J Exp Neurol. 2023;4(2):58-75.

Journal of Experimental Neurology Review Article

Late Decrease in Cerebral Blood Flow in Bacterial Meningitis: More than a Simple Normalization of Acute Inflammatory Vessel Wall Architecture?

Vivig Shantha Kumar[1,*], **Vignarth Shantha Kumar**[1]

[1]Internal Medicine, California Institute of Behavioral Neurosciences & Psychology, California, USA

[*]Correspondence should be addressed to Vivig Shantha Kumar, vivigsk@gmail.com

Received date: May 05, 2023, **Accepted date:** May 16, 2023

Citation: Kumar VS, Kumar VS. Late Decrease in Cerebral Blood Flow in Bacterial Meningitis: More than a Simple Normalization of Acute Inflammatory Vessel Wall Architecture?. J Exp Neurol. 2023;4(2):58-75.

Abstract

Acute bacterial meningitis is a disease with an overwhelmingly high mortality rate and high incidence of adverse neurological sequelae and poor neurological recovery amongst survivors. Amongst the numerous complications of bacterial meningitis, the presence of cerebrovascular disease represents a severe disease form. Vascular involvement during bacterial meningitis has long been established by numerous pathological and angiographic studies. Cerebrovascular changes known to occur in bacterial meningitis ranging from narrowing of large arteries by vasospasm to critical stenosis/obliteration of small to medium sized arteries/arterioles by vasculitis. Not surprisingly, alterations in CBF velocities have commonly been described during the inflammatory process and may represent an important component of brain injury during meningitis. In accordance with previous studies observing a biphasic cerebral flow pattern characterized by an early but transient increase in flow velocity, mostly due to reflexive vasospasm, and later by a sustained decrease in flow velocity, likely attributable to stenotic vasculitis, cerebral ischemia is a notable complication of bacterial meningitis during the advanced disease phase. Impaired cerebral perfusion during the late stages of disease may result from a variety of factors that contribute to a vital component of cerebral injury in bacterial meningitis. The pathogenesis of cerebral ischemia with progression of disease course is less clearly understood but may involve a complex interaction between inflammatory processes, systemic dysfunction, energy impairment, neuronal damage and intracranial pressure, factors of which we aim to more precisely understand and assign a more definite contributory role in the development of cerebrovascular ischemic consequences with advanced stages of bacterial meningitis.

Keywords: Brain imaging, Cerebrovascular regulation, Clinical Trials in Neurology, Experimental Neuro-pathology, Molecular neuroscience, Molecular Stroke Research, Neuro-immunology, Neurobiology, Translational neuroscience

Introduction

Cerebrovascular involvement has been commonly demonstrated in numerous models of bacterial meningitis. In adults with bacterial meningitis, cerebrovascular disorders have been described as one of the most common intracranial complications, accounting for a high incidence of poor neurological recovery. During the course of meningeal inflammation, alterations in cerebral blood flow (CBF) velocities are frequently observed, and are proposed to be important in the pathogenesis of brain injury. Earlier angiographic and pathologic studies have commonly described a narrowing of intracranial blood vessels as a possible cause of CBF fluctuations during different phases of bacterial meningitis. Further, from these studies, there is considerable evidence to suggest that dynamic changes in vessel caliber either as a consequence of transient or persistent narrowing of cerebral vessels closely influence CBF variations in bacterial meningitis. By analyzing several pieces of doppler studies, it is clear that CBF patterns during bacterial meningitis are divided into a biphasic response, characterized by an early increase and a subsequent late decrease in CBF velocity. Whilst numerous studies attempt to elucidate the pathomechanisms responsible for an early hyperemic phase in bacterial meningitis, very few studies probe the causative mechanisms underlying a late ischemic sequelae in bacterial meningitis. From our understanding of

the temporal fluctuations in CBF during the pathophysiology of bacterial meningitis, in this review, we specifically sought to understand the numerous factors responsible for a late/subsequent decrease in cerebral flow sufficient to initiate cerebral ischemic consequences following an initial hyperemic phase. With this, our review seeks to understand the contributory role of pathogenic factors particularly prominent during the late phase of meningitis, such as development of organic stenosis/vasculitis, decreased cardiac output and systemic hypotension, reduced cerebral metabolism and energy depletion, intense and prolonged inflammatory response, neuronal injury and attendant neuronal apoptosis and increased intracranial pressure, in the decrease of cerebral flow sufficient to initiate cerebral ischemic consequences and poor neurological recovery in these subsets of patients.

Decrease in Cardiac Output & Resultant Systemic Hypotension May Underlie a Late Decrease in CBF

Cardiovascular dysfunction is overwhelmingly common in patients with severe brain injury, accounting for a high incidence of in-hospital mortality [1-3]. Patients with severe traumatic brain injury (TBI) frequently exhibit signs of cardiac dysfunction including regional wall motion abnormalities, decreased left ventricular ejection fraction, and tachycardia amongst others. Additionally, TBI has been known to promote gradual and progressive ultrastructural cardiomyocyte modifications through the widespread activation and release of leukocytes and secretion of proinflammatory cytokines into the systemic circulation [4]. In response to a heightened expression of pro-inflammatory cytokines and chemokines, cardiac musculature undergoes remodeling in the form of increased collagen deposition, cardiac fibroblast proliferation and cardiomyocyte apoptosis [5]. The resulting cardiomyocyte apoptosis and resultant upregulation of chemokine expression may serve to recruit inflammatory/immune cells such as neutrophils and macrophages, which potentiate chronic cardiac remodeling to lead to a dysfunctional cardiac phenotype over time. In a well-constructed study to determine the significance of pathological immune responses following TBI in the advent of cardiac dysfunction, Zhao et al. remarked that TBI not only initiated acute cardiac defects, but also promoted chronic cardiac injury by decreasing left ventricular ejection fraction beginning at three days and continued to progressively decline at 30 days following TBI. At this chronic stage of 30 days after TBI, mice displayed an increased left ventricular volume, accelerated cardiac fibrosis and cardiac hypertrophy compared to the acute stage of three days after TBI or healthy control mice [6]. With this, it is likely that an early activation of proinflammatory responses following a TBI plays a critical role in the development and progression of heart failure by stimulating a host of pathological stimuli, such as angiotensin 2, norepinephrine, and oxidative stress, to ultimately drive a pathologically persistent myofibroblast activity and attendant cardiac fibrosis, effectively culminating in cardiac decline [7,8]. Not surprisingly, inhibition of inflammatory cell infiltration and proimmune responses with immunosuppressive therapies shortly following the onset of TBI may secondarily attenuate chronic cardiac remodeling and significant cardiac decline during the later stages.

