Journal of
Neuroinfectious Diseases
ISSN: 2314-7326

Review Article Open Access

Proinflammatory Cytokines, Lipopolysaccharide & Granulocytes Increase Brain Water Content & Initiate Cerebral Edema Development in Bacterial Meningitis

Vivig Shantha Kumar* and Vignarth Shantha Kumar

Department of Internal Medicine, California Institute of Behavioral Neurosciences & Psychology, Fairfield, California

Abstract

Bacterial meningitis remains an overwhelmingly serious disease worldwide, associated with a considerably high incidence of long term neurological morbidity or even death. Despite the institution of appropriate antibiotic therapy over recent years, these therapeutic advances have failed to produce a corresponding reduction in neurological complications. Amongst the long-term neurological sequelae in bacterial meningitis, the most important sequelae include cerebrovascular disease and brain edema with subsequent increases in intracranial pressure. Recent experimental evidence suggests that live meningeal organisms account for only a minor degree of neurological injury in models of bacterial meningitis. More importantly, bacterial derived products, including toxic cell wall fragments and endotoxins, persistent and accumulative in the subarachnoid space following bactericidal killing by antibiotics or a sustenance of bacterial invasion and subarachnoid inflammation represent highly active elements capable of initiating adverse neuronal injury. This, in conjunction with other pathophysiological alterations in the central nervous system augments cerebral edema formation, which begins to increase during the acute phase of infection and progressively continues to increase over the disease course to culminate in dangerously elevated intracranial pressure levels, secondarily accounting for a high incidence of morbidity and mortality.

Keywords: Bacterial meningitis; Cerebral edema; Proinflammatory cytokines; Lipopolysaccharide; Granulocytes; Blood brain barrier dysfunction

Introduction

The blood brain barrier plays a vital role in maintaining vascular integrity and preventing developing cerebral edema in bacterial meningitis. Cerebral edema, during the course of bacterial meningitis, arises from an inflammatory mediated breakdown of the blood brain barrier. Proinflammatory cytokines are implicated in mediating cerebral edema and increase in intracranial pressure. For example, IL-1 is a proinflammatory cytokine produced by macrophages, vascular endothelium, and the monocytes in response to TNF and bacterial lipopolysaccharide. IL-1, additionally, induces the production of other cytokines, IL-6 and TNF-alpha to increase inflammatory cell burden and aggravate blood brain barrier dysfunction, resulting in massive increases in blood brain barrier permeability and cerebral edema formation. Equally causative, cerebral edema development following gram negative bacterial infections appears to stem from cell wall components by the invading microbial agent. As such, release of lipopolysaccharide endotoxin and cell wall fragments appears to be an initiative for brain edema in bacterial meningitis. With this, in this review we seek to comprehensively understand the plausible mechanisms responsible for cerebral edema during bacterial meningitis, with a particular focus on the intensity of subarachnoid space inflammation as a crucial mediator of this edematous process.

Discussion

Proinflammatory cytokines, gram negative bacterial lipopolysaccharide, & granulocytes mediate disruption of the blood brain barrier

The blood brain barrier plays a vital role in maintaining vascular integrity and preventing the development of cerebral edema. Several pieces of clinical and experimental evidence indicate the role of cerebral edema in bacterial meningitis. Meningitis caused by Haemophilus influenza and E.coli was shown to lead to the development of cerebral edema [1]. Tuomanen et al. highlighted the pivotal role of the vascular endothelium in bacterial meningitis by demonstrating endothelial activation and adhesion of leukocytes leads to brain edema formation [2]. Further, McCord et al. demonstrated the importance of oxygen derived free radicals in the breakdown of the integrity of the blood brain barrier and increase in permeability with the development of brain edema and increased intracranial pressure as consequences [3]. Likewise, Kadurugamuwa et al, Tuomanen et al, Tureen et al suggested oxygen derived free radicals further contribute to the development of brain edema through the breakdown of the blood brain barrier [4-7]. In conjunction with the above, Wispelwey et al. and Saukkonen et al. further supported the assumption of blood brain barrier breakdown in bacterial meningitis as a contributory factor in cerebral edema by suggesting a possible role of proinflammatory cytokines [8,9].

Proinflammatory cytokines

The brain parenchyma responds to various traumatic, infectious, or inflammatory insults by an abnormal accumulation of fluid and a subsequent enlargement of brain tissue in a phenomenon described as brain edema [10-12]. Cerebral edema, during the course of bacterial meningitis, arises from an inflammatory mediated breakdown

***Corresponding author:** Vivig Shantha Kumar, Department of Internal Medicine, California Institute of Behavioral Neurosciences & Psychology, Fairfield, California, E-mail: vivigsk@gmail.com

Received: 19-Apr-2023, Manuscript No. JNID-23-96695; **Editor assigned:** 21-Apr-2023, PreQC No. JNID-23-96695(PQ); **Reviewed:** 05-May-2023, QC No. JNID-23-96695; **Revised:** 11-May-2023, Manuscript No. JNID-23-96695(R); **Published:** 18-May-2023, DOI: 10.4172/2314-7326.1000450

