Review Article

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Parainfectious cerebral vasculopathy complicating bacterial meningitis: Acute-short lived vasospasm followed by delayed-long lasting vasculitis

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Abstract:

Bacterial meningitis is a serious, life-threatening infection of the meninges. Several radiological studies highlight prominent structural alterations occurring in the cerebral vasculature, leading to significant cerebrovascular consequences during bacterial meningitis. Beginning with reflexive arterial vasospasm , cerebrovascular disease during bacterial meningitis proceeds through a orderly sequence of arterial vasculitis with inflammatory cell infiltration, medial smooth muscle migration and proliferation, medial necrosis, adventitial fibrosis and eventual intimal stenosis. As such, this review focuses on changes occurring within cerebral arteries during disease progression, highlighting the various structural modifications occurring in the arterial vessels that contribute to disturbances in cerebral hemodynamics and, ultimately, cerebrovascular consequences during bacterial meningitis.

Keywords:

Bacterial meningitis, cerebral infarction, cerebral ischemia, cerebrovascular disease, vasculitis, vasospasm

Introduction

Cerebral blood flow alterations are a prevailing theme in bacterial meningitis. Several studies have attempted to understand the alterations in cerebral blood flow that contribute to the development of ischemic cerebrovascular sequelae in bacterial meningitis. Although most studies can collectively agree that both vasospasm and vasculitis of cerebral arteries, as intertwined as they are in their individual contributions to flow alterations, disturb the normal cerebral hemodynamic profile, the structural changes that facilitate such blood flow alteration are minimally explored. Cerebrovascular complications are a dreaded consequence in bacterial meningitis and are associated with poor neurological recovery and prognosis.[1,2] In particular, ischemic cerebrovascular events occur secondary to parainfectious vasculopathy. Cerebral arteries and veins are equally affected by structural vascular changes resulting in vasculitis, vasculopathy, arterial thrombosis, intracranial aneurysm formation, and venous thrombosis.[3] Transcranial Doppler and cerebral angiographic studies commonly demonstrate cerebrovascular involvement and cerebral blood flow variations in acute bacterial meningitis.[4-12] The net outcome of flow alterations and cerebral vasculopathy in acute bacterial meningitis is the occurrence of ischemic stroke. In fact, 15%–60% of patients with tuberculous meningitis develop stroke. Furthermore, Cerebrovascular complications in the form

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of ischemic stroke occur reliably in *Group B streptococci* models of bacterial meningitis in approximately 30% of children.[13] Surprisingly, the burden of stroke secondary to parainfectious vasculopathy is influenced by the specific pathogen causing bacterial meningitis. Here, the incidence of stroke due to bacterial meningitis caused by *Streptococcus pneumonia* is 4 times higher compared to bacterial meningitis caused by *Neisseria meningitidis*.[14,15] Given the clear association between cerebrovascular disease and bacterial meningitis, the factors predisposing to cerebrovascular involvement in bacterial meningitis remain speculative.[13-16]