With this in mind, neurologic infections such as meningitis and encephalitis frequently have been implicated as a pivotal cause of cardiac dysfunction, mostly notably in severe cases associated with cerebral edema and a significantly elevated intracranial pressure [9-11]. In describing the presence of cardiac dysfunction during brainstem encephalitis of viral origin, Ooi et al. utilized cardiac autopsy studies and measurement of neuroinflammatory markers to highlight a primary neurogenic focus as a cause of cardiac injury during disease course, effectively ruling it viral myocarditis as a possible causative factor [12]. Likewise, Schut et al. observed that patients with bacterial meningitis who developed a post-infective cerebral ischemia/infarction sequelae had a 50% higher likelihood of systemic complications including cardiac failure [13]. A closer analysis of the relationship between mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) may underlie the main factor responsible for influencing CBF fluctuations during bacterial meningitis [14,15]. Although increased intracranial pressure and systemic hypotension are commonly observed during the late stages of bacterial meningitis, CPP can be maintained to sustain adequate cerebral metabolic need if mean arterial pressure is maintained. With a combination of both intracranial hypertension and low mean arterial pressure, CPP can be lowered to a critically low threshold level, unable to sustain healthy CBF rates sufficient for metabolic demand, resulting in cerebral ischemia [16]. Further, a poor association between MAP, cerebral ischemia, and neurological decline/death has been demonstrated in different studies of bacterial meningitis [17-19]. In line with this observation, critically ill patients with severe acute bacterial meningitis are frequently treated with vasopressors such as epinephrine and norepinephrine in order to increase MAP to adequately maintain organ perfusion. For example, in a rabbit murine model of pneumococcal meningitis, though an increase in intracranial pressure (ICP) occurred during the acute phase of infection, CPP and resultant neurological outcome was preserved into the late stages of disease if the corresponding MAP remained normal. In the event of a critical reduction of MAP, CPP was also markedly decreased in cerebral ischemia and death of experimental animals, and the institution of a high fluid therapy prevented cerebral ischemia through the maintenance of a healthy MAP [16,20]. Additionally, in predicting the advent of cerebrovascular sequelae in intracranial infections, the degree of ICP elevation is not a negative prognostic predictor if it is accompanied by a complementary increase in systemic MAP to sustain an adequate basal CPP [15,21]. Likewise, in another study, Moller et al. demonstrated that during norepinephrine infusion, MAP increased from a value of 79 to 99 mm Hg in patients with severe acute bacterial meningitis, whereas in control patients, a larger increase in MAP was seen from 87 to 123.

More interestingly, only in patients with meningitis did CBF increase from 51 to 59 mL/100 gm per minute, however it remained unchanged in control patients [22]. Due to the fact that norepinephrine increased both MAP and CBF in patients with severe bacterial meningitis, it is likely that impaired cerebral autoregulation persists in these patients during the late stages of disease effectively blunting a protective cerebrovascular myogenic response and permitting CBF to be directly influenced by changes in systemic arterial pressure as determined by norepinephrine. Additionally, during a rise in MAP following norepinephrine infusion, in severe acute bacterial meningitis Moller et al. measured relative changes in CBF and mean flow velocity to emphasize a pathogenic role of impaired autoregulation as a putative mediator of decreased cerebral flow during the late stages of bacterial meningitis, and found that cerebral autoregulation was impaired (defined as an increase in Vmean (velocity mean) by approximately 10% for every 30 mm Hg increase in MAP) in the majority of patients as Vmean initially increased from a mean value of 46 to 63 cm/sec when MAP was correspondingly raised from 69 mm Hg to 110 mm Hg. Moreover, in accordance with previous observations, following a recovery of cerebral autoregulation approximately 7 days later, a great majority of these patients had an uncomplicated course, whereas an unrestored autoregulation in two patients led to a more protracted clinical recovery and a fatal outcome, thereby emphasizing the role of an impaired autoregulatory process to maintain CBF patterns during coincident cardiac dysfunction/systemic hypotension during the late phase of meningeal disease [23]. As previously described, an increase in CBF closely paralleling a rise in MAP is indicative of an impaired cerebrovascular autoregulation, allowing increases in MAP to be directly relayed into the cerebral microvasculature without the blunting effect of cerebral autoregulation. As previously stated, in support a parallel increase in MAP and CBF during severe bacterial meningitis, Moller demonstrated that global CBF, not simply regional CBF, increased during norepinephrine infusion during the late stage of severe bacterial meningitis, thereby corroborating previous observations that a closely aligned increase in CBF and MAP is an indirect measure of an impaired CBF autoregulation in meningitis [24]. Although norepinephrine, traditionally known as a vasopressor, increases systemic arterial pressure through diffuse arteriolar vasoconstriction to effectively combat a decrease in CBF during the late stages of meningitis, an alternative explanation may be that increased norepinephrine levels permeates through a denuded/dysfunctional blood brain barrier (BBB), known to occur in severe cases, to increase cerebral metabolism and subsequently CBF [25-28]. Further, in cultured astrocytes, norepinephrine administration activates glycolytic and oxidative pathways to increase glycolysis and oxidative metabolism, subsequently resulting in an increase in CBF [29]. Moreover, the penetration of norepinephrine across an intact-functional BBB is markedly low, hindering the possibility of norepinephrine in influencing CBF patterns during the early stage of infection or during milder cases where the BBB is not sufficiently degraded to allow for an increase in solute permeance. However, in animal models, following a disruption of the BBB by intracarotid injection of hypertonic urea, norepinephrine permeability greatly increases with a corresponding and simultaneous increase in CBF and oxidative metabolism [27,28]. Given this relationship, it may be tempting to consider that increased norepinephrine permeance through a denuded BBB may result in increased metabolism and attendant CBF, however, such a response may not be so straightforward. Instead, the increased MAP and consequent CBF elevation during norepinephrine administration is a function of impaired autoregulation and not because of an increase in cerebral metabolism due to the fact that global CBF decreases markedly less than oxidative metabolic rates with propofol sedation, and a more potent underlying pathological process is responsible for the significant decreases in CBF during the advanced stage of disease.

In conclusion, whereas with a recovery of autoregulation, the cerebral vasculature regains its ability to modulate healthy regional cerebral flow patterns despite fluctuations in MAP, in contrast during severe bacterial meningitis, a failure to restore autoregulation makes the cerebral vasculature critically dependent on MAP to maintain adequate cerebral perfusion and with a cardiac dysfunction and systemic hypotension during the advanced disease phase of bacterial meningitis, a lower MAP is unable to sustain sufficient CPP to result in cerebral ischemic consequences and significant neurological disability amongst survivors.