Citation: Kumar VS, Kumar VS (2023) Proinflammatory Cytokines, Lipopolysaccharide & Granulocytes Increase Brain Water Content & Initiate Cerebral Edema Development in Bacterial Meningitis. J Neuroinfect Dis 14: 450.

of the blood-brain barrier, consequently increasing permeability [13,14]. In order to facilitate a structural alteration of the blood brain barrier, several mediators are involved, none more prominently than proinflammatory cytokines. As Wispelwey et al. and Saukkonen et al. suggested, proinflammatory cytokines have a definite role in mediating the development of cerebral edema and the increase in intracranial pressure observed in bacterial meningitis [8,9]. Cytokines play an important role in mediating the host's response to bacterial infection. Proinflammatory cytokines (TNF-alpha, IL-1, and IL-6) and anti-inflammatory cytokines (IL-10 and TGF-B) have all been implicated in mediating the sequential events of bacterial meningitis [15,16]. Animal models of bacterial meningitis have extensively proposed a role of inflammatory cytokines in mediating pathological alterations such as an increase in brain water content and the development of brain edema, as well as an increase in intracranial pressure commonly observed during the acute phase of bacterial meningitis. In particular, TNF-alpha and IL-1 are overwhelmingly implicated in many pathological responses to bacterial meningitis [16-19]. The influence of proinflammatory cytokines derived from the meningeal inflammatory process is emphasized by the observation of CSF leukocyte pleocytosis and the initiation of brain edema formation following inoculation of IL-1 and TNF. In support of a role of proinflammatory cytokines in initiating brain edema in bacterial meningitis, Bolton et al. observed that upon inoculation of pneumococci and the initiation of S. In P. pneumoniae meningitis, the blood-brain barrier was damaged at approximately 12 and 24 hour intervals. Moreover, the occurrence of structural perturbations of the blood-brain barrier strongly coincided with the highest levels of proinflammatory cytokines observed during the course of bacterial meningitis [20]. Similarly, de Vries et al., using cultured bovine models, supported the role of cytokines by demonstrating disruption of the blood-brain barrier in the presence of proinflammatory cytokines. Additionally, they proposed that cerebral endothelial cells exposed to cytokines increased production of vasoactive eicosanoids, with increased BBB permeability as a consequence [21]. Ultimately, The production of cytokines, leukocyte migration and recruitment, and breakdown of the blood brain barrier are pivotal events in mediating the sequential development of increased blood brain barrier permeability and cerebral edema development in bacterial meningitis.

In rabbit and human models of gram-negative bacterial meningitis, both TNF and IL-1 have been noted in the cerebrospinal fluid. During the course of bacterial meningitis, tumor necrosis factor has frequently been demonstrated in the cerebrospinal fluid [22-25]. In fact, monocytes and macrophages challenged with gram negative bacterial lipopolysaccharide endotoxin are commonly observed to upregulate synthesis of TNF [9] produced by endothelial cells, monocytes, macrophages, and supporting cells of the central nervous system (microglia and astrocytes), TNF is a proinflammatory cytokine with biological actions on the vascular endothelium and leukocytes. In vivo, TNF-alpha is responsible for the activation of proinflammatory functions of leukocytes and interleukin-1 production by the vascular endothelium. Building on this, TNF-alpha exerts its action on the cerebrospinal fluid and the adjacent blood brain barrier, leading to blood brain barrier injury followed by plasma and leukocyte cerebrospinal fluid influx with the attendant development of cerebral edema and accumulation of granulocytes in the cerebrospinal fluid. In an experimental model of pneumococcal meningitis involving rabbits, intracisternal injection of human recombinant TNF-alpha resulted in increased CSF leukocyte influx, blood brain barrier permeability, and brain edema. Likewise, the extent of blood-brain barrier damage in bacterial meningitis was positively correlated with levels of TNF in the cerebrospinal fluid. Moreover, antibodies directed against human recombinant TNF-alpha prevented the breakdown of the blood brain barrier, increase in permeability and the development of brain edema [26,27]. Similarly, rabbits with meningitis demonstrated decreased CSF leukocyte and protein influx followed by attenuation of brain edema formation following intrathecal administration of monoclonal antibodies against TNF-alpha [9]. Similarly, IL-1 is also a proinflammatory cytokine produced by macrophages, vascular endothelium, and monocytes in response to TNF and bacterial lipopolysaccharide. IL-1 exerts its inflammatory actions by acting on the vascular endothelium and granulocytes. For example, it induces the production of other cytokines, IL-6 and TNF-alpha, by the vascular endothelium and mediates disruption of the blood brain barrier, facilitating cerebrospinal fluid leukocyte trafficking. Further, IL-1 facilitates the development of cerebral edema by increasing the permeability of the blood-brain barrier, leading to the leakage of leukocytes, proteins, and plasma, ultimately contributing to an accumulation of inflammatory-rich exudate within the cerebrospinal fluid. Animal and human models of bacterial meningitis demonstrate increased levels of proinflammatory cytokines such as tumor necrosis factor alpha and IL-1 in the cerebrospinal fluid [28,29]. For example, when exposed to pneumococcal cell wall components and other bacterial products, monocytes and central nervous system supporting cells (astrocytes and microglia) produce IL-1 [8,30]. Intrathecal injection of lipopolysaccharides into the cerebrospinal fluid evoked a proinflammatory response defined by the release of the proinflammatory cytokines tumor necrosis factor, interleukin 1 and interleukin 6 [31]. As such, Injection of IL-1 into the CSF space has been demonstrated to lead to massive increases in BBB permeability with the attendant development of brain edema in different experimental models of bacterial meningitis [9,19]. Rat models of bacterial meningitis have been shown to undergo structural and functional modifications of the blood brain barrier following inoculation of bacteria and/or bacterial cell wall components, possibly mediated by IL-1. For instance, rats inoculated with human recombinant IL-1 were shown to display CSF leukocytosis, BBB injury, and increased BBB permeability [32]. Along the same lines, Quagliariello et al., using a rat model of bacterial meningitis, observed that inoculation of IL-1 was associated with an increase in CSF leukocytosis as well as an increase in blood brain permeability [19].

