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Structural Protein and Growth Factor Expression Patterns Leads to Extracellular Matrix Remodeling and Attendant Cerebral Vasculitis in Bacterial Meningitis

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Abstract

Cerebrovascular complications of bacterial meningitis account for an overwhelmingly high incidence of post infectious neurological decline amongst survivors. From several pieces of histological descriptions, angiographic models and radiographic studies, it is clear that the cerebral vessels are distinctively involved during the course of bacterial meningitis. Furthermore, it is evident that dynamic vessel wall changes take place during the course of infection with an early transient vasospasm and a more persistent vasculitis through angiographic studies documenting time course variations of cerebral blood flow. Even with this, our understanding of the deleterious vessel wall modifications predisposing to vasculitis in bacterial meningitis remains to be more closely elucidated. Interestingly, after analyzing a temporal relationship between subarachnoid space inflammation and cerebral vasculopathy in bacterial meningitis, it becomes somewhat definite that the development of cerebral vasculitis may originate from inflammatory byproducts synthesized in the subarachnoid space. Following synthesis and release of these soluble growth factors, they are relayed into surrounding penetrating cerebral vessels, where they subsequently gain access to specific components of the extracellular matrix to initiate the progressive process of vessel wall remodeling, eventually culminating in the development of ischemic consequences. With this, in this review, we specifically sought to understand the significance of disturbed expression of specific structural proteins and growth factors in the subarachnoid space and their potential role in triggering vasculitic adaptations of the cerebral vasculature.

Keywords: Bacterial meningitis; Cerebral vasculitis; Growth factor; Structural protein; Inflammation

Introduction

Cerebrovascular complications represent an important complication of acute bacterial meningitis and account for a high incidence of postinfective neurological decline. The involvement of the cerebral vasculature during bacterial meningitis points toward histological evidence of vessel wall modifications as a nidus for cerebral blood flow disturbances. As such, cerebral ischemia during the course of bacterial meningitis may be commonly attributed to either transient vasospasm or permanent vasculitis, with both pathogenic mechanisms distinctive responsible [1]. Although cerebral vasospasm is without significant neurological deficits, vasculitis on the other hand represents a greater disease burden owing to potential long term neurological damage. Vasculitis in the setting of bacterial meningitis appears to stem from distinctive structural modifications of the arterial vasculature, and such a pathological remodeling may be facilitated by specific growth factor and structural protein expression patterns within the cerebrospinal fluid space following an infectious insult. In close relation to subarachnoid space inflammation and the release of proinflammatory cytokines and attendant synthesis of structural proteins, deposition of extracellular matrix proteins through anatomical connections between the subarachnoid space and penetrating cerebral vasculature evokes specific deleterious matrix modifications resulting in vasculitic adaptations with the severity of these vessel wall adaptations corresponding to the duration of disease and intensity of subarachnoid space inflammation [2].

Literature Review

Structural proteins

Collagen: During the course of bacterial meningitis, changes in vascular wall extracellular matrix appear to be a critical determinant in influencing the development of ischemic consequences. A particularly notable transformation involves the soluble protein collagen. Within the vascular wall, collagen levels are maintained at a steady state through a healthy balanced interaction between synthetic and degradative components. Although synthetic elements responsible for collagen biosynthesis don't markedly change in the case of traumatic insults, degradative proteolytic enzymes such as matrix metalloproteinase significantly become upregulated in response to tissue injury and inflammation [3].

In experimental cerebral ischemia, noncellular matrix degradative proteolytic systems, including matrix metalloproteinases MMP-2 and MMP-9, known to degrade vessel wall type 4 collagen are upregulated. Alternatively, in the setting of central nervous system infections such as bacterial meningitis, Robert and

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Godeau and Rosenberg demonstrated that bacterial-derived collagenes were responsible for disrupting the structural integrity of the arterial wall extracellular matrix surrounding brain parenchyma. Given the clear role in matrix degrading proteases in traumatic/infectious central nervous system insults, numerous animal studies more closely emphasize the role of matrix metalloproteinase 9 as a critical mediator of brain damage in bacterial meningitis [4].

