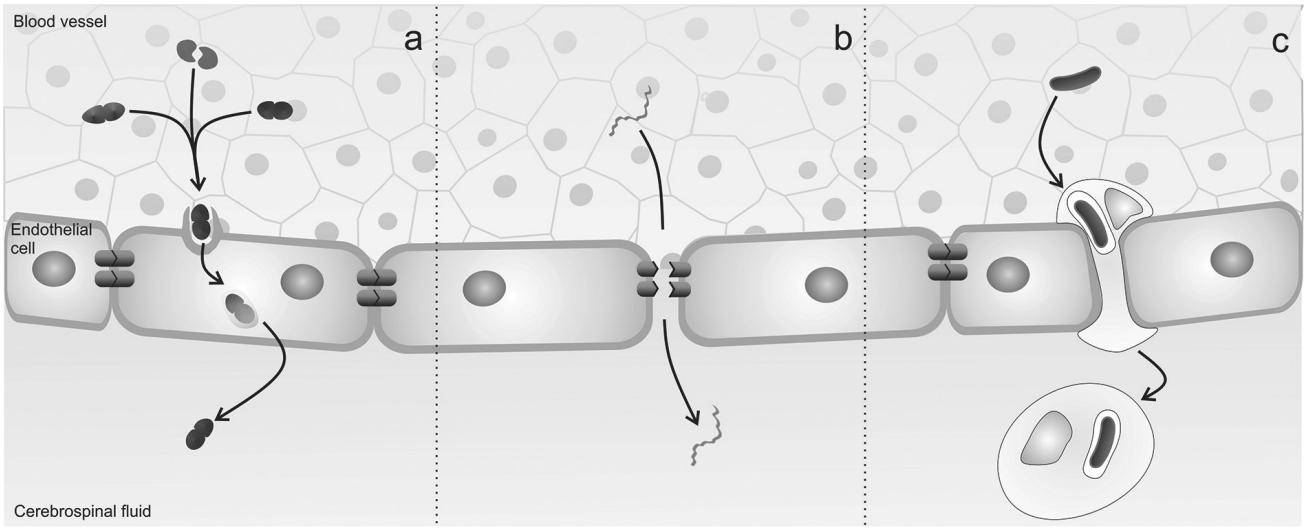

Figure 1 Mechanisms of microbial traversal of the blood-brain barrier: a. Transcellular traversal b. Paracellular traversal and c. the "Trojan horse" mechanism.

as pathogen-associated molecular patterns (PAMPs) are highly immunogenic and elicit strong inflammatory responses in the host. These compounds are recognized by antigen-presenting cells through binding to pattern recognition receptors (PRRs), including the Toll-like receptors (TLRs). Eleven members of the TLR family have been described to date in humans. TLRs are either expressed at the cell surface for extracellular ligand recognition or localized to endosomal compartments for the recognition of pathogen-associated nucleic acids.[19] Microglial cells express all TLRs identified to date, astrocytes express TLR 2, 3 and 9, neurons express TLR 3, 7, 8 and 9 and oligodendrocytes express TLR 2 and 3.[19] Most TLRs transduce their signal through a common intracellular adapter protein known as myeloid differentiation factor 88 (MyD88).[20] MyD88 is associated with Interleukin-1 (IL-1) and receptor-associated kinase-4 (IRAK-4), which is a serine/threonine kinase that plays an essential role in signal transduction by Toll/IL-1 receptors (TIRs).[21] Subsequently, IRAK interacts with the tumor necrosis factor (TNF) receptor-associated factor (TRAF) family, providing a link to NF-κB-inducing kinase, resulting in the nuclear translocation of NF-κB.[22] NF-κB comprises a closely associated family of transcription factors, which play a key role in the expression of genes implicated in the development of accessory cell and lymphocyte populations.[23] NF-κB is also a transcriptional activator of various genes involved in neuronal pathogenesis and in the production of cytokines and chemokines.[24,25] IL-1β production requires a second signal that is provided by intracellular protein complexes known as inflammasomes. The NLRP3 (cryopyrin) and the AIM2 (absent in melanoma 2) inflammasomes, which are activated by the exotoxin pneumolysin and bacterial DNA in pneumococcal infection, respectively, mediate cleavage of pro-IL-1β into mature IL-1β.[26] NLRP3 has been implicated in responses to the following bacteria: *Staphylococcus aureus*, *L. monocytogenes*, *Klebsiella pneumoniae* and *E. coli*.[27] Thus, when bacteria reach the CNS, PAMPs are recognized by PRRs, initiating the activation of the host immune response, which triggers the production of pro-inflammatory cytokines and chemokines and the expression of co-stimulatory molecules[1] (Figure 2). In response to these stimuli, leukocytes are attracted from the blood and activated. For instance, polymorphonuclear leukocytes cross the BBB by binding to selectins E and P along with IL-8 (CXCL-8). TNF-α induces production of adhesion molecules ICAM-1 and ICAM-2, which allow extravasation of the leukocyte along chemoattractant concentration gradients.[28] Leukocytes work to eliminate the invading pathogen through a rapid and robust production of reactive oxygen species (ROS). They release high amounts of superoxide anion (O_2-) and nitric oxide (NO), generating peroxynitrite (ONOO-).[29] The resulting oxidative stress leads to activation of cytokines, enhancing leukocyte activation, lipid peroxidation, mitochondrial damage and metalloproteinase activation.[4,30] In humans with meningococcal meningitis, TNF-α levels in the serum are correlated with