Anti-inflammatory cytokines such as TGF-b and IL-10 provide indirect evidence for the potent role of proinflammatory cytokines in initiating deleterious structural alterations predisposing to the development of cerebral edema. IL-10 and TGF-B, potent anti-inflammatory cytokines, thwart the inflammatory process in bacterial meningitis by antagonizing the production of corresponding proinflammatory cytokines (TNF-a and IL-1). IL-10 has been demonstrated in the CSF of patients with bacterial meningitis [33,34]. In patients with bacterial meningitis, leukocytes derived from the cerebrospinal fluid have been observed as a source of TGF-B using in-situ hybridization molecular techniques [35]. Produced by monocytes and B and T lymphocytes, IL-10 exerts its biological action by suppressing the synthesis of TNF-alpha [36-38]. Rabbits inoculated with either Listeria monocytogenes, Haemophilus influenzae type B, or Hib lipopolysaccharide developed bacterial meningitis. In the same study, intracisternal or intravenous administration of IL-10 resulted in a reduction of CSF TNF-alpha and a significant blunting of the CSF inflammatory response. As an anti-inflammatory cytokine, TGF-B acts by inhibiting monocyte production of TNF-a, IL-1, and IL-6 [39,40].

In experimental models of pneumococcal meningitis, intraperitoneal injection of TGF-B resulted in reduced formation of brain edema, procuring a favorable clinical course with bacterial meningitis [26].

Although the decisive role of proinflammatory cytokines in mediating brain edema in bacterial meningitis remains to be elucidated further, it is plausible that the cytokines TNF-alpha and IL-1 represent an important component in the pathway for the development of brain edema occurring during the course of bacterial meningitis by altering structural and functional properties of the blood brain barrier.

Lipopolysaccharide Endotoxin

In addition to proinflammatory cytokines, gram negative bacterial biologically active products also play a contributory role in the development of cerebral edema and increase in intracranial pressure. Cerebral edema is most commonly associated with meningitis caused by gram negative bacteria such as Haemophilus influenzae and Escherichia coli and less commonly in gram positive Streptococcus pneumonia [1,41]. The predilection for gram negative bacteria causing meningitis to lead to the development of cerebral edema stems from specific released bacterial structural components. More specifically, the endotoxin lipopolysaccharide released during the course of gram negative bacterial meningitis is vital to influencing the development of cerebral edema [42,43]. Indeed endotoxin released during the course of gram negative bacterial infections is clearly associated with adverse outcomes and the development of complications [44,45]. Gram negative bacterial products such as the cell wall and the endotoxin lipopolysaccharide released following the initiation of antibiotic therapy are important stimulators of brain edema development. In line with the above, gram negative models of bacterial meningitis frequently demonstrate the presence of endotoxin in the cerebrospinal fluid of patients during the time of diagnosis [7]. In an experimental model of E.coli meningitis, antibiotic therapy with cefotaxime, a third generation cephalosporin, induced rapid bacterial cell wall lysis leading to a significant increase in endotoxin concentration in the cerebrospinal fluid. Further, the increase in endotoxin concentration in the cerebrospinal fluid was positively correlated with an increase in cerebral edema development. Similarly, in a different experimental model of pneumococcal meningitis, lysed components of the cell wall were shown to be associated with the formation of brain edema and an increase in intracranial pressure [46]. Moreover, rats when inoculated intracisternal with Hib lipopolysaccharide were observed to have a significant increase in the breakdown of the blood brain barrier with an attendant increase in permeability and CSF leukocyte trafficking [1].