In using *in-situ* zymography, Leib, et al. found a significantly heightened gelatinolytic activity within the meninges, subarachnoid space, intervening vessels, as well as the perivascular space in close association with cortical damage. A closer analysis of the source of this gelatinolytic activity points squarely towards matrix metalloproteinases, MMP 2 and MMP 9, as crucial effectors of this vascular transformation and an peak concentration of these proteases at 20 hours, corresponds to the acute phase of bacterial meningitis. Moreover, an altered transcription of matrix metalloproteinase-2 and 9 in bacterial meningitis may further support the advent of ischemic parenchymal insults. In addition to a differential matrix metalloproteinase expression in bacterial meningitis, the tissue inhibitor of matrix metalloproteinase also displays a similar pattern [5]. Tissue inhibitor of matrix metalloproteinase, as the name suggests, regulates the enzymatic activity of matrix metalloproteinases to prevent overactive proteolysis and attendant brain damage. Focal increases in TIMP-1 levels have been demonstrated in neurovascular structures surrounding the cerebrospinal fluid, however the increase in TIMP-1 expression fails to timely follow increases in corresponding matrix metalloproteinases. Instead, TIMP-1 increases are delayed in comparison to increases in matrix metalloproteinase 9, thereby allowing unhindered proteolytic vessel wall degradation for a period of time, before related increases in TIMP-1 expression limit drastic pathological remodeling. Within the central nervous system, TIMP-1 expression is significantly heightened in the setting of focal inflammation and ischemia, where pro-inflammatory cytokines such as interleukin 1 and tumor necrosis factor alpha can upregulate TIMP-1 synthesis by surrounding endothelial cells and astrocytes [6]. In confirming local cellular elements of the meninges in modulating regional increases in TIMP-1 synthesis and release, Jaworski and Rivera, et al. documented a focal increase in TIMP-1 in close proximity with perivascular astrocytes, in which sense these activated cells maintain the structural integrity of the extracellular matrix by inhibiting matrix metalloproteinase production.

Although increases in matrix metalloproteinase are attenuated by a related increase in TIMP to blunt significant vessel wall remodeling, the MMP/TIMP ratio, however, is not linear with a commonly observed higher MMP-9/TIMP-1 ratio corresponding to a surplus of MMP-9 expression subsequently followed by a delayed increase in TIMP-1 expression [7]. Interestingly enough, MMP-9 levels were significantly elevated when to TIMP-1 levels, precluding an effective compensation until the end of the acute disease phase to allow unrestricted pathological intramural remodeling. As expected, therefore, inflamed penetrating cerebral vessels were found to have an increased gelatinase activity coinciding with the development of cortical lesions, ultimately postulated that a disruption of the neurovascular unit in bacterial meningitis is associated with perivascular matrix damage and consequential brain injury. Therefore, early vascular protein loss or differential expression in bacterial meningitis may supersede brain injury and the attendant development of cerebrovascular insults [8].

In spite of significant collagen degradation in bacterial meningitis through the release of structural matrix proteases, collagen synthesis may partially compensate for the loss by de no synthesis. Hydroxyproline, a critical precursor of collagen biosynthesis, is increased within the cerebrospinal fluid of animals with bacterial meningitis, emphasizing that a heightened level of MMP-9 and matrix protease leading to collagen degradation is attended to by an reflexive increase in collagen synthesis [9]. Whereas such a compensatory equilibrium may underlie a normally appearing cortex, in bacterial meningitis, conversely, an unstable reparative response coinciding with extensive vascular remodeling and inadequate collagen synthesis may be responsible for the development of cortical lesions. Eventually, the failure of the vessel wall to adequately respond to collagen degradation by compensatory collagen synthesis, leads to an adverse vessel wall remodeling and the advent of cerebral vasculopathy in bacterial meningitis. Initially, a heightened proteolytic degradation of collagen in the basal lamina and inadequate replacement increases vessel permeability to circulating blood proteins [10]. Subsequently, extravasation of circulating cellular blood proteins such as fibrinogen and inflammatory polymorphonuclear leukocytes and a loss of endothelial cell anchorage promote inflammatory remodeling. Deposition of fibrinogen, as a consequence of increased microvascular permeability, results in subendothelial matrix fibrinogen accumulating, thereby activating a pathological cascade of vascular remodeling. Soon after, fibrinogen is rapidly polymerized to soluble fibrin and along with other adhesive glycoproteins in the extracellular matrix promotes binding to growth factors. Simultaneously, neutrophilic infiltration contributes to the proteolytic burden of the arterial wall by further impairing inter-endothelial tight junctions leading to subendothelial protein rich fluid trafficking and consequent edematous transformation, subsequently resulting in transient luminal narrowing [11]. With progression of disease, continued neutrophilic infiltration and endothelial damage progressively expand interendothelial gaps, thereby exposing a greater amount of subendothelial matrix to circulating platelets.