Discussion

Parainfectious cerebral vasculopathy - Arterial narrowing

Cerebral vasculopathy is a recognized event in bacterial meningitis. Several pathological studies dating back to the late 19th and early 20th centuries recognize pathological changes occurring in cerebral blood vessels and brain infarcts.[17] Vasculitis changes in cerebral blood vessels have been observed in a quarter of children with *streptococcal* meningitis.[8,18] On the corollary, up to a quarter of adults show similar vasculitic changes in their cerebral vessels in bacterial meningitis.[14] Although the occurrence of vascular wall changes in bacterial meningitis is clearly demonstrated, the exact structural modifications that initiate such vessel wall morphological alterations are largely unknown. Several pieces of cerebral angiographic evidence identify arterial narrowing as a critical initial point, contributing to ischemic consequences. First, Taft *et al*. identified a significant association between *H. influenzae meningitis* and the development of vascular complications in the pediatric population.[13] Interestingly, Adams *et al*., in a necropsy study of children with bacterial meningitis, observed pathological alterations of the vasculature in the brain parenchyma similar to those seen following a recent infarction.[19] Greitz also observed the narrowing of arteries in tubercular meningitis, particularly at the base of the brain.[20] As noted above, Lehrer confirmed earlier reports of arterial stenosis in bacterial meningitis by observing diffuse narrowing of the entire circle of willis and associated branches in tubercular meningitis.[21] In an attempt to delineate the cause of arterial narrowing in bacterial meningitis, Lyons and Leeds observed cerebral blood flow patterns during the acute phase of bacterial meningitis. In addition to documenting stenotic changes in the supraclinoid region of the internal carotid artery (ICA), Lyons and Leeds proposed vasospasm of the cerebral vasculature as a contributory factor leading to these changes.[22] As noted above, cerebral angiographic studies support a clear association of bacterial meningitis with the narrowing of particular cerebral arteries such as the supraclinoid portion of the ICA, middle cerebral, or anterior cerebral artery. However, the dilemma arises in assigning an organic cause to this structural narrowing vasospasm or vasculitis. Histological studies of cerebral vessels help narrow down a presumptive cause of arterial narrowing. Currently, it is agreed that arterial narrowing due to reflexive vasospasm in response to vascular wall encroachment by inflammatory exudate is characterized by minimal histopathological changes, whereas vasculitis is marked by significant inflammatory changes such as inflammatory cellular trafficking with attendant development of wall edema and intimal thickening.[23-25]

Surrounding purulent exudate and pro-inflammatory cytokines trigger early reflexive vasospasm

Support for early reflexive vasospasm occurring in bacterial meningitis stems from several pieces of clinical and experimental evidence. Yamashima *et al*. analyzed ultrastructural changes occurring in cerebral vessels during bacterial meningitis and demonstrated two different origins of the narrowing of cerebral vessels. The first occurrence of cerebral narrowing was attributed to vasospasm and the second occurrence to vasculitis. Instead of suggesting vasospasm and vasculitis are two separate entities, it was suggested that the initial vasospasm damages the vascular endothelium leading to inflammatory changes that evolved into vasculitis. Yamashima *et al*. proposed that vasospasm initiated endothelial damage due to a reduction in caliber of the cerebral blood vessel leading to ischemia.[26] Likewise, in addition to documenting stenotic changes in the supraclinoid region of the ICA, Lyons and Leeds proposed vasospasm of the cerebral vasculature as a contributory factor leading to these changes.[22] Further, Ferris *et al*. similarly agreed that vasospasm leads to stenotic changes in purulent meningitis.[27] In an attempt to assign an organic cause for cerebral vasospasm, Wertham analyzed several pieces of necropsy data from children and adults with bacterial meningitis, observed the sparse frequency of cerebral lesions during purulent meningitis, and, coincidentally postulated that these benign-appearing lesions are a consequence of vasoactive circulatory factors released during infection.[17] Similarly, Hassin observed similar changes to the cerebral vasculature and attributed these findings to the accumulation of inflammatory metabolic by-products.[28] Crompton extended the pathological sequelae of cerebral vasospasm by providing the first histopathological evidence of cerebral vasospasm-induced vasculopathy by demonstrating microscopic changes suggestive of myonecrosis in involved cerebral arteries.[29]

The precise etiology of vasospasm in bacterial meningitis remains to be fully elucidated, but inflammatory cytokines, cerebrospinal fluid (CSF) leukocytes, oxygen-derived-free radicals, and inflammatory exudate may be reasonable mediators.[30,31] Under normal