Experimental models of bacterial meningitis document an increase in brain water content secondary to infection in the subarachnoid space. In experimental models of pneumococcal meningitis, an increased formation of brain edema is commonly noted during the acute phase of infection. Cerebral edema development following gram negative bacterial infections appears to stem from cell wall components by the invading microbial agent. In particular, release of bacterial cell products fragments appears to be initiative- most commonly lipopolysaccharide endotoxin and cell walls. For example, pneumococcal cell wall fragments have been demonstrated to induce marked meningeal inflammation with the attendant development of brain edema and an increase in intracranial pressure [5,6]. Further, intracisternal injection of purified pneumococcal cell wall fragments resulted in the formation of brain edema, thereby supporting the observation that bacterial cell products, either cell wall components or LPS endotoxin) initiates the formation of brain edema in bacterial meningitis [47]. Besides the release of LPS endotoxin by the invading microorganism during the course of bacterial meningitis, endotoxin release during antibiotic treatment also contributes to the development of brain edema. Following the institution of antibiotics, cellular damage and lysis of the microorganism results in the large elaboration of a number of bacterial components- none more biologically active as the LPS endotoxin. Several pieces of clinical and experimental evidence agree that the introduction of antibiotics in treating gram negative bacterial infections is associated with the release of massive amounts of LPS endotoxin [48-50]. The common association of LPS endotoxin with local and systemic complications of gram negative bacterial infections lends support to its deleterious effect in bacterial meningitis [46]. Bacterial release of endotoxin into the surrounding CSF space exerts direct deleterious effects on the brain. One notable consequence is the development of brain edema, arising from the observation of a dramatic increase in brain water content following initiation of antibiotic therapy. In an experimental model of E. coli meningitis, antibiotic therapy with cefotaxime, a third generation cephalosporin, procured a significant increase in cerebrospinal fluid endotoxin levels. Moreover, the massive increase in endotoxin levels netted a corresponding increase in cerebral edema formation. Separately, chloramphenicol and cefotaxime were studied in an attempt to substantiate changes in CSF concentrations of endotoxin in gram negative models of meningitis with pathological alterations such as brain edema. Cefotamine, a cell wall synthesis inhibitor belonging to cephalosporins, resulted in massive increases in endotoxin concentration. Contrastingly, Chloramphenicol, an inhibitor of protein synthesis belonging to tetracyclines netted only a marginal increase in endotoxin concentrations [51]. In a separate study with similar results, rabbits with gram-negative sepsis were observed to orchestrate a massive release of endotoxin following antibiotic therapy.

Experimental models of bacterial meningitis demonstrate structural modifications of the blood brain barrier following exposure to bacterial cell wall components- namely lipopolysaccharide. In particular, increased vascular permeability to proteins and fluid in bacterial meningitis positively correlates with structural modifications of the vascular endothelium of the blood-brain barrier. More specifically, gap junctions between endothelial cells have been shown to be distorted and widely placed [52]. LPS endotoxin, released during the course of bacterial meningitis, exerts its biological actions either by directly damaging the vascular endothelium leading to an impairment of endothelial structural integrity or by activating granulocytes with the subsequent release of inflammatory cytotoxic byproducts [53-55]. Similarly, intrathecal injection of lipopolysaccharide endotoxin derived from bacterial cell membranes elicits an inflammatory reaction culminating in the development of brain edema [56]. Following inoculation of endotoxin, activation of granulocytes sets into precedent an inflammatory reaction resulting in the release of proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1 and interleukin-6. Subsequently, released proinflammatory cytokines lead to an upregulation of granulocyte specific adhesion molecules (ICAM and VCAM) on the vascular endothelium, facilitating leukocyte rolling, adherence and transcellular endothelial migration to the paracellular spaces, and breakdown of the blood brain barrier [57]. Additionally, rats intracisternally inoculated with Hib LPS were observed to have a marked increase in the permeability of the blood brain barrier and CSF white blood cell concentrations, highlighting previous suggestions that LPS contributes to brain edema formation through a inflammatory mediated perturbation of the structural integrity of the vascular endothelium. In a separate study, involving rabbits with E. coli meningitis, monoclonal antibodies directed against the lipopolysaccharide endotoxin prevented the formation of brain edema

[58]. Given the potent role of lipid A in mediating the biological activity of endotoxin in gram negative bacterial infections, therapies directed against protein A appear to be protective against the development of cerebral edema. Polymyxin B is a polypeptide antibiotic that binds to lipid A, thereby neutralizing the deleterious effects of endotoxin [59-62]. Similarly, pretreatment with polymyxin B followed by inoculation of Haemophilus influenzae type b lipopolysaccharide prevented inflammatory CSF changes provoked by LPS [1].

Granulocytes: Neutrophils

Several pieces of experimental evidence propose that the development of post-infectious neurological sequelae and increased morbidity and mortality in bacterial meningitis may begin with inflammatory central nervous system perturbations mediated by granulocytes- namely neutrophils. Tuomanen et al. independently suggested that during the course of bacterial meningitis, increased leukocyte-endothelial interaction is observed, potentially highlighting a role of granulocytes in mediating cerebral alterations such as cerebral edema and increases in intracranial pressure [5]. Granulocytes are able to interact with the cerebral endothelium through two specialized interactions involving CD18 receptor complexes present on leukocytes as well as endothelial-leukocyte adhesion molecules present on the vascular endothelium [2,5]. Following stimulation by infectious stimuli, activated leukocytes upregulate cell surface expression of CD18 receptor complex molecules allowing adhesion to the vascular endothelium. Alternatively, the vascular endothelium induces expression of endothelial-leukocyte adhesion molecule in the presence of infectious/inflammatory stimuli (Lipopolysaccharide, TNF, or IL-1), facilitating leukocyte-endothelial cell interactions [63]. During meningeal inflammation, infiltrating leukocytes, in addition to combating invading microorganisms, contribute to tissue injury through the elaboration of potentially cytotoxic byproducts - namely cellular proteases, reactive oxygen derived species, nitric oxide, polyunsaturated fatty acids and glutamate [64-66]. Specifically, arachidonic acid and polyunsaturated fatty acids, derived from the granulocyte cell wall, are present in high concentrations in inflammatory exudates [67]. Furthermore, these leukocyte derived products appear to be involved in the nascent genesis of brain edema in experimental bacterial meningitis models. Likewise, Fishman et al. [68], Chan et al. [69], and Chan et al. [70] observed that leukocyte products- polyunsaturated fatty acids and oxygen-free radicals- were capable of mediating the formation of brain edema and increases in intracranial pressure in cortical specimens of rats, thereby emphasizing the role of granulocytes in the development of cerebral edema following bacterial meningitis.