In response, platelets adhere to the subendothelial matrix by binding to subendothelial fibrinogen and secondarily become activated to subsequently release a variety of growth factors, the most important of which is platelet derived growth factor. Once elaborated by endothelial-derived platelets, continuous diffusion of platelet derived growth factor in the subendothelial vascular wall facilitates a intimal stenotic transformation through potent vascular smooth muscle cell migratory and proliferative actions. Following inflammatory cell mediated remodeling of the subendothelial extracellular matrix, degraded fibronectin fragments additionally contribute to vessel wall remodeling by increasing interendothelial cell permeability, enhancing leukocyte adhesion and migration, facilitating smooth muscle cell mitogenesis and attendant collagen synthesis, and suppressing vasodilatory-prostaglandin biosynthesis by endothelial cells and smooth muscle cells, additionally potentiating arterial wall remodeling. Eventually, with greater disease duration, pathological remodeling transforms the arterial wall into a markedly stenotic vessel unable to sustain healthy cortical flow patterns and the advent of ischemic cerebrovascular disease and attendant poor neurological recovery [12].

Discussion

Fibronectin

Fibronectin is a soluble protein produced and secreted by a number of cell types such as fibroblasts, myofibroblasts and smooth muscle cells and widely distributed in the extracellular matrix. Soluble fibronectin is deposited into the tissue extracellular matrix by numerous cellular elements. Normally, the concentrations of extracellular matrix proteins are physiologically present at lower levels in the cerebrospinal fluid. However, following brain injury, cerebrospinal fluid concentrations of extracellular matrix proteins are often increased [13]. Within the central nervous system, fibronectin expression is tightly regulated in accordance with perturbations in the regional pathological microenvironment. In case of cerebral infection, such as bacterial meningitis, when an increased permeability of the blood brain barrier is increased or cerebrospinal fluid circulation is decreased, fibronectin concentrations tend to rise. An increase in fibronectin concentration at the foci of infection in bacterial meningitis traverses into the extracellular space of the cerebral vasculature due to a sparsity or absence of a physical barrier impending macromolecule passage from the subarachnoid space into the extracellular spaces of surrounding cerebral vasculature. Therefore, the high fibronectin concentration observed during the course of bacterial meningitis may similarly reflect a predominance of fibronectin expression in the extracellular matrix of the cerebral vessel [14].

Within the central nervous system, fibronectin is synthesized by a number of resident host cells in response to tissue injury. Following infectious insults and attendant traumatic injury to the central nervous system, infiltrating polymorphonuclear leukocytes as well as host astrocytes respond by reflexively synthesizing fibronectin. In addition to observing an elevated extracellular matrix protein concentration and bacterial titer in the cerebrospinal fluid in bacterial meningitis. Goos, et al. described a higher fibronectin concentration in bacterial meningitis in patients with obvious cerebrospinal fluid abnormalities, when compared with control patients without cerebrospinal fluid abnormalities, thus suggesting that acute inflammatory changes of the subarachnoid space underlie increased fibronectin production. In order to more closely elucidate modifications of the subarachnoid space as a nidus for increased extracellular matrix production, Torre, et al. not only demonstrated a significantly higher cerebrospinal fluid concentration of fibronectin in bacterial meningitis, but further elaborated that fibronectin expression in the cerebrospinal fluid is partly related to central nervous system inflammation and may represent a pathological consequence of tissue damage by the infectious foci. Given that polymorphonuclear leukocytes represent the primary cellular population involved in mediating acute inflammatory responses in bacterial meningitis and can respond to diverse stimulatory stimuli and traverse from the circulation to traffic within the inflamed meningeal layer, polymorphonuclear leukocytes may represent a primary source of *de-novo* fibronectin synthesis in the cerebrospinal fluid during the course of bacterial meningitis. In support of primary fibronectin synthesis in bacterial meningitis, polymorphonuclear neutrophils retain the intrinsic ability to synthesize specific mRNA and proteins in the activated state. For example, La Fleur, et al. found that activated polymorphonuclear neutrophils increase fibronectin and associated mRNA synthesis under states of inflammation.