circumstances, the arterial wall is resistant to infection; with the development of an infectious foci occurring due to the spread of infection from an external, but an adjacent site in close proximity to the vasculature.[3,32] Histological studies suggest that early arterial vasospasm may be initiated due to increased pressure exerted on the cerebral vessels by the surrounding purulent exudate.[23,24] Furthermore, histopathological examinations of the cerebral vasculature demonstrate that the vascular adventitia is continuous with the surrounding purulent exudate in the CSF.[33] Initial involvement of the arterial adventitia is supported from observations that the adventitial layer is most severely affected in bacterial meningitis.[34-39] Given that the inner arachnoid region of the meninges forms the outer adventitial layer of focal subarachnoid blood vessels, the early preferential involvement of the adventitial layer may represent a primary initial extension of infection. Additionally, the intracranial arteries demonstrate a significant deficiency of the external elastic lamina and instead have only a sparse adventitial layer, easily facilitating the early involvement of the adventitial layer by the infectious process in a nearby adjacent foci.[40] Anatomically, the predilection for the adventitia as the primary site of involvement stems from the course of the ICA through the subarachnoid spaces. Following the course of vertebral arteries and the ICA in the vertebral column and the neck respectively, these vessels pass through the meninges to enter the skull. On entering the skull, the dense purulent exudate in the subarachnoid space and basal cisterns wrap the traversing blood vessels, causing the particular segments to undergo vasospasm.[35,38,41-44] Closer examination of these vessels reveals a marked sparsity of vessel wall infiltration, with evidence of vasospasm correlating strongly with the surrounding subarachnoid exudate in which these vessels coexist in.[37,38,42,43,45] Moreover, these vessels demonstrating a significant vasospastic process coincide with those located at the base of the brain as well as in the Sylvian fissures, a region of the brain characterized by a rich accumulation of purulent exudate derived from the meningitic process in the subarachnoid process.[35,38,41,42,44] The vasospasm observed in these blood vessels may be attributed to either pressure exerted by the surrounding subarachnoid exudate or due to the interaction of the cerebral vessels with vasoactive pro-inflammatory cytokines released in the vicinity. From this viewpoint, given the proximity of the vascular adventitia to the subarachnoid space, identification of the adventitia as the initial site of inflammation leading to arterial vasospasm seems more than plausible.[46] Similarly, the common involvement of supraclinoid portions of the ICA, distal vertebral, and basilar arteries strengthens the argument for subarachnoid purulent exudates in initiating vasospasm in bacterial meningitis. Vessel narrowing, in this context, may represent a reflexive early transient reversible muscular contraction as a response to the surrounding infectious process, ultimately culminating in vasospasm.

Vasospasm occurring due to exposure of humoral factors released locally in the CSF or the blood vessel wall corroborate observations of the tunica adventitia as the initial site of vasculopathy in bacterial