Reduced Cerebral Metabolism & Energy Depletion Attenuates Increases in Cerebral Flow Leading to Cerebral Hypoperfusion

In various animal experiments, severe infections such as septicemia have been shown to induce mitochondrial dysfunction, resulting in defective cellular metabolism and energy production [30,31]. As such, in the clinical setting, a poor correlation has been observed between the extent of mitochondrial dysfunction and recovery from septic shock [32]. Furthermore, in patients with sepsis, mitochondrial dysfunction was found to correspond to the degree of Adenosine triphosphate (ATP) depletion, and interestingly to the magnitude of organ failure and poor clinical recovery [33]. During the early phase of TBI, dramatic increases in energy needs ineffectively coupled with insufficient CBF increases lead to a state of overwhelming energy dysfunction and metabolic crisis, with consequent post-TBI energy depletion associated with a reduced neurological prognosis [34,35]. A closer analysis of the cellular events taking place during TBI suggests that following TBI, cerebral cells are exposed to dramatic ionic disturbances and need to expand a significant degree of energy to sustain healthy Na^+/K^+ ATPase activity for the restoration of a healthy membrane gradient. Coinciding with an overall significant energy depletion, oxygen consumption is simultaneously decreased, thereby prompting a switch

in cerebral metabolic pathways to result in hyperactivation of anaerobic glycolysis and lactate production and ensuing neurological dysfunction and cerebrovascular insults [36-39].

Similarly, in cases of severe acute bacterial meningitis, inadequate oxidative metabolism and resultant energy synthesis are frequently observed [40, 41]. During the advanced stage of meningitis, cerebral aerobic glycolysis is significantly blunted leading to a hyperactivation of anaerobic glycolysis and a subsequent increase in Cerebrospinal Fluid (CSF) lactate levels [42-44]. In agreement with other observations, a linear correlation is noted between the development of CSF lactic acidosis and the occurrence of anaerobic glycolysis. Experimental studies have demonstrated a suppression of oxidative mitochondrial function during the late stages of severe acute bacterial meningitis. For example, in pneumococcal meningitis models, the cerebral mitochondrial chain complex 1 is frequently inhibited, resulting in impaired energy metabolism [32]. Consistent with this suggestion, patients with severe community acquired meningitis overwhelmingly demonstrate a significantly compromised cerebral metabolism and attendant intracerebral energy production. Separately, in a retrospective study of patients with advanced bacterial meningitis, oxidative metabolism was found to be significantly suppressed in nearly 50% of patients, who subsequently showed a poor neurological recovery [45]. Additionally, a recent experimental model of purified, gram negative derived, lipopolysaccharide induced aseptic meningitis confirmed earlier descriptions of decreased intracerebral oxidative metabolism as a nidus for cerebral ischemic sequelae [46]. Likewise, another study demonstrated that in severe bacterial meningitis, observed cortical neuronal injury is most likely the consequence of inadequate energy production and resultant energy depletion as opposed to extensive cortical oxidative stress production. Further, the strong correlation between decreased ATP and total adenine nucleotide (TAN) levels, a consequent increase in xanthine and urate levels as well as a marked upregulation of xanthine oxidoreductase highlights a significant, accelerated & premature metabolic degeneration of adenine nucleotides to temporarily attenuate a compromised energy production [47]. From this observation, it seems reasonable that elevated urate levels in the brain & CSF represent degradative metabolic end products derived from ATP inadvertently released from energy-deprived/failing neuronal cells. Moreover, in the same study, the observation of a wedge-shaped cortical injury in these patients corroborates a plausible role of ineffective metabolism and defective energy production as the most likely underlying cause of cerebral ischemia, as opposed to a deleterious consequence of sporadic neuronal death. In considering a significant decrease in cerebral metabolism of oxygen and glucose, elevated lactate levels have been frequently reported in the CSF of patients with meningitis as well as in the brain parenchyma in pneumococcal models in meningitis in rabbits [48,49]. Coincidently, a large proportion of CSF lactate efflux is increased by a carrier mediated diffusion process from the brain to the blood stemming from an infection-mediated suppression of aerobic metabolism and not because of an exogenous systemic arterial concentration [50]. Interestingly, patients with a considerable degree of lactate efflux were subsequently found to develop poor neurological outcomes including cerebral ischemia and later infarction, findings closely resemblant to that found in patients suffering from severe head trauma [51,52]. Additionally, in a study analyzing cerebral energy metabolism by way of changes in lactate:pyruvate ratio (L:P) amongst patients with acute bacterial meningitis, inadequate cerebral energy metabolism was more prominent in patients with severe disease compared to milder disease forms, and this compromised energy production was not a direct consequence of insufficient tissue oxygenation, but rather an immediate consequence of the pathogenic micro-organism. In a well-constructed study, Rosenthal et al. postulated that regional cerebral tissue oxygen correlates strongly with local CBF patterns, raising the possibility that defective oxygen metabolism impairs healthy regional CBF to account for the late decrease in flow and onset of ischemic/infarction consequences [53]. As expected, Larsen et al. described a close association between an initial significant increase in the LP ratio, with elevated lactate levels and decreased pyruvate levels, followed by/occurring simultaneously with a correspondingly pronounced and transient decrease in local CBF [54]. This decrease in pyruvate levels agrees with earlier studies describing the relationship of low pyruvate levels with cerebral ischemia [55,56].

In considering decreased oxidative metabolism as a putative trigger for decreased CBF in meningitis models, a closer analysis of the relationship between glucose consumption/metabolism and CBF is necessary. In human studies, parallel increases between glucose consumption and CBF have commonly been demonstrated [57-59]. Additionally, in experimental studies in rats, CBF increase correlated better to an increase in glucose uptake compared to an increase in oxygen uptake, lending support to a possible metabolic coupling between CBF increase and glucose consumption during functional activation. Consistent with this viewpoint, during epileptic seizures associated with increased neuronal activity and energy metabolism, both glucose uptake and CBF parallelly increased by a factor of at least 2 [60]. From these previous studies, an increased oxidative metabolism of glucose and energy production correspond to relevant increases in CBF, and a suppressed glucose metabolism and hampered energy production attenuate CBF increases, predisposing to low flow patterns and resultant cerebral ischemia. Not surprisingly, the extent of cerebral ischemia can be determined by the degree of extracellular accumulation of anaerobic metabolites and associated substances. The vulnerability of the brain to cerebral ischemia is often attributed to its limited supply of high-energy metabolites, thereby becoming highly dependent on a continuous and sufficient delivery of oxygen and substrates for energy production [56].