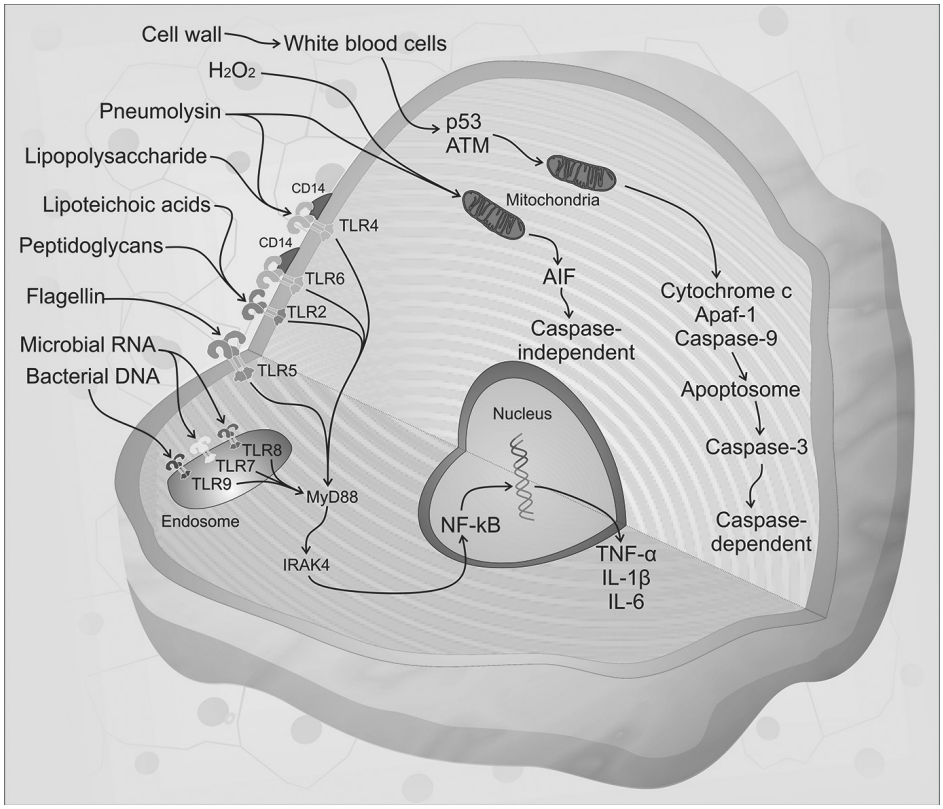

Figure 2 Pathogenesis and pathophysiology of bacterial CNS infections. The majority of TLRs utilize a common intracellular adapter protein known as myeloid differentiation factor 88 (MyD88), which activates IRAK. Subsequently, NF-κB is activated and induces the production of cytokines and chemokines. Bacterial toxins increase reactive oxygen species resulting in mitochondrial dysfunction that leads to the release of apoptosis-inducing factors into the cytosol. The host immune response, initiated by white blood cells, activates p53 and ATM, which converge on the mitochondria to initiate the release of cytochrome-c. This release activates the apoptosome composed of Apaf-1 that active caspase-9, finally resulting in the activation of caspase-3 -3; ATM: ataxia telangiectasia-mutated; TLR: toll-like receptor; IRAK: receptor-associated kinase.