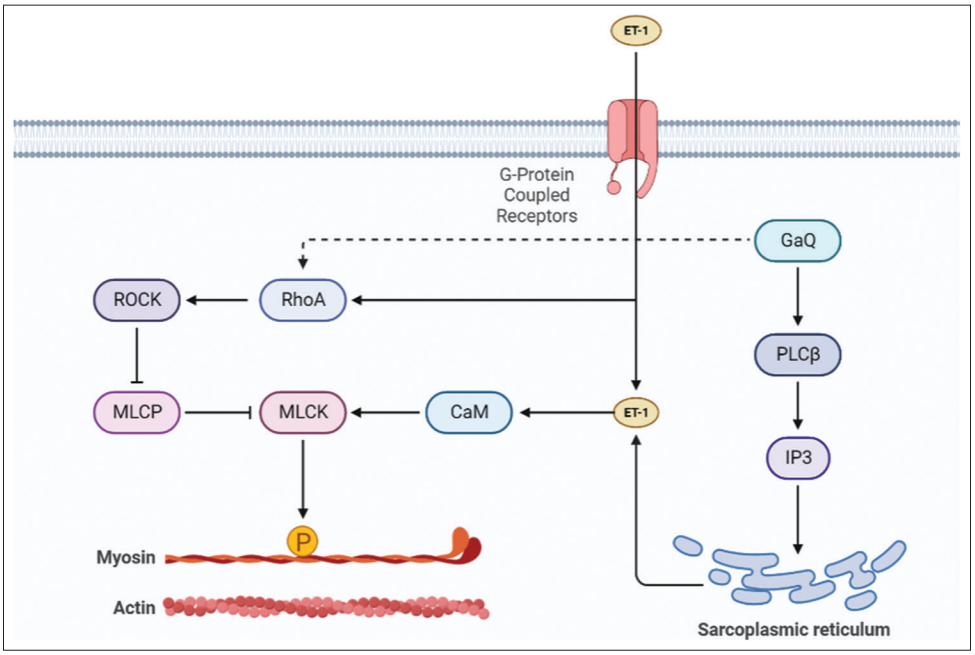

Figure 1: ET-1, elaborated in the CSF, diffuses into the tunica media through adventitial defects, where it comes in contact with smooth muscle cells to elicit contraction, resulting in vasoconstriction through the activation of downstream pathways such as rho-kinase[121]

meningitis. Such an interaction is permitted due to ultrastructural modifications of the cerebral vasculature. In contrast to other arteries elsewhere in the body, the cerebral vasculature is unique in that it is not heavily surrounded and wrapped by a dense layer of collagen or fibroblasts, but rather is devoid of such a constrictive environment, allowing for direct contact with the CSF.[47] This ultrastructural modification of the cerebral vasculature allows humoral factors such as vasoactive mediators and pro-inflammatory cytokines to directly modulate vascular tone either through direct actions or by indirect actions such as inducing the synthesis of endothelin-1 (ET-1) by the vascular endothelium.[48,49] In line with this suggestion, given the greatest exposure of the cerebral vasculature to the surrounding inflammatory noxious microenvironment occurs in the outermost layer, the tunica adventitia, it is reasonable to speculate that if locally released humoral factors were causative in the initiation of cerebral vasospasm in bacterial meningitis, the adventitia would be most severely affected.[50] Moreover, given that the predominant inflammatory process of bacterial meningitis occurs in the region of the large intracranial blood vessels, vasospasm caused by pro-inflammatory cytokines seems plausible given the focal involvement of nearby blood vessels. Additionally, the sparsity of inflammatory cell infiltration into the vessel wall with a greater predominance of CSF leukocytosis in the surrounding CSF, strengthens the argument for a role of humoral factors released within the CSF or the blood vessel wall as the inciting agent.[51]

Vasospasm attributed to humoral factors begins with a perturbation of normal endothelial cell function following bacterial meningitis. Injury to the vessel endothelium plays a vital role in the development of vasospasm through the modulation of synthesis of humoral mediators capable of influencing smooth muscle cell activity. In particular, a loss of endothelial-derived nitric oxide synthesis, a vasodilator, or upregulation of endothelin, a vasoconstrictor, is implicated in the establishment of vasospasm.[52] Consequently, in bacterial meningitis, the decreased availability of NO and unopposed activation and action of ET-1 is overwhelmingly implicated in the mediation of cerebral vascular responses leading to vasospasm.[53] ET-1, a potent vasoconstrictor, is synthesized by leukocytes following exposure to bacterial lipopolysaccharides and pro-inflammatory cytokines released during cerebral inflammation.[7,48,49,54] Consistent with this suggestion, patients with bacterial meningitis have a markedly elevated CSF level of ET-1, coinciding with cerebral blood flow disturbances.[30] Surprisingly, increased CSF levels of pro-inflammatory cytokines (tumor necrosis factor [TNF], Interleukin-1 [IL-1]) positively correlate with cerebral blood flow alterations in bacterial meningitis.[31] Here, patients displaying increased cerebral blood flow velocities were observed to show a coincident increase in CSF concentrations of IL-1 and IL-6.[33] These studies suggest that pro-inflammatory cytokines released in response to an infectious foci in the CSF influence cerebral blood flow patterns by activating the synthesis of ET-1 by the cerebral vascular endothelium.[47-49] Upon release into the subarachnoid space, ET-1, a vasoconstrictor of molecular size 2.5 kDA, may appear to gain access into the nearby vascular wall from the adventitial side, where it may come into contact with vascular smooth muscle cells (VSMCs), triggering contraction of smooth muscle contraction (SMCs) and the advent of cerebral vasospasm [Figure 1].[47] Such an interaction between humoral factors released into the CSF and constituents of the vascular wall is permitted due to structural modifications of the pial cerebral arteries, wherein the outer adventitial layer of these vessels is in direct contact with the surrounding subarachnoid space, not hindered by extracellular matrix (ECM) cellular components such as collagen or fibroblasts, allowing for easy diffusion of vasoactive factors into the vessel wall to mediate vasoactive vascular wall alterations.[47] Consistent with this suggestion is the demonstration of ET-1 acting from the adventitial side of the blood vessel, rather than the luminal side of the blood vessel, thereby providing a link between ET-1 release by leukocytes and other central nervous system cells in the subarachnoid space and vasospasm of adjacent cerebral blood vessels.[47,50]