Following states of TBI such as central nervous system (CNS) infections, rising energy needs of the brain parenchyma are attended to by a preferential hyperglycolysis to fuel these cells [61,62]. This is accomplished by a rapid increase in glutamate release into the neuronal synapse, where it may consequently stimulate astrocyte glycolysis and blood glucose uptake to produce lactate in order to satisfy short-bursts of high cerebral energy needs, generally lasting for only a few minutes [63-66]. Therefore, increased lactate concentrations represent a quintessential energy source in an energy deprived brain, allowing a fast and readily available source to meet energy needs in a brain devoid of oxidative metabolism [67-70]. As expected, in a rabbit model of pneumococcal meningitis, high CSF lactate concentrations, indicative of a blunted oxidative metabolism and a heightened anaerobic glycolysis in the brain, were observed in relation to a consequent reduction of CBF [71]. Interestingly, in determining changes in oxidative metabolism and glutamate levels as a critical precedent to the development of cerebral ischemia in severe acute bacterial meningitis, Poulsen et al. observed that the pattern of cerebral ischemia closely mirrored increases in extracellular glutamate concentrations [45]. While extracellular glutamate concentration is normally kept under very low circumstances due to an energy-demanding uptake process into surrounding astrocytes to support their metabolic needs, increased extracellular glutamate concentration may therefore signal a loss of oxidative metabolism and energy production in energy-deficient, dysfunctional astrocytes [72-74]. Although the possible mechanisms responsible for decreased CBF during states of decreased cerebral oxidative metabolism and energy production are not clearly elucidated, indirect evidence in the form of a considerably rapid rise in extracellular brain glutamate concentrations during ischemia can be interpreted as a marker of severity of ischemic neuronal injury, stemming from a progressive decrease in CBF.

Intense & Sustained Inflammatory Response Aggravates Energy Depletion to Blunt Early Increases in CBF Leading to a Late Decrease in Flow

Separately, energy depletion in bacterial meningitis may represent a deleterious consequence of the marked inflammatory response. Severe models of bacterial meningitis are associated with a significant upregulation of inducible nitric oxide (NO) synthase in invading inflammatory cells within the subarachnoid and ventricular space, demonstrated by elevated nitrite/nitrate CSF levels [75]. Inducible NO is generally well known to have profound effects on cellular metabolism and energy production in neuronal cells, wherein it may result in both inhibition of mitochondrial respiration and glycolysis [76,77]. With a prominent and sustained inflammatory response in the subarachnoid space, elevated NO levels may considerably decrease cerebral energy production and result in reduced cerebral flow demand. Consistent with this suggestion, PBN, a NO scavenger, not only inhibited intracerebral NO production but more importantly significantly attenuated cortical neuronal injury in close association with improved brain energy metabolism in bacterial meningitis [78]. Additional supportive evidence for the role of therapeutic mitigation of proinflammatory responses in bacterial meningitis as a nidus for blunted cerebral flow disturbances and cerebral ischemic consequences comes from the studies investigating the neuroprotective role of sedatives such as propofol and supportive measures such as hypothermia. Sedatives including propofol are frequently used in severe acute meningitis patients in order to achieve a reduction in cerebral metabolism, resulting in an efficacious reduction of cerebral blood volume and CBF and a consequent diminution of ICP. Propofol reduces global cerebral metabolism and associated CBF provided that metabolic coupling is intact [79]. In determining the role of propofol on global cerebral metabolism and CBF in severe acute bacterial meningitis, Moller et al. reported an unchanged CBF in relation to reduced cerebral metabolic rates of oxygen and glucose, emphasizing that metabolic coupling was impaired in these patients compared to healthy subjects [24]. Although propofol administration is associated with a normal cerebrovascular reactivity to carbon dioxide and autoregulation process, a commonly associated dose-dependent reduction of cerebral metabolic rate with propofol administration is instead due to a thwarting of neuronal injury by the inflammatory process. As an intense inflammatory reaction and induction of inflammatory genes mediate many of the pathophysiological processes conducive to ischemic brain damage in bacterial meningitis, propofol's neuroprotective role in reducing ischemic brain damage may be due to a downregulation of these inflammatory responses [80-83]. In bacterial meningitis, the neuroprotective effects of propofol may be related to an increase in GABA A (γ-Aminobutyric acid type A) signaling, which secondarily inhibits release of excitatory amino acids as well as blocks intracellular free radical formation by suppressing phospholipase A2 activation [84]. Further, the protective effect of propofol may include a decrease in ATP degradation, antagonization of NMDA receptors as well as antioxidant effects [85-87]. Several reports demonstrate a beneficial anti-inflammatory property of propofol to limit extent of neuronal energy depletion and consequent cerebral ischemic consequences in bacterial meningitis models. Chen et al. demonstrated that propofol administration blocks biosynthesis of proinflammatory mediators including tumor necrosis factor-alpha (TNF-α), interleukin-1b (IL-1β), interleukin 6 (IL-6) and NO in lipopolysaccharide stimulated macrophages [88]. Additionally, Sun et al. highlighted that propofol suppresses gene expression and synthesis of proinflammatory mediators such as nuclear-factor kappa B (NF-κB), TNF-α and IL-6 to provide protective effects to the intestine following a TBI in rats. [89]. Similarly, Shi et al. remarked that propofol exerts its anti-inflammatory actions by considered blunting NF-κB activation, thereby downregulation COX-2 expression and TNF-α secretion following cerebral ischemia to limit extension of infarction and ischemic sequelae [90]. Further, during aortic surgery propofol may exert a renal protective function through

a downregulation of the systemic inflammatory response as well as may attenuate neuroinflammation during cerebral ischemia-reperfusion injury [91,92]. As previously stated, Shi et al. described a significant reduction of neurological deficit scores, cerebral infarct size as well as neuronal injury approximately 24 hours following permanent regional cerebral ischemia in rats, wherein propofol considerably decreased myeloperoxidase activity (MPO) and attendant inflammatory vessel wall remodeling in rat models of cerebral ischemia [90]. In addition to directly modulating CSF inflammatory responses in models of bacterial meningitis, propofol also influences neuronal survival through a downregulation of inflammation mediated neuronal apoptosis. Following TBI, propofol has been shown to attenuate cerebral ischemic consequences by inhibiting neuronal apoptosis. Li et al. demonstrated that propofol limits the extent of cerebral ischemic damage by blocking neuronal apoptosis, and propofol's anti-apoptotic function may be mediated by an inhibition of caspase-3 and a corresponding increase of Bcl-2 expression [80]. Similarly, in rats suffering from cerebral ischemia-reperfusion injury, Xi et al. remarked that propofol improves neuronal survival and attendant neurobehavioral outcome by neuronal activation of restorative CBF patterns to prevent ischemic damage to the hippocampus by an upregulation of antiapoptotic Bcl-2 expression [81]. Collectively these studies emphasize that the neuroprotective effect of propofol in severe acute bacterial meningitis may be due to a diminution of cerebral proinflammatory responses and a protection against neuronal apoptosis to prevent considerable decreases in cerebral energy states and neuronal demand for CBF.