fatal outcomes.[31] TNF-α is released into serum before IL-6 in meningococcal septic shock. High serum levels of IL-6 are also associated with unfavorable outcomes. In addition, IL-1 was exclusively detected in patients who also had high serum levels of IL-6, TNF-α, LPS and rapid fatal outcomes.[32] However, in the CSF of patients with meningitis, higher concentrations of TNF-α were observed than patients with septic shock/bacteremia and the CSF/blood glucose was inversely correlated with TNF-α, IL-6 and IL-1.[33] Patients with pneumococcal meningitis also exhibit a cerebral production of TNF-α, IL-1ß and IL-6.[34]

Neuronal damage in the context of bacterial infection of the CNS

Brain injury and neuronal death are not mediated simply by the presence of a viable pathogen, but they also occur as a consequence of the host's reaction to bacterial compounds.[35] Bacterial cell wall compounds, mainly polysaccharide capsules, are most likely the most important virulence factor. Bacterial cell wall compounds trigger a host inflammatory response from leukocytes and activate the tumor suppressor protein p53 and the ataxia telangiectasia-mutated (ATM) kinase, triggering caspase dependent-apoptosis.[36] The presence of the capsule also prevents the binding of iC3b (a complement factor that stimulates phagocytosis) and Fc (which stimulates receptor-mediated phagocytose) to the bacterial cell surface, affecting antiphagocytic activity.[37,38] Pathogens such as *S. pneumoniae*, *N. meningitidis*, *E. coli* K1 and *H. influenzae* use this pathogenic mechanism.[37,39,40] The virulence of other bacteria is based on the production of enzymes such as coagulase, proteolytic enzymes, hyaluronidase, neuraminidase and catalase.[37,41] Hemolysin and cytolysin from *Streptococcus* have the ability to cause inflammatory activation, and these same enzymes produced by *S. agalactiae* induce chemokines and ICAM-1 in brain microvascular endothelium cells.[36] Teichoic acids present in Gram+ bacteria can induce TNF-α and NO production, as well as the expression of ICAM-1.[42] Exotoxins are also produced by some bacteria as part of their growth and metabolism,[39,41] while endotoxins are part of the external portion of Gram (-) bacteria.[39] *S. pneumoniae* bacterial compounds like peptidoglycans and lipoteichoic acids are recognized in the CNS by TLR2.[43] The exotoxin pneumolysin is recognized by TLR4[22] and bacterial DNA is recognized by TLR9, which is an intracellular PRP activated by CpG.[44] Pneumolysin and H_2O_2 are produced and released by pneumococcus, causing neuronal cell death through mitochondrial damage.[45,46] This damage leads to the release of apoptosis-inducing factor (AIF) into the cytosol. AIF induces apoptosis by a caspase-independent pathway.[36,46] When pneumococcal cell wall compounds are released, they activate the host immune response and a large number of polymorphonuclear cells are attracted. p53 and ATM converge on mitochondria to initiate the release of cytocrome-c, which is necessary to form the apoptosome (Apaf-1) and activate caspase-9, resulting in activation of caspase-3 and caspase-dependent apoptosis.[36] *S. agalactiae* produces lipoteichoic acid that is through to activate TLR2, while TLR7 and/or TLR8 interact with microbial RNA.[2] *In vitro*, *L. monocytogenes* cell wall components such as lipoteichoic acids are recognized by TLR2 with the help of CD14 and TLR6.[47-50] The protein flagellin is recognized by TLR5.[49] *L. monocytogenes* is a classic example of a cytosol-adapted pathogen. It can escape quickly from the phagosomes of macrophages (or other cell types) and it reproduces rapidly in the cytosol.[51] This microorganism also expresses the toxin listeriolysin O, which is responsible for forming pores in the cell and causing lymphocyte apoptosis.[52] *E. coli* produces the endotoxin lipopolysaccharide, which is recognized by TLR4.[53] Furthermore, *E. coli* damages the microvascular endothelial cells that constitute the BBB in the human brain.[54] Another important pathogen, *S. pyogenes*, produces bacterial virulence factors such as, M protein, hyaluronic acid, capsule, fibronectin-binding proteins, streptolysin O and streptolysin S. The M protein binds to complement factors and other host proteins, allowing the pathogen to avoid activation of the alternate complement pathway evade phagocytosis.[55] The M protein has also been implicated in the internalization process, which involves cytoskeletal rearrangements. It is possible that these proteins provide an intraepithelial refuge for the organism, sheltered from phagocytes and humoral antibodies.[56,57] Another intracellular bacterium, *Mycobacterium tuberculosis*, infects the CNS and causes different manifestations of disease, like meningitis, space-occupying lesions in the brain parenchyma, and focal disease of the spinal cord and its osseous structures.[58] In previous studies of *S. agalactiae meningitis*, oxidative damage was elevated and enzymatic defense was decreased.[59] TNF-α, IL-1ß, IL-6 and cytokine-induced neutrophil chemoattractant-1 (CINC-1) levels were increased in the first hours after neonatal meningitis induction, prior to BBB breakdown in the hippocampus and cortex.[59] In infant rats with pneumococcal meningitis, the peak of pro-inflammatory cytokine and chemokine production was also associated with a disruption of the BBB.[60] TNF-α and CINC-1 levels were increased in the blood from jugular veins in comparison with arterial blood in the first hours after pneumococcal meningitis induction, indicating their production in the CNS.[61] Moreover, animals that survived bacterial meningitis showed impairments of memory and learning, depressive-like-behavior and anxiety-like symptoms.[62-64]