Angiographic evidence of the cerebral vasculature during bacterial meningitis further strengthens the argument for vasospasm occurring in the acute phase of infection by suggesting an early short-lived alteration of cerebral blood flow not sustained during the later stages of infection. C.H. LU used magnetic resonance angiography to demonstrate arterial vascular changes occurring in acute bacterial meningitis, measuring cerebral blood flow in the basilar, posterior, middle, and anterior cerebral arteries across various days over a 21-day period. It was noted that cerebral blood flow velocity sequentially increased over the course of days 1–4 before reaching a peak on day 4, and gradually returning to the normal baseline value over the remainder of 21 days.[55] Similarly, in a study performed by Müller *et al.*, using a transcranial Doppler to measure the blood flow velocity in 4 cerebral vessels, during the acute phase of bacterial meningitis, cerebral blood flow velocity maximally increased between days 1 and 3 before gradually returning to the normal baseline value after 21 days.[56] In addition, as observed by Hans-Peter Haring, the cerebral blood flow velocity gradually increased from day 1 to day 5, before reaching a peak flow velocity on the 5th day. Subsequently, the cerebral blood flow velocity decreased gradually after the 5th day until the 21st day, where it resembled normal baseline values. In an attempt to more closely elucidate the precise

vascular response characteristic of the acute phase of bacterial meningitis, Hans-Peter Haring proposed that in the acute setting of bacterial meningitis with an attendant infective foci in the cerebral vasculature, the accompanying inflammatory response will damage the vascular endothelium. The vascular endothelium will respond with a reflexive transient vasospasm, leading to narrowing and obstruction of the affected vessel which by virtue of creating a turbulent blood flow within the vessel contributes to an increased blood flow velocity. Moreover, he postulated that the increase in cerebral blood flow commonly observed during the acute stages of infection that was not corroborated by an equally elevated cerebral blood flow pattern over the later periods of the disease may very well represent a resolution of the inflammatory process with restoring of the normal cerebral vascular architecture by reduction of the vasospasm and reversal of narrowing and obstruction of the affected vessel.[25] According to this viewpoint, as vasospasm of cerebral arteries in bacterial meningitis is primarily mediated by either a surrounding purulent exudate or soluble vasoactive humoral factors in the CSF, both of which represent components of the acute inflammatory response in bacterial meningitis, resolution of the inflammatory process by host defenses may explain the normalization of the cerebral blood flow over the later stages of bacterial meningitis. Ultimately, these angiographic studies corroborate the critical influence of reversible vasospasm during the acute phase of bacterial meningitis. Conclusively, cerebral vasospasm in bacterial meningitis may be attributed to either a reflexive reversible contraction in response to surrounding purulent inflammatory exudate in the CSF or due to pro-inflammatory cytokines.