In addition to sedatives such as propofol, supportive therapeutic measures such as hypothermia have been frequently considered to attenuate secondary brain damage following traumatic brain insults. While hypothermia has previously been used for neuroprotection in a number of different neurological diseases, this therapeutic modulation has been extensively utilized for the treatment of severe CNS infections, where it has shown a considerable improvement in clinical outcome [93-98]. Although it may be tempting to speculate that the neuroprotective role of hypothermia in the advent of brain injury may merely be the consequence of a reduction of hyperthermia-induced hypermetabolism, induced by activation of the host's immune response to the invading microorganism, such a response may not be straight forward. In accordance with a frequent observation of a disrupted cerebral metabolic oxygen demand (CMRO2) and CBF coupling with severe models of meningitis, Busija et al. noted while patients with bacterial meningitis had a median higher body temperature compared to healthy controls, an increase in body temperature would be expected to increase cerebral metabolism and associated CBF if metabolic coupling was closely intertwined [99]. Interestingly, since CMRO2 was found to be reduced rather than elevated in these patients, the regional high CBF cannot be solely and adequately explained by hyperthermia-induced hypermetabolism. Hence, hypothermia's neuroprotective effect following brain injury may be the function of a blunted inflammatory host response to limit inflammatory cell invasion and reduced cellular metabolic demand for oxygen. Hypothermia exerts neuroprotection through a variety of mechanisms including reduced production of reactive oxygen and nitrogen species, reduction of proinflammatory cytokines & chemokines, suppression of neuroexcitatory pathways and an attendant decrease in neuronal apoptosis [100-106]. Additionally, in animal studies of meningitis, moderate hypothermia exerts favorable effects such as modulating nuclear factor κB activation (NFκB) and suppressing excessive host inflammatory responses to decrease cerebral metabolic needs [104,105,107,108]. Interestingly, for each degree of Celsius reduction in temperature, the cerebral metabolic rate decreases by approximately 7%, thereby allowing for maintenance of adequate CPP [109]. Further, through a quintessential reduction of meningeal inflammatory responses, hypothermia preserves cellular energy stores, reduces cerebral metabolic demand for oxygen associated with physiological activity of invading inflammatory cells to maintain hemostatic cellular function and subsequently regional CBF patterns [109-111]. The particular efficacy of mild to moderate therapeutic hypothermia during severe bacterial meningitis may be due to the predominance of pathogenic mechanisms that are temperature dependent [112,113]. For example, McCredie et al. initially demonstrated a good clinical outcome with strong neurological recovery in four children with advanced stage meningococcal meningitis treated with hypothermia [114]. Subsequently, Irazuzta et al. observed that moderate hypothermia was associated with a marked reduction of excitatory amino acids in the CSF of adult patients with bacterial meningitis, and this corresponded with improved neurological outcome and reduced cortical ischemic injury [108]. More recently, Lepur et al. demonstrated the clinical efficacy of therapeutic hypothermia, in adults with severe bacterial meningitis, with temperatures between 32 and 34 degree Celsius for a duration of 72 to 96 hours, and found that 8 patients had a favorable neurological outcome characterized by attenuated ischemic neurological damage and reduced neurological post-infective sequelae, thereby confirming previous reports that secondary neurological injury in acute bacterial meningitis is mediated by hyperpyrexia [115-118]. Similarly, Irazuzta et al. observed that application of moderate hypothermia in a model of severe bacterial meningitis considerably downregulated proinflammatory responses by decreasing CSF inducible NO levels as well as lowering myeloperoxidase activity in brain tissue, effectively lowering cerebral energy needs to preserve regional blood flow patterns [106]. Eventually, a decrease in cerebral metabolism, preservation of energy reserves and limitation of oxygen consumption through a marked suppression of meningeal inflammatory responses during the late stages of disease may underlie a crucial preservation of CBF to thwart the development of cerebral ischemia and neurological disability with progression of disease [119-121].

Conclusively, the adjuvant use of propofol and therapeutic hypothermia may serve neuroprotective roles in attenuating the development of cerebral ischemia during the advanced stages of severe acute bacterial meningitis through a critical reduction of meningeal inflammation and energy depletion.

Significant Neuronal Injury & Apoptosis Decreases Neuronal Blood Flow Demand

Significant neuronal injury and consequent apoptosis is commonly observed in the setting of a variety of brain insults, including TBI, CNS infections, and cerebral ischemia. [122-125]. In bacterial meningitis, neuronal apoptosis most frequently is described in the hippocampal neurons, and unilateral/bilateral hippocampal atrophy is notably observed amongst patients who survived meningitis [126,127]. The frequent observation of hippocampal neuronal cell death has been considered a pathogenic morphological correlate of severe bacterial meningitis in survivors following disease course. Similarly, in a rabbit model of pneumococcal meningitis, neuronal cell apoptosis is commonly found in the hippocampus formation, namely the dentate gyrus, approximately 24 hours following infection [122,123]. Given the occurrence of neuronal apoptosis in severe bacterial meningitis, this damage may be mediated by a primary activation of caspases. Numerous diseases of the brain- including cerebral ischemia, neurodegenerative diseases, and bacterial infections- are associated with the activation of caspases [128,129]. Caspase-dependent neuronal apoptosis is primarily stimulated by the host's immune/inflammatory response, namely leukocyte infiltration into the central nervous system, in bacterial meningitis [128]. In bacterial meningitis, numerous hosts derived and/or bacterial factors are neurotoxic, but an upregulation of host-derived inflammatory mediators appears to be chiefly pathogenic. For example, plausible "neuronal activating signals" include prostaglandins, cytokines, chemokines, reactive oxygen and nitrogen species, and excitatory amino acids such as a glutamate, soluble products representative of a severe and sustained inflammatory process [130]. Interestingly, the diversity of these inflammatory mediators in collectively contributing to neuronal damage subserves the intensity of the inflammatory process, suggesting that neuronal apoptosis represents a late consequence of severe acute bacterial meningitis. Consistent with this suggestion, Nau et al., demonstrated that the density of apoptotic neurons was greatest between days 3 and 18 following the onset of clinical symptoms, emphasizing the idea that time is required to mount a sufficient pro-inflammatory response capable of exerting toxic effects on neuronal cells. As expected, a progressive increase in density of apoptotic neurons towards day 18 corroborates a progressive buildup of proinflammatory mediators, capable of activating neurotoxic caspases, as a stimulus for neuronal cell apoptosis [126]. An inflammatory basis for neuronal damage in severe bacterial meningitis is further strengthened by the observation of a considerable attenuation of neuronal damage in association with diminished leukocyte recruitment as well as a continued & sustained CSF cellular cytotoxicity despite the presence of bacteria, highlighting that the primary elements capable of evoking significant neuronal injury and apoptosis are representative of host responses to infection. For instance, elevated levels of pneumococcal surface components such as the cell wall may represent a possible trigger for caspase-dependent neuronal apoptosis in response to severe meningeal inflammation as these cellular components are derived by the intensity of the meningeal inflammatory response in the CSF, and a consistent observation of significant neuronal apoptosis/injury during the advanced stages of bacterial meningitis may be a consequence of time-dependent intensification of CSF inflammatory processes to allow an accumulation of neurotoxic factors [131-133]. Given that neuronal apoptosis is caspase mediated, secondarily activated in response to the intensity of the host's inflammatory response in the cerebrospinal fluid, inhibition of leukocyte invasion or caspase activation during pneumococcal meningitis, merely protects half the neurons of the dentate gyrus, raising the possibility that overactivation of caspases may only partly represent the cause of neuronal apoptosis in bacterial meningitis [126]. As such, in animal models, administration of both a broad-spectrum caspase inhibitor and a caspase-3-specific inhibitor considerably attenuated neuronal apoptosis during pneumococcal meningitis [128]. Consistent with this observation, increased levels of activated caspase-3 have been frequently found in the hippocampus of humans with severe/fatal bacterial meningitis, wherein caspase 3, a crucial apoptotic mediator, may be responsible for neuronal apoptosis during severe bacterial meningitis [134]. Additionally, putative evidence of upregulated caspase-3 levels and heightened activation of downstream p53 and ATM signaling pathways in orchestrating neuronal injury in bacterial meningitis may be ascertained by a substantial reduction of neuronal loss and disease severity with induction of meningitis in caspase-3 knockout mice [135].