Given the role of leukocyte derived products in the formation of brain edema, several studies indirectly highlight the role of neutrophil inflammation and granulocytic influx into the CSF as a contributory factor towards the development of cerebral edema, increases in intracranial pressure and adverse neurological sequelae in bacterial meningitis. In cytokine induced models of meningitis, mice devoid of vascular endothelial cell selectin expression

were shown to have decreased leukocyte flux into the CSF [9]. Alternatively, intravenous injection of monoclonal antibodies (MAb) directed against b2 integrins (anti-CD18, leukocyte-specific endothelial adhesion molecules, was shown to influence leukocyte migration across the vascular endothelium. Here, it was shown that b2-integrin directed MAbs prevented transcellular migration of leukocytes into the CSF and the development of brain edema following inoculation of rats with either live Streptococci pneumonia or pneumococcal cell wall components, Neisseria meningitidis, and Haemophilus influenzae B [71]. Similar results were observed, in a separate study, involving rabbits inoculated with Hemophilus influenza B lipopolysaccharide or live Haemophilus influenza B. Rabbits with either Hib LOS-induced or live Hib meningitis were treated with MAB directed against anti-CD18 molecules. Anti-CD18 directed monoclonal antibodies blocked inflammatory responses in the cerebrospinal fluid, preventing the influx of granulocytes into the leukocytes [72]. In an experimental model of meningitis, McAllister et al. documented that rabbits challenged with pneumococci displayed a positive association between the time of death and the degree of inflammation noted in the CSF. Rabbits with a more significant degree of meningeal inflammation were found to suffer from fatal consequences earlier compared to rats with lesser degrees of inflammation [73]. Similarly, Petersdorf and Luttrell et al. showed that granulocytic knockout dogs challenged with pneumococci were able to survive for approximately 62 hours compared to normal animals without impairments in the acute inflammatory response [74]. Tauber MG et al. demonstrated that, in rabbit models of pneumococcal meningitis, intracisternal administration of formyl methionyl leucyl phenylalanine lead to increased activation of granulocytes. Further, heightened activation of CSF granulocytes was accompanied by a corresponding increase in cerebral edema formation. Interestingly, in the same study, no marked differences in brain water content were observed between normal and neutropenic rabbits even after 24 hours of pneumococcal infection, hinting at the possibility that granulocytes mediate a late occurring but sustained structural modification of the blood brain barrier that contributes to the development of cerebral edema. Along the same lines, normal rabbits were shown to develop brain edema following intracisternal inoculation of salmonella minnesota Re 595 endotoxin compared to neutropenic rabbits [75].

Conclusion

Bacterial meningitis is a serious disease of the central nervous system, despite the widespread prevalence of multiple modern antimicrobial regimens. Even with the use of effective antimicrobial agents, complications of bacterial meningitis remain ever so prevalent. In particular, our understanding of the development of brain edema and increase in intracranial pressure following bacterial meningitis remains to be more clearly elucidated, but several pieces of experimental work advance our knowledge of the underlying pathogenic mechanisms at play. In particular, inflammatory byproducts (proinflammatory cytokines and granulocyte products) and bacterial cell wall components (lipopolysaccharide endotoxin) have all been implicated in the development of brain edema. Inflammatory cytokines and granulocyte derived products increase brain water content by interfering with the structural integrity of the blood brain barrier leading to an increase in blood brain barrier permeability and large fluxes of water into the brain parenchyma.

Acknowledgement

Not applicable.

Conflicts of Interest

The authors have no conflicts of interest to declare.

References

1. Syrogiannopoulos GA, Hansen EJ, Erwin AL, Munford RS, Rutledge J, et al. (1998) Haemophilus influenzae type B lipooligosaccharide induces meningeal inflammation. J Infect Dis 157:237-244.

2. Tuomanen EI, Saukkonen K, Sande S, Cioffe C, Wright SD, et al. (1989) Reduction of inflammation, tissue damage, and mortality in bacterial meningitis

in rabbits treated with monoclonal antibodies against adhesion-promoting receptors of leukocytes. J Exp Med 170:959-969.