Behavioral disorders

Neuronal infection causes intense an inflammatory host immune response; it is potentially fatal and contributes to neurological symptoms.[1] There are several studies describing a probable role of cytokines and oxidative stress in behavioral disorders.[65,66] Epidemiological research over the last twenty years has indicated that the risk for schizophrenia is enhanced in offspring exposed to viral or bacterial infections in utero, possibly by a disruption in the programmed maturation of the brain in prenatal and early neonatal life.[67] This association between prenatal exposure to bacterial infection and risk of schizophrenia was evaluated, for example, in the Copenhagen Perinatal Cohort, which showed that prenatal exposure to bacterial infections in pregnant women were correlated with an increased risk of schizophrenia in their offspring.[68] It has been proposed that this association might be mediated through transplacental passage of maternally produced cytokines in response to these bacterial infections.[68,69] Individuals with meningitis during childhood had a 4.4-fold increased risk for schizophrenia and a 4.6-fold

increased risk for psychosis in adulthood when compared to their siblings without childhood meningitis.[70] The immune system may signal the CNS through the action of cytokines, which have also been implicated in the development of schizophrenia. For instance, IL-1ß is capable of inducing the differentiation of mesencephalic progenitor cells into dopaminergic neurons.[71,72] IL-6 is highly effective in decreasing the survival of fetal brain serotonergic neurons[73] and is increased in patients with schizophrenia.[74] There was a significant association between maternal IL-8 levels during the second trimester of pregnancy and the risk of schizophrenia in the offspring.[75] Cytokines in the CNS are also implicated to depressive disorders.[65] Animals subjected to pneumococcal meningitis and sepsis models had increased levels of pro-inflammatory cytokines in parallel with depressive-like behavior.[62,76] Interestingly, treatment with imipramine reversed these depressive-like symptoms and decreased TNF-α levels in the cortex 10 days after pneumococcal meningitis induction.[77] Impairment of learning and memory has also been demonstrated in bacterial meningitis in a neonatal animal model. Neonatal Wistar rats subjected to *S. agalactiae meningitis* showed aversive memory impairment in adulthood and a decrease of the brain-derived neurotrophic factor (BDNF) levels in the hippocampus and cortex.[58] Furthermore, the decreased BDNF levels in the hippocampus were correlated with memory impairment in adult animals subjected to pneumococcal meningitis in the neonatal period.[69] Other neuronal disorders are also related to bacterial infection. Obsessive-compulsive disorder or "tic" disorders are examples of pediatric neuropsychiatric disorders that have been associated with autoimmune disease secondary to *S. pyogenes*, a group A ß-hemolytic streptococcal infection.[78,79] The involvement of the host immune response is suggested by quantitative changes in circulating levels of TNF-α, IL-1ß and IL-6 levels in these patients. Pathogenic mechanisms include antibodies targeting the streptococcal epitope GlcNAc cross-reacting with neuronal molecules like tubulin, lysoganglioside and dopamine receptors.[80] Cytokines have an important role in the pathophysiology of brain infections, and they are implicated in a variety of common diseases that have been associated with production of cytokines, such as psychiatric disorders.[4,65]

Conclusion

Understanding the interactions between the complex networks of cytokines, other inflammatory mediators and leukocytes, and bacterial virulence factors may help to establish more effective therapeutic strategies for CNS infections and, therefore, a better outcome for affected subjects. Moreover, these diseases highlight the role of the immune system in the pathophysiology of psychiatric disorders, which represents an interesting research venue.