The influence of neuronal apoptosis on regional/global CBF patterns during severe acute bacterial meningitis may be more closely ascertained by a determination of vasodilatory substances derived from active neurons. For the first time, Roy & Sherrington et al. proposed that active neurons release vasodilator molecules into the interstitial space of the brain, from where, these agents could secondarily diffuse into the extracellular space to come into contact with local blood vessels and thereby initiate vasodilation [136]. Such a mechanism of the brain may explain its ability to intrinsically regulate its own blood flow during neuronal activation. To evoke such a response, first a signal must be generated by activated neurons, followed by a transmission of this signal not only to the local vasculature, but also to resistance arterioles (the primary site of flow control) that are located away from the activated area. Within the cerebral cortex, these resistance arterioles (pial arteries) distinctively lie outside the brain parenchyma and not in direct proximity

with neuronal cells. Hence, the signal from activated neurons must be translated into appropriate microvascular adjustments to permit necessary changes in flow specifically directed at the activated area [137]. So, while vasoactive agents produced by active neurons may be responsible for local hyperdynamic vascular responses, the ideal mediator responsible for initiating local CBF changes is less generally agreed upon. While several candidate molecules implicated in coupling neuronal activity and CBF include K^+ & H^+ ions, particular neurotransmitters, CO_2, and adenosine, the perfect mediator in modulating local increases in CBF with changes in neural activity would be a substance that rapidly & maximally accumulates in the extracellular space during neural activity, is highly soluble/diffusible, is short lived/rapidly inactivated, and most importantly, is a potent vasodilator [136,138-142]. Although these agents may account for different components of CBF regulation in particular experimental states, they can't completely account for changes in CBF stimulated by neuronal activation [137]. Thus, the ideal agent for coupling neural activity to vascular tone by NO, and such a hypothesis is robustly supported by numerous experimental evidence demonstrating increased NO presence during increases in CBF following neuronal activation [142-145]. NO, a potent vasodilator, is produced by active neurons, thereby raising the possibility that NO is involved in coupling CBF to brain activity. In the central nervous system, nitric oxide synthase (NOS) is principally situated in neurons widely distributed in the brain, wherein increases in intracellular calcium induce NOS to stimulate the production of NO [146,147]. Subsequently, NO diffuses out of neuronal cells and into neighboring cells, where it activates soluble guanylyl cyclase. In line with this suggestion, NOS containing nerves originate from the sphenopalatine ganglion and innervate the pial vessels, large cerebral arteries and circle of Willis [148,149]. Ultrastructural studies, in fact, have demonstrated that NOS-containing neurons display fine dendritic processes and axonal terminals closely affixed with the outer surface of intracerebral arterioles and capillaries, and so, NO produced by these neurons may stimulate adenyl cyclase in adjacent arteriolar smooth muscle cells to influence microvascular tone through vasodilation and a regional increase in blood flow [150-152]. Consistent with this viewpoint, several studies highlight a role of NO as a mediator of increased CBF induced by activation of local neurons/central neuronal pathways. For example, stimulation of neuronal pathways involving the rat cerebellar fastigial nucleus globally increased CBF, and electrical stimulation of separate segments of the middle cerebral artery resulted in vascular relaxation that was presumably blunted by agents that inhibit NO synthesis or action [153,154]. Similarly, following activation of an isolated group of cortical neurons by pathways mediating a focal increase in cortical CBF through the basal forebrain, local application of NOS inhibitors or the guanylyl cyclase inhibitor methylene blue nearly abolished expected increases in cortical CBF, supporting that vasodilation is mediated by a local release of NO by active neurons [155]. Likewise, activation of thalamo-cortical afferents lead to increases in CBF in the neocortex, with the increase in cortical blood flow initiated by electrical stimulation of intact/functional sciatic nerves, an effect that was attenuated by administration of NOS inhibitors [156,157]. Interestingly, as thalamocortical neurons lack intrinsic NOS activity, it is improbable that NO is directly released from stimulation of thalamocortical afferents; instead, activated thalamocortical afferents interact with NOS containing cortical neurons and consequently activate them in order to produce NO [158]. Additionally, on a similar parallel, vasodilation in the cerebral cortex does not represent global metabolic activation, but rather an increase in local release of acetylcholine and resultant NO levels [159]. For example, direct stimulation of neurons in the rat forebrain resulted in acetylcholine release into the cerebral cortex, followed by an increase in CBF, in which this vasodilatory response was abolished by the administration of NOS inhibitors [159,160]. Hence, it seems reasonable that following forebrain stimulation, NO may be synthesized by an upregulation of eNOS (endothelial nitric oxide synthase) within the endothelium in response to a local release of acetylcholine. [161]. Separately, heightened cortical nNOS (neuronal nitric oxide synthase) expression increases NO production to participate in regional increases in CBF induced by direct stimulation of cortical neurons. As such, activation of focal cortical neurons following topical application of the glutamate agonist, N-methyl-D-aspartate, lead to a local vasodilation, which was readily and reversibly abolished by administration of nNOS inhibitors, thereby raising the possibility that nNOS-dependent NO also participates in regional cerebral hyperemia during neuronal activation [162]. Thus, from these studies it is evident that increases in CBF elicited by stimulation of functional neuronal activity involves vasodilatory properties of NO, and an upregulation of both neuronal and endothelial isoforms contribute to such a response, and a functional suppression of e/nNOS NO production may be an important contributor to deranged CBF dynamics in severe bacterial meningitis.