3. McCord JM (1974) Free radicals and inflammation: Protection of synovial fluid by superoxide dismutase. Science 185: 529-531.
4. Kadurugamuwa JL, Hengstler Phdb, Zak O (1987) Effects of anti-inflammatory drugs on arachidonic acid metabolites and cerebrospinal fluid proteins during infectious pneumococcal meningitis in Rabbits. J Pediatr Infect Dis 6:1153-1154.
5. Tuomanen E, Liu H, Hengstler B, Zak O, Tomasz A, et al. (1985) The induction of meningeal inflammation by components of the pneumococcal cell wall. J Infect Dis 151:859-868.
6. Tuomanen E, Tomasz A, Hengstler B, Zak O (1985) The relative role of bacterial cell wall and capsule in the induction of inflammation in pneumococcal meningitis. J Infect Dis 151:535-540.
7. Tureen Jay H, Stella FB, Clyman R, Mauray F, Sande MA, et al. (1987) Effect of indomethacin on brain water content, cerebrospinal fluid white blood cell response and prostaglandin E2 levels in cerebrospinal fluid in experimental pneumococcal meningitis in Rabbits. J Pediatr Infect Dis 6:1151-1153.
8. Wispelwey B, Long WJ, Castracane JM, Scheid WM (1988) Cerebrospinal fluid interleukin- 1 activity following intracisternal inoculation of Haemophilus influenzae type b lipooligosaccharide into rats. Interscience Conference on Antimicrobial Agents and Chemotherapy, Los Angeles, California.
9. Saukkonen K, Sande S, Cioffe C, Wolpe S, Sherry B, et al. (1990) The role of cytokines in the generation of inflammation and tissue damage in experimental gram-positive meningitis. J Exp Med 171:439-448.
10. Klatzo I (1967) Neuropathological aspects of brain edema. J Neuropathol Exp Neurol 26:1-14.
11. Klatzo I (1985) Brain Edema following brain ischaemia and the influence of therapy. Br J Anaesth 57:18-22.
12. Klatzo I (1987) Pathophysiological aspects of brain edema. Acta Neuropathol 72:236-239.
13. Quagliarello VJ, Scheld WM (1986) Recent advances in the pathogenesis and pathophysiology of bacterial meningitis. Am J Med Sci 292:306-309.
14. Leib SL, Täuber MG (1999) Pathogenesis of bacterial meningitis. Infect Dis Clin North Am 13:527-548.
15. Frei K, Nadal D, Pfister HW, Fontana A (1993) Listeria meningitis: Identification of a cerebrospinal fluid inhibitor of macrophage listericidal function as interleukin 10. J Exp Med 178:1255-1261.
16. Mustafa MM, Ramilo O, Llorens XS, Olsen KD, Magness RR, et al. (1990) Cerebrospinal Fluid Prostaglandins, Interleukin 1β, and Tumor Necrosis Factor in Bacterial Meningitis: Clinical and Laboratory Correlations in Placebo-Treated and Dexamethasone-Treated Patients. Am J Dis Child 144:883-887.
17. Ohga S, Aoki T, Okada K, Akeda H, Fujioka K, et al. (1994) Cerebrospinal fluid concentrations of interleukin-1 beta, tumour necrosis factor-alpha, and interferon gamma in bacterial meningitis. Arch Dis Child 70:123-125.
18. Pfister H-W, Fontana A, Tauber MG (1994) Mechanisms of brain injury in bacterial meningitis: Workshop summary. Clin Infect Dis 19:463-479.
19. Quagliarello VJ, Wispelwey B, Long WJ, Scheld WM (1991) Recombinant human interleukin-1 induces meningitis and blood-brain barrier injury in the rat characterization and comparison with tumor necrosis factor. J Clin Invest 87:1360-1366.
20. Bolton SJ, Anthony DC, Perry VH (1998) Loss of the tight junction proteins occludin and zonula occludens-1 from cerebral vascular endothelium during neutrophil-induced blood–brain barrier breakdown in vivo. Neuroscience 86: 1245-1257.
21. de Vries HE, Kooij G, Frenkel D, Georgopoulos S, Monsonego A, et al. (2012) Inflammatory events at blood-brain barrier in neuroinflammatory and neurodegenerative disorders: Implications for clinical disease. Epilepsia 53:45-52.
22. Arditi M, Manogue KR, Caplan M, Yogev R (1990) Cerebrospinal fluid cachectin/tumor necrosis factor-alpha and platelet-activating factor concentrations and severity of bacterial meningitis in children. J Infect Dis 162:139-147.
23. Glimaker M, Kragsbjerg P, Forsgren M, Olcen P (1993) Tumor necrosis factor (TNF) in cerebrospinal fluid from patients with meningitis of different etiologies: High levels of TNF indicate bacterial meningitis. J Infect Dis 167:882-889.