Similarly, also Kreis, et al. demonstrated that isolated polymorphonuclear neutrophils from the synovial fluid of inflammatory arthropathies were capable of synthesizing and secreting large amounts of fibronectin. Once synthesized by infiltrating polymorphonuclear leukocytes in the inflamed meninges, Weller, et al. found that not only were cerebrospinal fluid levels of fibronectin elevated in bacterial meningitis, but such a distinction of cerebrospinal fluid fibronectin levels helps identify disorders with significant blood brain barrier disruption such as bacterial meningitis. By virtue of the high molecular weight and vehement adhesive properties of fibronectin, a significant portion of plasma fibronectin would be unable to traverse through an intact blood brain barrier, and instead a positive relation between cerebrospinal fluid levels of fibronectin and albumin support a dysfunctional altered blood brain barrier as a intermediary in facilitating fibronectin passage into the subarachnoid space, where it subsequently gains access to the neighboring cerebral vasculature [15].

Upon gaining access to the extracellular matrix of the vessel wall, fibronectin plays a quintessential role in vascular remodeling beginning with the activation of intracellular signaling pathways regulating proinflammatory, promatrix vessel wall activity. For example, fibronectin deposition in the subendothelial matrix results in endothelial cell dysfunction with a consequent suppression of nitric oxide production and upregulation of proinflammatory gene expression. In particular, fibronectin has been known to modulate the activity of nuclear factor kB in the vascular endothelium which in turn stimulates intracellular ICAM-1 and VCAM-1 synthesis and cell surface expression. Subsequently, fibronectin promotes an increased leukocyte recruitment into the vessel wall and with continued leukocyte trafficking and release of degradative proteases, fibronectin is broken down into smaller fragments. Soon after, fibronectin fragments serve as potent chemotactic factors for further neutrophil and monocyte influx to replace the initial inflammatory infiltrate and propagate vascular remodeling. Additionally, a fibronectin rich matrix influences smooth muscle cell function to potentiate a stenotic vessel wall remodeling. By virtue of stimulatory actions on vascular smooth muscle cells, fibronectin initially promotes smooth muscle cell dedifferentiation from a contractile to a synthetic, promatrix phenotype. Thereafter, following smooth muscle cell phenotypic modulation, fibronectin contributes to vessel wall remodeling by promoting smooth muscle cell migration and proliferation. In addition to a direct mitogenic effect on smooth muscle cells, a dense fibronectin matrix regulates the deposition, organization and stability of other extracellular matrix molecules including collagen 1 and 3. So, fibronectin interactions with newly synthesized collagen by stimulated smooth muscles may serve to potentiate intimal narrowing, resulting in a stenotic transformation of the vessel wall. In support of fibronectin mediated stenotic vessel wall remodeling, inhibition of a fibronectin matrix assembly prevented type 1 and 3 collagen deposition and markedly attenuated vessel wall remodeling. Interestingly, proper assembly of type 1 and 3 collagen could be restored following supplementation with soluble fibronectin, which may be subsequently assembled into a dense fibronectin matrix.

Growth factors

TGF-Beta: Amongst the numerous growth factors implicated in vascular remodeling, TGF-beta is exceedingly implicated in modulating the bulk of pathological remodeling following vascular injury. TGF-beta is normally situated in the arterial media, with relatively low concentrations in the cerebrospinal fluid. Following

infectious/traumatic insults to the brain, cerebrospinal fluid levels of TGF-Beta correspondingly increase. During the course of bacterial meningitis, Huang et al. documented a significantly higher cerebrospinal fluid level of TGF-Beta compared to normal subjects. Such a finding is consistent with *in-situ* hybridization techniques demonstrating an increased expression of TGF-Beta 1 mRNA expression in cerebrospinal fluid cells in patients with bacterial meningitis. Given the heightened expression of TGF-B1 in the cerebrospinal fluid of patients with bacterial meningitis, a central nervous system source appears to be primarily responsible for synthesis and secretion. In particular, the brain itself appears to be primarily involved in upregulating CSF TGF-B1 levels in traumatically challenged neurons, astrocytes, and endothelial cells. During the acute phase of bacterial meningitis, there are several putative sources of TGF-B1 production, including neutrophils, macrophages, lymphocytes and endothelial cells. As there is a continual neutrophil and monocyte influx into the cerebrospinal fluid following the advent of bacterial meningitis, these recruited inflammatory cells may serve as either an initial or contributory source of TGF-B1 levels. Soon after, macrophages replace neutrophils as the dominant CSF cellular type and contribute to the proliferative phase of arterial vasculopathy through the release of a myriad of growth factors, including TGF-B.