Given the role of eNOS and nNOS in producing vasculoprotective/functional NO during physiological states of neuronal activation, overproduction of Inducible nitric oxide synthase (iNOS) appears to be a pivotal contributor to neuronal injury in bacterial meningitis. iNOS represents a likely source of increased pathogenic NO production during severe/advanced stages of meningitis due to the profound and sustained inflammatory process associated with the disease. As the name implies, iNOS is activated by the meningeal inflammatory process, wherein proinflammatory cytokines such as TNF-α, interleukin 1 (IL-1) and interferon gamma (IFN-γ) and bacterial lipopolysaccharide upregulate its expression [163,164]. Thus, with a greater duration of meningeal inflammation and elaboration of proinflammatory cytokines, iNOS levels progressively increase contributing to neurological damage in bacterial meningitis. For instance, Visser et al. observed that patients with meningococcal meningitis had a substantially higher CSF level of nitrite and nitrate, considered end products of sustained iNOS

activation, than control subjects [165]. Additionally, Milstien et al. reported elevated levels of nitrate and nitrate in patients with bacterial meningitis in close association with increased iNOS expression [166]. Further, in corroborating a role of pathogenic role of iNOS in neuronal injury and poor neurological recovery during bacterial meningitis, studies in children with meningitis have demonstrated increased levels of CSF nitrites in these patients, wherein the CSF nitrite levels closely parallels an adverse clinical course with neurological disability [167]. Given the linear correlation between heightened iNOS expression and extent of neurological injury, several studies highlight a causative role of iNOS levels in the development of cerebral ischemia. For example, expression of the Nos2 gene, responsible for encoding iNOS, is increased following transient cerebral ischemia in rats and may be considered a reliable marker of short-lived ischemic insults. Iadecola et al. found that iNOS mRNA peaked nearly 12 hours following transient cerebral ischemia and that heightened Nos 2 expression was primarily localized in vascular cells of the infarcted area. Subsequently, Iadecola et al. demonstrated that expression of Nos 2 in neurons begins to increase approximately 24 to 48 hours following the onset of ischemia, peaks at nearly 96 hours and subsides a week after vascular occlusion [168]. Additionally, the pathological significance of iNOS in orchestrating cerebral ischemic deficits is further advanced by observations that extent of motor deficits and infarct size produced by middle cerebral artery occlusion are considerably smaller in Nos2 knockout mice with abolished iNOS expression compared to wild-type mice with complete iNOS expression [169]. Likewise, in a recent model of rat bacterial meningitis, administration of aminoguanidine, a specific inhibitor of iNOS, attenuated brain damage secondary to occlusion of the middle cerebral artery through a reduction in neocortical infarct volume, suggesting that elevated iNOS is actively involved in mediating ischemic brain damage through a reduction in CBF. From these studies, it is clear that NO produced by iNOS from dysfunctional/apoptotic neurons during states of increased meningeal inflammation contribute to a critical reduction in CBF and resultant ischemic brain damage, and an inhibition of iNOS may serve to preserve CBF and prevent cerebral ischemia during the late/advanced stages of disease.

Increased ICP Decreases CPP & Attenuates CBF

Intracranial hypertension is a usual consequence of CNS infections and contributes to an overwhelmingly high risk of progression toward neurological decline. The pathophysiology of increased intracranial pressure in bacterial meningitis is multifactorial and principally involves cerebral edema and an increased CSF production. This brain edema is the consequence of an intense inflammatory reaction activated by a bacterial infection, and the attendant elaboration of proinflammatory cytokines/chemokines and destructive proteases that weaken the BBB to cause a disturbance in brain volume regulation to consequently result in an edematous transformation [170-173]. More closely, the release of bacterial cell wall components into the subarachnoid space result in inflammatory processes that contribute to an increased permeability of the BBB leading to extracellular edema, cytotoxic intracellular edema and increased CBF (due to an impaired autoregulation) that collectively contribute to an early elevation of ICP, with the extent of ICP elevation corresponding to the intensity of meningeal inflammation during the advanced stages of disease [174,175].

It is generally accepted that intracranial hypertension/ elevated intracranial pressure indicates a more severe disease course with a significantly higher mortality compared to patients with uncomplicated bacterial meningitis & a lower ICP [176-178]. During the late phase of increased ICP, the cerebral vessel resistance index is significantly greater than normal, particularly in the presence of a decreased mean CBFV, suggesting a significant cerebral perfusion compromise. As normal CBF predominantly depends on a vital balance between intracranial pressure and MAP, untoward increases in ICP subsequently lead to a progressive narrowing of intracranial vessels until a specific "tipping point" of vessel lumen diameter reduction is reached, at which point, cerebral blood becomes considerably compromised to result in a reduction of CBFV [179,180]. For instance, animal studies of bacterial meningitis have demonstrated an initial increase in CBFV coinciding with the early advent of ICP development, but subsequently highlight a nearly 30% decrease in CBFV as the illness severity worsens in the presence of considerable increase in ICP. [18]. An early study by Kety and associates demonstrated that increased ICP is associated with an increase in cerebrovascular resistance, restricted CBF and progressive cerebral hypoxia [181]. In an experimental rabbit model of pneumococcal meningitis, Goitein et al. showed a progressive increase in ICP and a consecutive decrease in perfusion pressure [182]. Similarly, Lindvall et al. reported that the incidence of cerebral ischemia/poor neurological recovery was higher among patients with severe bacterial meningitis (GCS score ≤ 8), where 93% of patients admitted to the neuro-intensive care unit developed intracranial hypertension. [183]. Similarly, Goh & Minns et al. documented a decreased pulsatility index (PI), indicative of cerebrovascular resistance, in close relation with an increased mean CBFV following mannitol infusion. [184]. Given the fact that mannitol is a potent osmotic diuretic frequently administered in the setting of increased ICP, an observed decrease in PI and resultant mean CBFV following mannitol infusion lends support to a late increase in ICP as a crucial determinant of decreased CBF. Along the same lines, Okten et al. observed that during the acute phase of meningitis, patients with an elevated CBFV and a normal PI value did not show any neurological deficits, whereas those with elevated PI values in the presence of a normal/reduced CBF were more likely to display adverse neurological sequelae. This relationship, therefore, appears to suggest that newborns with adverse neurological sequelae had severe cerebral perfusion compromise due to a significant