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Disclosures

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References

1. Sellner J, Tauber MG, Leib SL. Pathogenesis and pathophysiology of bacterial CNS infections. Handb Clin Neurol. 2010;96:1-16.
2. Mook-Kanamori BB, Geldhoff M, van der Poll T, van de Beek D. Pathogenesis and pathophysiology of pneumococcal meningitis. Clin Microbiol Rev. 2011;24:557-91.
3. Kim KS. Mechanisms of microbial traversal of the blood-brain barrier. Nat Rev Microbiol. 2008;6:625-34.
4. Barichello T, Generoso JS, Collodel A, Moreira AP, Almeida SM. Pathophysiology of acute meningitis caused by *Streptococcus pneumoniae* and adjunctive therapy approaches. Arqu Neuropsiquiatr. 2012;70:366-72.
5. Somand D, Meurer W. Central nervous system infections. Emerg Med Clin North Am. 2009;27:89-100, ix.
6. Hoogman M, van de Beek D, Weisfelt M, de Gans J, Schmand B. Cognitive outcome in adults after bacterial meningitis. J Neurol, Neurosurg, Psychiatry. 2007;78:1092-6.
7. Holt DE, Halket S, de Louvois J, Harvey D. Neonatal meningitis in England and Wales: 10 years on. Arch Dis Child Fetal Neonatal Ed. 2001;84:F85-9.
8. Heath PT, Okike IO, Oeser C. Neonatal meningitis: can we do better? Adv Exp Med Biol. 2011;719:11-24.
9. Roos KL, van de Beek D. Bacterial meningitis. In: PJ Vinken, GW Bruyn, editors. Handbook of clinical neurology. 2010;96:51-63.
10. Pamer EG. Immune responses to *Listeria monocytogenes*. Nat Rev Immunol. 2004;4:812-23.
11. Feigin RD. Bacterial meningitis in the newborn infant. Clin Perinatol. 1977;4:103-16.
12. Arda B, Sipahi OR, Atalay S, Ulusoy S. Pooled analysis of 2,408 cases of acute adult purulent meningitis from Turkey. Med Princ Pract. 2008;17:76-9.
13. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. New Eng J Med. 2004;351:1849-59.
14. Grandgirard D, Leib SL. Meningitis in Neonates: Bench to Bedside. Clin Perinatol. 2010;37:655-76.