Additionally, leptomeningeal cells may proliferate and upregulate synthesis of TGF-B1 in response to infection, thus increasing CSF TGF-B1 levels, with increased TGF-B1 principally deposited in the arachnoid cells and media of intervening arterioles. Once synthesized, TGF-B1, in relation to subarachnoid inflammation, may facilitate additional leptomeningeal cell proliferation and extracellular matrix production, thereby increasing CSF TGF-B1 burden. In addition to CNS cellular elements directly upregulating TGF-B synthesis and release, focal release of proinflammatory cytokines may also contribute to increased CSF TGF-B1 levels. Consistent with this suggestion, CSF and tissue levels of proinflammatory cytokines TNF-alpha and IL-1 are increased in patients with bacterial meningitis. Given that both of these cytokines are stimulators of TGF-B1 production, high levels of proinflammatory cytokines during bacterial meningitis may adversely affect vessel wall remodeling and result in poor neurological outcome.

Once synthesized and secreted in excess into the cerebrospinal fluid and subsequently deposited in the vessel wall of intracranial arteries, TGF-Beta incites a pathological cascade of vessel wall remodeling culminating in a stenotic transformation of the vascular wall. TGF-B1 initially participates in inflammatory vessel wall remodeling by upregulating surface expression of chemokine receptors responsible for leukocyte and monocyte tissue chemotaxis. Within the subendothelial matrix, TGF-B1 facilitates monocyte adhesion to type 4 collagen, laminin and fibronectin. Subsequently, macrophages persist in the subendothelial matrix owing to a combination of apoptosis inhibition as well as downregulation of cytokine-mediated increases in elastase activity and chemokine macrophage inhibitor protein 2 expression. During the course of inflammatory cell chemotaxis, the intervening endothelial layer is denuded progressively exposing regions of the subendothelial matrix to circulating cellular elements. Of particular importance, in response to a dysfunctional-denuded endothelium, circulating platelets adhere to the injury site and degrade releasing huge quantities of TGF-Beta. The focal increase in TGF-Beta within the vessel wall further promotes endothelial cell apoptosis, secondary increases in platelet aggregation, intimal smooth muscle mitogenesis and smooth muscle cell survival. Through the release of mitogenic growth factors, PDGF-AA, PDGF-BB, and FGF, TGF-Beta promotes a smooth muscle cell proliferation in the arterial intima, contributing to a stenotic transformation of the vessel lumen.

In close association with a heightened TGF-Beta expression, TGF-B inhibitory binding protein is conversely downregulated, further permitting smooth muscle cell growth and stenotic adaptations. Within the intima, newly proliferated smooth muscle cells increase collagen synthesis by upregulating surface TGF-Beta 1 receptor expression, and increased TGF-B1 and receptor interactions within the intima ultimately generate large amounts of extracellular matrix, additionally promoting luminal narrowing and stenotic vessel wall changes. The role of TGF-B1 in possibly mediating a stenotic fibrotic adaptation of the vessel wall in bacterial meningitis is strengthened by observations of reduced intimal proliferation and attendant collagen accumulation in the neointima following genetic or pharmacological inhibition of TGF-B1. Conclusively, restenosis in the context of cerebral vasculitis in bacterial meningitis may represent an excessive intimal fibrocellular proliferative response and receptive inward intramural remodeling.