increase in ICP during the acute phase of disease [185]. Hence, it is reasonable to ascertain that elevated PI values, especially in the presence of a reduced CBFV, indicate an elevated ICP, and with a rising PI value, CPP would be consequently decreased due to an increase in cerebrovascular resistance. Likewise, in a retrospective study in Europe, Depreitere et al. evaluated clinical outcome in several patients with severe bacterial meningitis, specifically monitoring ICP. During this study, they were able to demonstrate a positive correlation with the Glasgow coma scale (GCS) in relation to the highest observed ICP and lowest recorded CPP, wherein a higher ICP and lower CPP were associated with a significantly greater cerebral perfusion compromise and poor neurological recovery, consequently leading to a lower GOS [186]. Additionally, Shetty et al. observed that patients with bacterial meningitis who either survived with significant neurological sequelae or died experienced wide variations in CPP, wherein the mean CPP generally exceeded 60 mm Hg in survivors without sequelae compared to those with sequelae or who died as well as a greater time sustenance of CPP greater than 50 mm hg amongst healthy survivors compared to those who died during the monitoring period [187]. Such an observation is consistent with the physiological principle that CPP is a primary stimulus for cerebral autoregulation, in such a manner that an inadequate CPP leads to a progressive increase in ICP, whereas maintenance of adequate CPP abolishes increases in ICP to further augment improvements in cerebral perfusion. This physiological response may be the result of an increased CPP activating compensatory autoregulatory cerebral vasoconstriction to reduce cerebral blood volume and attenuate consequent ICP increases. As previously described by Shetty et al., as CPP was generally lower amongst non-survivors and consistent with observations of an impaired autoregulation in severe acute bacterial meningitis, the observed CPP here would be unable to abolish increases in ICP during severe meningeal inflammation leading to a considerably high ICP, which would additionally hamper cerebral flow patterns to eventually result in cerebral ischemia and contribute to poor neurological recovery/death observed in these patients. [187]. From these clinical/experimental evidence, elevated ICP conceding in a compromised CBF and resultant CPP appears to be an exceedingly important cause of unfavorable outcome/poor recovery in severe acute bacterial meningitis. Cerebral ischemia and hypoxia are the most important factors leading to neuronal injury and poor neurological recovery during severe acute bacterial meningitis. Ischemia during bacterial meningitis stems from a variety of insults including increased ICP, systemic hypotension and a loss of CBF autoregulation, and hence appropriate monitoring of ICP and maintenance of relevant CPP is vital to preserve CBF during the advanced disease stages and attenuate brain injury during brain meningitis [20,188]. In patients with severe acute bacterial meningitis, a critical reduction in elevated ICP to normal values may lower mortality. For instance, intensive neurocritical care treatment modality involving ICP-lowering treatment in studies of severe acute bacterial meningitis patients with elevated ICP and impaired consciousness was associated with favorable results. [183,189,190]. As such, of particular importance, moderate hyperventilation & osmotherapy may be a promising option in critical cases of ABM with elevated ICP in order to maintain CPP and prevent cerebral ischemia. [191-194]. For example, intensive administration of osmotic agents such as glycerol, hypertonic saline, or mannitol is one of the principal treatment modalities to lower elevated ICP and subsequently increase CPP in bacterial meningitis [195]. The early identification of deteriorating cerebral hemodynamics resulting from vascular narrowing in patients with bacterial meningitis may help create a therapeutic time frame during which supportive measures to increase CPP may be introduced. Therefore, the primary goal of CPP support during severe bacterial meningitis would be to overcome increased resistance of cerebral arteries and provide sufficient nutrient support to sustain healthy metabolic demand in a dire attempt to mitigate secondary ischemic injury [196,197]. For instance, when such a supportive CPP-directed treatment was administered to a number of children with CNS infections in India, children with severe bacterial meningitis were observed to have a considerable 3 month reduction in mortality, possibly attributable to a lower incidence of cerebral ischemia/infarction with resultant neuronal injury/disability [23]. With this in mind, hypertonic saline has been demonstrated to suppress a rising ICP and improve CPP and regional CBF in various animal studies [198,199]. Hypertonic saline (HTS) possesses numerous anti-inflammatory properties making it an attractive therapeutic agent to attenuate neuronal injury by down-regulating acute inflammatory responses in bacterial meningitis. As such, HTS has been described to block inflammatory neutrophil-endothelial cell interactions, inhibit lipopolysaccharide-activated NOS expression by downregulating NFκB, and suppressing degradative neutrophil cytotoxic processes by interfering with intracellular signaling cascades [200-202]. Thus, these anti-inflammatory actions of HTS may be pivotal in limiting the development of intracranial pressure. In line with this suggestion Liu et al. ascertained that maintenance of adequate CPP by a simultaneous reduction of increased ICP with rigorous HTS infusion further strengthens the role of HTS as an adjunctive therapy to prevent cerebral ischemia and ensuing brain injury in bacterial meningitis. [203]. Additionally, in a piglet model of bacterial meningitis, 7% of HTS was shown to considerably downregulate acute inflammatory responses leading to a significant reduction in ICP and improvement in CPP, thereby decreasing the likelihood of cerebral ischemia and resultant brain injury [204]. Separately, a comparative study between 3% HTS and 20% mannitol (MN) in severe acute bacterial meningitis, HTS was reported to more consistently and efficiently decrease ICP and improve CPP, thus better attenuating brain edema development to subsequently lower cerebral vessel resistance and improve CBF and prevent cerebral ischemic damage [205].

Conclusion

Acute bacterial meningitis is a severe disease that often leads to poor neurological outcomes, including a high mortality rate and adverse post-infectious neurological sequelae. In considering the numerous complications of bacterial meningitis, cerebrovascular complications account for an overwhelming incidence of severe neuronal injury and neurological disability attributable to the development of cerebral ischemia. Following meningeal inflammation, CBFV are frequently disturbed and appear to be responsible for the pathogenesis of brain injury. Consistent with previous angiographic and histological studies, dynamic vessel caliber changes such as a narrowing of intracerebral blood vessels represent a possible cause of CBF variations during different stages of bacterial meningitis. These dynamic vessel changes, either a consequence of short-lived reflexive arterial vasospasm or sustained/progressive arterial stenosis associated closely with CBF variations in bacterial meningitis. Thus, with analysis of several pieces of doppler studies, CBF patterns during bacterial meningitis may be divided into a biphasic response, with an early increase in flow velocity during the acute stage of infection followed by a progressive and late decrease in regional flow patterns to culminate in cerebral ischemia. Although several studies highlight a late ischemic sequela in severe models of bacterial meningitis, an understanding of the patho-mechanisms responsible for such a consequence remain incompletely understood. With this, an understanding of the possible causative pathophysiology of cerebral ischemia during the advanced stages of bacterial meningitis may involve an interconnected relationship between severe inflammatory processes, systemic cardiovascular dysfunction, metabolic energy impairment, neuronal injury and intracranial pressure elevations, all of which may function synergistically to contribute to neurological decline/injury with severe disease. In the future, we hope additional contributory pathogenic factors responsible for decreased CBFV during the advanced/late stages of severe acute bacterial meningitis are more closely elucidated, to help develop more effective treatments to attenuate/abolish cerebrovascular insults and improve neurological recovery in patients with severe bacterial meningitis.

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