15. Kihara M, de Haan M, Were EO, Garrashi HH, Neville BG, Newton CR. Cognitive deficits following exposure to pneumococcal meningitis: an event-related potential study. BMC Infect Dis. 2012;12:79.
16. Kim KS. Microbial translocation of the blood-brain barrier. Int J Parasitol. 2006;36:607-14.
17. Lopez-Castejon G, Corbett D, Goldrick M, Roberts IS, Brough D. Inhibition of calpain blocks the phagosomal escape of *Listeria monocytogenes*. PloS one. 2012;7:e35936.
18. Bobadilla K, Sada E, Esther Jaime M, González Y, Ramachandra L, Rojas RE, et al. Human phagosome processing of *Mycobacterium tuberculosis* antigens is modulated by IFN-gamma and IL-10. Immunol. 2012 Aug; [epub].
19. Hanke ML, Kielian T. Toll-like receptors in health and disease in the brain: mechanisms and therapeutic potential. Clin Sci (Lond). 2011;121:367-87.
20. Kronfol Z, Remick DG. Cytokines and the brain: implications for clinical psychiatry. The Am J Psychiatry. 2000;157:683-94.
21. Ichiyama T, Isumi H, Yoshitomi T, Nishikawa M, Matsubara T, Furukawa S. NF-kappaB activation in cerebrospinal fluid cells from patients with meningitis. Neurol Res. 2002;24:709-12.
22. Malley R, Henneke P, Morse SC, Cieslewicz J, Lipsitch M, Thompson CM, et al. Recognition of pneumolysin by Toll-like receptor 4 confers resistance to pneumococcal infection. Proc Natl Acad Sci. 2003;100:1966-71.
23. Tato CM, Hunter CA. Host-pathogen interactions: subversion and utilization of the NF-kappa B pathway during infection. Infect Immun. 2002;70:3311-7.
24. Koedel U, Bayerlein I, Paul R, Sporer B, Pfister HW. Pharmacologic interference with NF-kappaB activation attenuates central nervous system complications in experimental Pneumococcal meningitis. J Infect Dis. 2000;182:1437-45.
25. Kastenbauer S, Koedel U, Weih F, Ziegler-Heitbrock L, Pfister HW. Protective role of NF-kappaB1 (p50) in experimental pneumococcal meningitis. Eur J Pharmacol. 2004;498:315-8.
26. Koppe U, Suttorp N, Opitz B. Recognition of *Streptococcus pneumoniae* by the innate immune system. Cell Microbiol. 2012;14:460-6.
27. Davis BK, Wen H, Ting JP. The inflammasome NLRs in immunity, inflammation, and associated diseases. Annu Rev Immunol. 2011;29:707-35.
28. Granert C, Raud J, Xie X, Lindquist L, Lindbom L. Inhibition of leukocyte rolling with polysaccharide fucoidin prevents pleocytosis in experimental meningitis in the rabbit. J Clin Investig. 1994;93:929-36.
29. Klein M, Koedel U, Pfister HW. Oxidative stress in pneumococcal meningitis: a future target for adjunctive therapy? Prog Neurobiol. 2006;80:269-80.
30. Sellner J, Täuber MG, Leib SL. Chapter 1 - Pathogenesis and pathophysiology of bacterial CNS infections. In: Karen LR and Allan RT, editors. Handbook of Clinical Neurology. Elsevier; 2010. p. 1-16.
31. Waage A, Halstensen A, Espevik T. Association between tumour necrosis factor in serum and fatal outcome in patients with meningococcal disease. Lancet. 1987;1:355-7.
32. Waage A, Brandtzaeg P, Halstensen A, Kierulf P, Espevik T. The complex pattern of cytokines in serum from patients with meningococcal septic shock. Association between interleukin 6, interleukin 1, and fatal outcome. J Exp Med. 1989;169:333-8.
33. Waage A, Halstensen A, Shalaby R, Brandtzaeg P, Kierulf P, Espevik T. Local production of tumor necrosis factor alpha, interleukin 1, and interleukin 6 in meningococcal meningitis. Relation to the inflammatory response. J Exp Med. 1989;170:1859-67.
34. Moller K, Tofteng F, Qvist T, Sahl C, Sonderkaer S, Pedersen BK. Cerebral output of cytokines in patients with pneumococcal meningitis. Cri Care Med. 2005;33:979-83.