Platelet derived growth factor

Platelet-derived growth factor is a group of cysteine-type growth factors that are synthesized by a variety of brain cells such as neurons, astrocytes and oligodendrocytes and inflammatory cells such as macrophages. Under normal circumstances, PDGF levels are significantly low in the cerebrospinal fluid, however following infectious, ischemic or traumatic insults, PDGF levels increase. In response to tissue damage, the brain is capable of synthesizing a multitude of trophic growth factors, including PDGF, that may serve to protect resident neuronal cells of the brain. However, contrary to their neuroprotective role, these neurotrophic growth factors also promote neuronal degeneration by interacting with structural elements of the vessel wall. Of note, PDGF signaling is vital for endogenous tissue repair and functional recovery by way of neurons, vascular smooth muscle cells and astrocytes, but significantly elevated PDGF levels during the course of bacterial meningitis contribute to the development of cerebral vasculopathy in bacterial meningitis. In a comparative analysis of CSF PDGF levels between bacterial meningitis and control patients, Morichi, et al. described an increased cerebrospinal fluid level of PDGF in patients with bacterial meningitis. Moreover, increases in PDGF level were found to coincide with a poor neurological outcome during the course of bacterial meningitis, effectively hinting at a possible role of PDGF in vessel wall remodeling. Similarly, in a *E. coli* murine model of meningitis, Rui Cheng Yang, et al. observed an upregulation of cell surface PDGF-B expression in close conjecture with the initiation of inflammatory responses associated with the development of cerebral vasculitis. Although traditionally thought to originate from activated platelet alpha-granules, neuronal cells of the central nervous system represent another important source of PDGF following traumatic/infectious insults. Additionally, as PDGF is principally synthesized within macrophages, an accumulation of macrophages within the central nervous system during the chronic proliferative phase of bacterial meningitis may substantiate a role of PDGF in mediating stenotic vessel wall changes.

Similar to TGF-Beta, platelet derived growth factor is primarily involved with mediating extracellular matrix remodeling in relation to smooth muscle cells. PDGF is commonly known as one of the most important chemoattractants and mitogen for quiescent medial smooth muscles. In addition to stimulating a intimal fibrocellular response by

vascular smooth muscle cells, PDGF upregulates a variety of genes, such as monocyte chemoattractant protein, leading to the development of an inflammatory mural wall. The chemotactic actions of PDGF subsequently result in heightened inflammatory cell recruitment with leukocyte and monocyte tissue trafficking. Inflammatory cell chemotaxis is associated with damage to interendothelial tight junctions and with sustained influx, endothelial cells as well. In response to subendothelial collagen exposure, underlying collagen promotes platelet adherence and release of alpha granules, which contain PDGF. Following an increase in PDGF release and secondarily high concentration at the luminal surface, disruption of the internal elastic lamina through the proteolytic actions of infiltrating tissue macrophages disrupts the internal elastic lamina, subsequently allowing PDGF diffusion into the medial layer. Within the media, PDGF progressively accumulates and stabilizes within the media by binding to proteoglycans in the extracellular matrix. Over time, continued PDGF-proteoglycan interactions prevent PDGF clearance from the media, thereby effectively establishing a localized concentration gradient, where PDGF may be able to promote a directed migration of quiescent medial smooth muscles into the intimal layer to evoke neointima formation and intimal narrowing. Additionally, upon migration into the intima, PDGF acts on intimal smooth muscle cells to initiate a mitogenic response leading to cellular proliferation and secondary extracellular matrix synthesis by increasing collagen synthesis. Consistent with the role of PDGF in evoking mitogenic and proliferative smooth muscle cell responses in bacterial meningitis, following endothelial injury PDGF receptor is upregulated on smooth muscle cell surface, resulting in increased receptor and growth factor interactions to generate neointima formation. Further, administration of exogenous PDGF to rats resulted in a significantly upregulated stimulation of intimal smooth muscle cell accumulation and neointima formation. As expected, blockade of PDGF action with anti-PDGF antibody, receptor mutations or pharmacological inhibitors of PDGF attenuated PDGF signaling and ultimately precluded neointimal development.

Vascular endothelial growth factor

Vascular endothelial growth factor is a dimeric, endothelial cell specific cytokine primarily involved in regulating increases in vascular permeability, expression of inflammatory cell adhesion molecules and release of cytokines and chemokines. Vascular endothelial derived growth factor levels are elevated in the cerebrospinal fluid of patients with bacterial meningitis. In a comparative study of CSF VEGF levels between normal patients and patients with tuberculous meningitis, Matsuyama, et al. reported a higher VEGF expression in tuberculous meningitis patients compared to normal patients. Similarly, in relating VEGF expression to disease severity, Misra, et al. not only reported a higher CSF VEGF level in patients with tuberculous meningitis and MRI evidence of cerebral infarction, but interestingly noted a clinical improvement closely paralleling the reduction in CSF VEGF levels. In addition to describing a heightened CSF VEGF level in tubercular meningitis, Matsuyama, et al. found an intensely positive staining of VEGF in relation to mononuclear inflammatory cells around the vasculitic lesion. Likewise, Misra, et al. too reported VEGF localization in proximity to inflammatory mononuclear cells of the pathologic vasculitic lesion. Concerning the synthesis of VEGF in bacterial meningitis, it is clear that infiltrating mononuclear inflammatory cells such as macrophages are the prime producers of VEGF. Apart from infiltrating inflammatory cells, proinflammatory cytokines, including tumor necrosis factor-alpha also have the potential to induce VEGF synthesis. For example, in tuberculous models of meningitis, Husain, et al. observed a high expression of VEGF in granulomatous regions with an intense staining in infiltrating inflammatory mononuclear cells and Langerhans giant cells.