24. Leist TP, Frei K, Kam-Hansen S, Zinkernagel RM, Fontana, A (1998) Tumor necrosis factor alpha in cerebrospinal fluid during bacterial, but not viral, meningitis. evaluation in murine model infections and in patients. J Exp Med 167:1743-1748.
25. Mustafa M, Ramilo O, Saez-Llorens X, Mertsola J, McCracken Jr GH (1989) Role of tumor necrosis factor alpha (cachectin) in experimental and clinical bacterial meningitis. Pediatr Infect Dis J 8:907-908.
26. Pfister HW, Frei K, Ottnad B, Koedel U, Tomasz A, et al. (1992) Transforming growth factor beta 2 inhibits cerebrovascular changes and brain edema formation in the tumor necrosis factor alpha-independent early phase of experimental pneumococcal meningitis. J Exp Med 176:265-268.
27. Kim SK, Wass CA, Cross AS, Opal SM (1992) Modulation of blood-brain barrier permeability by tumor necrosis factor and antibody to tumor necrosis factor in the rat. Lymphokine Cytokine Res 11:293-298.
28. Mustafa MM, Lebel MH, Ramilo O, Olsen KD, Reisch JS, et al. (1989) Correlation of interleukin-1β and cachectin concentrations in cerebrospinal fluid and outcome from bacterial meningitis. J Pediatr 115:208-213.
29. Frei Karl, Nadal David, Fontana Adriano (1990) Intracerebral synthesis of tumor necrosis factor-a and interleukin-6 in infectious meningitis. Ann N Y Acad Sci 594:326-335.
30. Riesenfeld-Orn I, Wolpe S, Garcia-Bustos JF (1989) Production of interleukin-1 but not tumor necrosis factor by human monocytes stimulated with pneumococcal cell surface components. Infect Immun 57:1890-1893.
31. Waage A, Halstensen A, Shalaby R, Brandtzaeg P, Kierulf P, et al. (1989) Local production of tumor necrosis factor alpha, interleukin 1, and interleukin 6 in meningococcal meningitis. relation to the inflammatory response. J Exp Med 170:1859-1867.
32. Ramilo O, Sáez-Llorens X, Mertsola J, Jafari H, Olsen KD, et al. (1990) Tumor necrosis factor alpha/cachectin and interleukin 1 beta initiate meningeal inflammation. J Exp Med 172:497-507.
33. Kornelisse RF, Savelkoul HF, Mulder PH (1996) Interleukin-10 and soluble tumor necrosis factor receptors in cerebrospinal fluid of children with bacterial meningitis. J Infect Dis 173:1498-1502.
34. Lehmann AK, Halstensen A, Sornes S, Rokke O, Waage A (1992) High levels of interleukin 10 in serum are associated with fatality in meningococcal disease. Infect Immun 63:2109-2112.
35. Ossege LM, Voss B, Wiethege T, Sindern E, Malin JP (1994) Detection of transforming growth factor beta1 mrna in cerebrospinal fluid cells of patients with meningitis by non-radioactive in situ hybridization. J Neurol 242:14-19.
36. Wang P, Wu P, Siegel MI, Egan RW, Billah MM (1995) Interleukin (IL)-10 inhibits nuclear factor κB (NFκB) activation in human monocytes. J Biol Chem 270:9558-9563.
37. Wanidworanun C, Strober W (1993) Predominant role of tumor necrosis factor-alpha in human monocyte IL-10 synthesis. J Immunol 151:6853-6861.
38. Van Furth AM, Seijmonsbergen EM, Langermans JA, Groeneveld PH, de Bel CE, et al. (1995) High levels of interleukin 10 and tumor necrosis factor in cerebrospinal fluid during the onset of bacterial meningitis. Clin Infect Dis 21: 220-222.
39. Musso T, Espinoza-Delgado I, Pulkki K, Gusella GL, Longo DL, et al. (1990) Transforming growth factor beta downregulates interleukin-1 (IL-1)- induced IL-6 production by human monocytes. Blood 76:2466-2469.
40. Chantry D, Turner M, Abney E, Feldmann M (1989) Modulation of cytokine production by transforming growth factor-beta. J Immunol 142:4295-4300.
41. Tauber MG (1989) Brain edema, intracranial pressure and cerebral blood flow in bacterial meningitis. Pediatr Infect Dis J 8:915-917.
42. Burroughs M, Cabellos C, Prasad S, Tuomanen E (1992) Bacterial components and the pathophysiology of injury to the blood-brain barrier: Does cell wall add to the effects of endotoxin in gram-negative meningitis? J Infect Dis 165.
43. Prins JM (2020) Endotoxin, antibiotics, and inflammation in gram-negative infections. Endotoxin in Health and Disease.
44. Morrison DC, Ulevitch RJ (1978) The effects of bacterial endotoxins on host mediation systems. Am J Pathol 93: 525-618.