35. Scheld WM, Koedel U, Nathan B, Pfister HW. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. J Infect Dis. 2002;186(Suppl 2):S225-33.
36. Mitchell L, Smith SH, Braun JS, Herzog KH, Weber JR, Tuomanen EI. Dual phases of apoptosis in pneumococcal meningitis. The Journal of infectious diseases. 2004; 190: 2039-46.
37. Mitchell AM, Mitchell TJ. *Streptococcus pneumoniae*: virulence factors and variation. Clin Microbiol Infect. 2010;16:411-8.
38. Jonsson S, Musher DM, Chapman A, Goree A, Lawrence EC. Phagocytosis and killing of common bacterial pathogens of the lung by human alveolar macrophages. J Infect Dis. 1985;152:4-13.
39. Raymond J. [*Neisseria meningitidis*: characterisation and epidemiology]. Archives de pediatrie: organe officiel de la Societe francaise de pediatrie. 2012;19(Suppl 2):S55-60.
40. Gilsdorf JR, Marrs CF, Foxman B. Haemophilus influenzae: genetic variability and natural selection to identify virulence factors. Infect Immun. 2004;72:2457-61.
41. Xu SX and McCormick JK. Staphylococcal superantigens in colonization and disease. Front Cell Infect Microbiol. 2012;2:52.
42. Freyer D, Manz R, Ziegenhorn A, Weih M, Angstwurm K, Döcke WD, et al. Cerebral endothelial cells release TNF-alpha after stimulation with cell walls of *Streptococcus pneumoniae* and regulate inducible nitric oxide synthase and ICAM-1 expression via autocrine loops. J Immunol. 1999;163:4308-14.
43. Mitchell D, Yong M, Schroder W, Black M, Tirrell M, Olive C. Dual stimulation of MyD88-dependent Toll-like receptors induces synergistically enhanced production of inflammatory cytokines in murine bone marrow-derived dendritic cells. J Infect Dis. 2010;202:318-29.
44. Hemmi H, Takeuchi O, Kawai T, Kaisho T, Sato S, Sanjo H, et al. A Toll-like receptor recognizes bacterial DNA. Nature. 2000;408:740-5.
45. Braun JS, Hoffmann O, Schickhaus M, Freyer D, Dagand E, Bermpohl D, et al. Pneumolysin causes neuronal cell death through mitochondrial damage. Infect Immun. 2007;75:4245-54.
46. Braun JS, Sublett JE, Freyer D, Mitchell TJ, Cleveland JL, Tuomanen EI, et al. Pneumococcal pneumolysin and H(2)O(2) mediate brain cell apoptosis during meningitis. J Clin Invest. 2002;109:19-27.
47. Flo TH, Halaas O, Lien E, Ryan L, Teti G, Golenbock DT, et al. Human toll-like receptor 2 mediates monocyte activation by *Listeria monocytogenes*, but not by group B streptococci or lipopolysaccharide. J Immunol. 2000;164:2064-9.
48. Seki E, Tsutsui H, Tsuji NM, Hayashi N, Adachi K, Nakano H, et al. Critical roles of myeloid differentiation factor 88-dependent proinflammatory cytokine release in early phase clearance of *Listeria monocytogenes* in mice. J Immunol. 2002;169:3863-8.
49. Janot L, Secher T, Torres D, Maillet I, Pfeilschifter J, Quesniaux VF, et al. CD14 works with toll-like receptor 2 to contribute to recognition and control of *Listeria monocytogenes* infection. J Infect Dis. 2008;198:115-24.
50. Hayashi F, Smith KD, Ozinsky A, Hawn TR, Yi EC, Goodlett DR, et al. The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. Nature. 2001;410:1099-103.
51. Lam GY, Czuczman MA, Higgins DE, Brumell JH. Interactions of *Listeria monocytogenes* with the autophagy system of host cells. Advances in immunology. 2012;113:7-18.
52. Carrero JA, Unanue ER. Mechanisms and immunological effects of apoptosis caused by *Listeria monocytogenes*. Advances in immunology. 2012;113:157-74.
53. Rivest S. Molecular insights on the cerebral innate immune system. Brain Behav Immun. 2003;17:13-9.