Further, a strong positive correlation was observed between intra-granulomatous VEGF expression and surrounding microvessel density, highlighting a role of VEGF in mediating vasculopathic effects during the course of bacterial meningitis. In support of an intracerebral production of growth factors in bacterial meningitis, Mankhambo, et al. found an increased CSF concentration of growth factors, including VEGF, amongst non survivors, thereby postulating that increases in VEGF level may be primarily responsible for endothelial dysfunction and vessel remodeling seen in severe bacterial meningitis or may alternatively represent an host attempt to repair endothelial damage by an infectious insult. A closer analysis of the intracranial source of VEGF production in bacterial meningitis points toward a meningeal inflammatory infiltrate as the primary source, with neutrophils and monocytes as the predominant cellular type responsible. Such a localization of VEGF in infiltrating neutrophils and monocytes is further supported by a linear relationship between CSF WBC counts and CSF VEGF levels as well as an upregulation of VEGF secretion in response to proinflammatory stimuli, including tumor necrosis factor alpha.

Once synthesized by infiltrating inflammatory cells in the subarachnoid space following an infectious insult, VEGF predominantly acts on the intervening vascular endothelial cell to evoke proinflammatory vessel wall responses. Initially, VEGF interacts with the vascular endothelium to increase vascular permeability by stimulating nitric oxide synthase and cyclooxygenase activities, with resultant nitric oxide and prostacyclin mediating attendant vasodilation and increases in vascular permeability. Additionally, VEGF may also induce fenestrations in the endothelial cells to further increase vascular permeability. The increase in vascular permeability is closely followed up a VEGF-induced upregulation of inflammatory cell adhesion molecules such as vascular cell adhesion molecule and intercellular adhesion molecule 1 on the endothelial cell surface as well as a direct stimulation of monocyte chemotaxis to promote increased inflammatory cell infiltration further propagating endothelial damage and attendant subendothelial matrix exposure and in conjunction with VEGF-induced activation of procoagulant von Willebrand Factor, promotes platelet adhesion and aggregation. Bound platelets subsequently contribute to VEGF synthesis and release, thereby increasing focal concentrations of protein to initiate pathological vessel wall remodeling. Within the arterial media, VEGF stimulates smooth muscle cell expression of matrix metalloproteinases, including MMP-1, MMP-3 and MMP-9, which may degrade extracellular matrix collagen layers, to later promote the migration of smooth muscle cells from the media to the intima, where they may gain access to mitogenic factors responsible for neointima formation. In response to a continual microenvironmental milieu of mitogenic growth factors elaborated by adherent platelets, increased VEGF-VEGF receptor signaling sustains and progressively advances the development of a neointimal lesion resulting in stenotic arterial narrowing due to the activation of numerous transduction pathways such as mitogen activated protein kinase, protein kinase c and phospholipase C involved in smooth muscle cell migration, proliferation and survival.

Conclusion

Cerebral vasculitis in the setting of bacterial meningitis may follow increases in growth factor and extracellular matrix protein synthesis in the subarachnoid space. These soluble protein products find their way to the adjacent cerebral vessel wall through anatomical connections between the outer vessel wall layer and the subarachnoid space, where they become deposited. Within the arterial wall, these proteins interact with other structural components of the extracellular matrix to evoke a range of immune/inflammatory responses resulting in increased inflammatory cell adhesion and infiltration and consequent smooth muscle cell migration and proliferation. Through the mitogenic response of vascular smooth muscle cells, the vessel wall commonly displays neointima formation leading to luminal narrowing and, over time, such an adaptation leads to a decrease in cerebral blood flow and even ischemic/infarction insults. Inevitably, the severity of extracellular matrix remodeling and cerebral vasculitis depends on the virulence of the infecting organism and duration of disease, with a greater duration of disease resulting in more maladaptive patterns of vessel adaptation and poor neurological recovery.

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