45. Ryan JL (1985) Microbial factors in pathogenesis: lipopolysaccharides. Churchill Livingstone, New York.

46. Berman NS, Siegel SE, Nachum R, Lipsey A, Leedom J (1976) Cerebrospinal fluid endotoxin concentrations in gram negative bacterial meningitis. J Pediatr 88:553-556.

47. Tauber MG, Khayam-Bashi H, Sande MA (1985) Effects of ampicillin and corticosteroids on brain water content, cerebrospinal fluid pressure, and cerebrospinal fluid lactate levels in experimental pneumococcal meningitis. J Infect Dis 151:528-534.

48. Niemöller UM, Täuber MG (1989) Brain oedema and increased intracranial pressure in the pathophysiology of bacterial meningitis. Eur J Clin Microbiol 8:109-117.

49. Andersen BM, Solberg O (1980) The endotoxin-liberating effect of antibiotics on meningococci in vitro. Acta Pathol Microbiol Scand 88:231-236.

50. Shenep JL, Mogan KA (1984) Kinetics of endotoxin release during antibiotic therapy for experimental gram-negative bacterial sepsis. J Infect Dis 150:380-388.

51. Shenep JL, Barton RP, Mogan KA (1985) Role of antibiotic class in the rate of liberation of endotoxin during therapy for experimental gram-negative bacterial sepsis. J Infect Dis 151:1012-1018.

52. Quagliarello VJ, Long WJ, Scheld WM (1986) Morphologic alterations of the blood-brain barrier with experimental meningitis in rats. J Clin Invest 77:1084-1095.

53. Harlan JM, Harker LA, Reidy MA, Gajdusek CM, Schwartz SM, et al. (1983) Lipopolysaccharide-mediated bovine endothelial cell injury in vitro. Lab Invest 48:269-274.

54. Gaynor E (1973) The role of granulocytes in endotoxin-induced vascular injury. Blood 41:797-808.

55. Yamada O, Moldow CF, Sacks T, Craddock PR, Boogaerts MA, et al. (1981) Deleterious effects of endotoxin on cultured endothelial cells: an in vitro model of vascular injury. Inflammation 5:115-126.

56. Wispelwey B, Lesse AJ, Hansen EJ, Scheld WM (1988) Haemophilus influenzae lipopolysaccharide-induced blood brain barrier permeability during experimental meningitis in the rat. J Clin Invest 82:1339-1346.

57. Galea I (2021) The blood–brain barrier in systemic infection and inflammation. Cell Mol Immunol 18:2489-2501.

58. Tauber MG, Shibl AM, Hackbarth CJ, Larrick JW, Sande MA, et al. (1987) Antibiotic therapy, endotoxin concentration in cerebrospinal fluid, and brain edema in experimental Escherichia coli meningitis in rabbits. J Infect Dis 156:456-462.

59. Corrigan JJ, Bell BM (1971) Endotoxin-induced intravascular coagulation. Prevention with polymyxin B sulfate. J Lab Clin Med 77:802-10.

60. Palmer JD, Rifkind D (1974) Neutralization of the hemodynamic effects of endotoxin by polymyxin B. Surg Gynecol Obstet 138:755-759.

61. Rifkind D, Hill RB (1967) Neutralization of the Shwartzman reactions by polymyxins. J Immunol 99:564-569.

62. Dubor F, Dosne AM, Chedid LA (1986) Effect of polymyxin B and colistin on induction of plasminogen anti activator by lipopolysaccharide in human endothelial cell culture. Infect Immun 52:725-729.

63. Bevilacqua MP, Pober JS, Mendrick DL, Cotran RS, Gimbrone MA, et al. (1987) Identification of an inducible endothelial-leukocyte adhesion molecule. Proc Natl Acad Sci USA 84:9238-9242.

64. Chan PH, Fishman RA, Caronna J, Schmidley JW, Prioleau G, et al. (1983) Induction of brain edema following intracerebral injection of arachidonic acid. Ann Neurol 13:625-632.

65. Chan PH, Fishman RA, Longar S (1984) The role of arachidonic acid in vasogenic brain edema. Fred Proc 141-152.

66. Chan PH, Kerlan R, Fishman RA (1984) Reductions of gamma-aminobutyric acid and glutamate uptake and (Na+ + K+)-ATPase activity in brain slices and synaptosomes by arachidonic acid. J Neurochem 40:309-316.

67. Chan PH, Fishman RA (1980) Transient formation of superoxide radicals in polyunsaturated fatty acid-induced brain swelling. J Neurochem 35:1004-1007.

68. Fishman RA, Sligar K, Hake RB (1977) Effects of leukocytes on brain metabolism in granulocytic brain edema. Ann Neurol 2:89-94.

69. Chan PH, Fishman RA (1978) Brain edema: Induction in cortical slices by polyunsaturated fatty acids. Science201:358-360.

70. Chan PH, Schmidley JW, Fishman RA, Longar SM (1984) Brain injury, edema, and vascular permeability changes induced by oxygen-derived free radicals. Neurol 34:315-315.

71. Petersdorf RG, Luttrell CN (1962) Studies on the pathogenesis of meningitis. I. Intrathecal infection*. J Clin Invest 41:311-319.

72. Weber JR, Angstwurm K, Bürger W, Einhäupl KM, Dirnagl U (1995) Anti ICAM-1 (CD 54) monoclonal antibody reduces inflammatory changes in experimental bacterial meningitis. J Neuroimmunol 63:63-68.

73. Sáez-Llorens X, Jafari HS, Severien C, Parras F, Olsen KD, et al. (1991) Enhanced attenuation of meningeal inflammation and brain edema by concomitant administration of anti-CD18 monoclonal antibodies and dexamethasone in experimental haemophilus meningitis. J Clin Invest 88:2003-2011.

74. McAllister CK, O'Donoghue JM, Beaty HN (1975) Experimental pneumococcal meningitis II characterization and quantitation of the inflammatory process. J Infect Dis 132:355-360.

75. Tauber MG, Borschberg U, Sande MA (1988) Influence of granulocytes on brain edema, intracranial pressure, and cerebrospinal fluid concentrations of lactate and protein in experimental meningitis. J Infect Dis 157:456-464.