54. Khan NA, Iqbal J, Siddiqui R. *Escherichia coli* K1-induced cytopathogenicity of human brain microvascular endothelial cells. Microb Pathog. 2012;53(5-6):269-75.
55. Cole JN, Barnett TC, Nizet V, Walker MJ. Molecular insight into invasive group A streptococcal disease. Nat Rev Microbiol. 2011;9:724-36.
56. Gordon N. Sydenham's chorea, and its complications affecting the nervous system. Brain Dev. 2009;31:11-4.
57. Osterlund A, Engstrand L. Intracellular penetration and survival of Streptococcus pyogenes in respiratory epithelial cells in vitro. Acta Otolaryngol. 1995;115:685-8.
58. Drevets DA, Leenen PJ, Greenfield RA. Invasion of the central nervous system by intracellular bacteria. Clin Microbiol Rev. 2004;17:323-47.
59. Barichello T, Lemos JC, Generoso JS, Cipriano AL, Milioli GL, Marcelino DM, et al. Oxidative stress, cytokine/chemokine and disruption of blood-brain barrier in neonate rats after meningitis by *Streptococcus agalactiae*. Neurochem Res. 2011;36:1922-30.
60. Barichello T, Pereira JS, Savi GD, Generoso JS, Cipriano AL, Silvestre C, et al. A kinetic study of the cytokine/chemokines levels and disruption of blood-brain barrier in infant rats after pneumococcal meningitis. J Neuroimmunol. 2011;233:12-7.
61. Barichello T, Generoso JS, Silvestre C, et al. Circulating concentrations, cerebral output of the CINC-1 and blood-brain barrier disruption in Wistar rats after pneumococcal meningitis induction. Eu J Clin Microbiol Infect Dis. 2012;31:2005-9.
62. Barichello T, Dos Santos I, Savi GD, Simões LR, Generoso JS, Comim CM, et al. Depressive-like-behavior and proinflamatory interleukine levels in the brain of rats submitted to pneumococcal meningitis. Brain Res Bull. 2010;82:243-6.
63. Barichello T, Lemos JC, Generoso JS, Carradore MM, Moreira AP, Collodel lA, et al. Evaluation of the brain-derived neurotrophic factor, nerve growth factor and memory in adult rats survivors of the neonatal meningitis by *Streptococcus agalactiae*. Brain Res Bull. 2012 Jun [epub].
64. Barichello T, Silva GZ, Generoso JS, Savi GD, Michelon CM, Feier G, et al. Time-dependent behavioral recovery after pneumococcal meningitis in rats. J Neural Transm. 2010;117:819-26.
65. Marques AH, Cizza G, Sternberg E. [Brain-immune interactions and implications in psychiatric disorders]. Rev Bras Psiquiatria. 2007;29(Suppl 1):S27-32.
66. Brietzke E, Kapczinski F. TNF-alpha as a molecular target in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1355-61.
67. Brown AS, Susser ES. In utero infection and adult schizophrenia. Ment Retard Dev Disabil Res Rev. 2002;8:51-7.
68. Sorensen HJ, Mortensen EL, Reinisch JM, Mednick SA. Association between prenatal exposure to bacterial infection and risk of schizophrenia. Schiz Bull. 2009;35:631-7.
69. Gilmore JH, Jarskog LF. Exposure to infection and brain development: cytokines in the pathogenesis of schizophrenia. Schiz Res. 1997;24:365-7.
70. Abrahao AL, Focaccia R, Gattaz WF. Childhood meningitis increases the risk for adult schizophrenia. World J Biol Psychiatry. 2005;6(Suppl 2):44-8.
71. Potter ED, Ling ZD, Carvey PM. Cytokine-induced conversion of mesencephalic-derived progenitor cells into dopamine neurons. Cell Tissue Res. 1999;296:235-46.
72. Ling ZD, Potter ED, Lipton JW, Carvey PM. Differentiation of mesencephalic progenitor cells into dopaminergic neurons by cytokines. Exp Neurol. 1998;149:411-23.
73. Jarskog LF, Xiao H, Wilkie MB, Lauder JM, Gilmore JH. Cytokine regulation of embryonic rat dopamine and serotonin neuronal survival in vitro. Int J Dev Neurosci. 1997;15:711-6.
74. Kunz M, Cereser KM, Goi PD, Fries GR, Teixeira AL, Fernandes BS, et al. Serum levels of IL-6, IL-10 and TNF-alpha in patients with bipolar disorder and schizophrenia: differences in pro- and anti-inflammatory balance. Rev Bras Psiquiatria. 2011;33:268-74.
75. Brown AS, Hooton J, Schaefer CA, Zhang H, Petkova E, Babulas V, et al. Elevated maternal interleukin-8 levels and risk of schizophrenia in adult offspring. Am J Psychiatry. 2004;161:889-95.
76. Comim CM, Cassol-Jr OJ, Constantino LC, Petronilho F, Constantino LS, Stertz L, et al. Depressive-like parameters in sepsis survivor rats. Neurotox Res. 2010;17:279-86.
77. Barichello T, Milioli G, Generoso JS, Cipriano lAL, Costa CS, Moreira AP, et al. Imipramine reverses depressive-like parameters in pneumococcal meningitis survivor rats. J Neural Transm. 2012;119:653-60.
78. Marconi D, Limpido L, Bersani I, Giordano A, Bersani G. [PANDAS: a possible model for adult OCD pathogenesis]. Riv Psichiatria. 2009;44:285-98.
79. Tan J, Smith CH, Goldman RD. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. Can Fam Phys. 2012;58:957-9.
80. Church AJ, Dale RC, Giovannoni G. Anti-basal ganglia antibodies: a possible diagnostic utility in idiopathic movement disorders? Arch Dis Child. 2004;89:611-4.