Upregulation of vascular cell adhesion molecule and intercellular adhesion molecule-1 and leukocyte trafficking initiate myonecrosis and vasodilation

In addition to vasospasm, cerebral arteries frequently demonstrate the occurrence of vasodilation. In search of histopathological changes providing further insight into cerebral vasculopathy occurring in bacterial meningitis, Davis *et al*. described angiographic evidence of significant vasodilation occurring in purulent meningitis. However, much to the contrary, angiographically demonstrated vasodilation was not accompanied with similar histopathological changes.[57] Crompton provided the first histopathological evidence of cerebral vasospasm-induced vasculopathy by demonstrating microscopic changes suggestive of myonecrosis in involved cerebral arteries.[29] Oberc and Engel provided a plausible sequence of events leading to the formation of myonecrosis following the initiation of vasospasm in cerebral arteries. Initial vasospasm interferes with the smooth muscle cell plasmalemma, allowing the massive entry of intracellular calcium. Accumulation of calcium in intracellular organelles such as the mitochondria and sarcoplasmic reticulum leads to calcium overload. Cytoplasmic increases in calcium allow sustained repeated aberrant contractions of myofilaments, resulting in myofilament breakdown and mechanical destruction. Further, increases in intracellular calcium enhance the breakdown of myofilaments into smaller nonfunctional thin granular or filamentous material. On the other hand, increases in mitochondrial and sarcoplasmic reticulum calcium sequestration leads to adenosine triphosphate (ATP) wastage by active calcium transport processes. In addition, the sustained

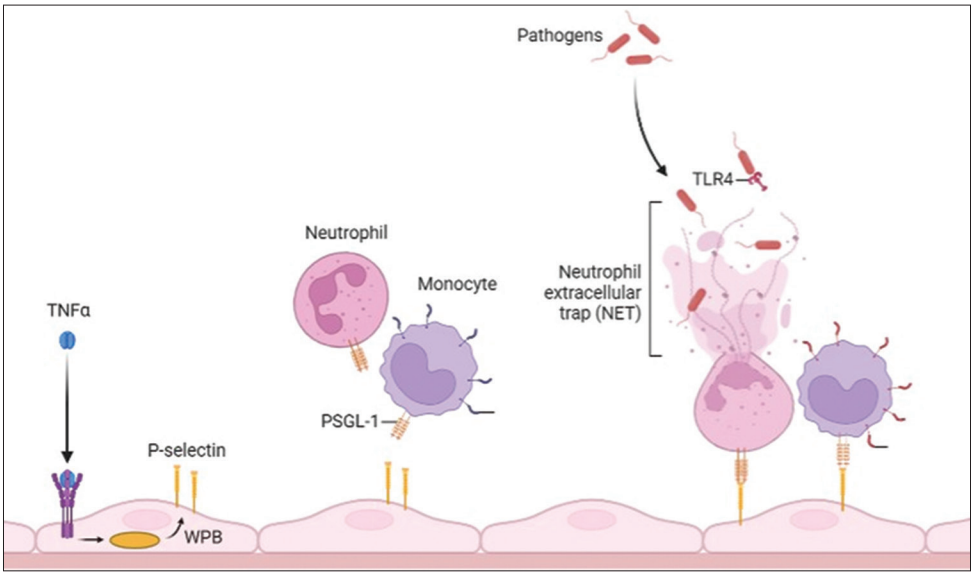

Figure 2: Upregulation of leukocyte specific adhesion molecules during the acute phase of meningitis promotes neutrophil/monocyte migration, adherence and invasion of the endothelium, following which meningococci may be able to enter the intima through endothelial gaps.[121]

myofilament contractions, in response to high calcium levels, further consume ATP. The net outcome of these effects is a depletion of intracellular ATP, leading to further disruption of the plasmalemmal barrier and an eventual depletion of intracellular glycogen reserves to replenish ATP through anaerobic glycolysis, ultimately culminating in myonecrosis and a weakly sustained muscle contraction leading to vasodilation.[58]

More closely, following cerebral vasospasm, the initiation of hypoxic injury to the cerebral vasculature triggers endothelial cell injury and endothelial dysfunction, characterized by dysfunctional properties of the vascular endothelium. Vascular damage and dysfunction are responsible for many of the pathophysiological features of severe meningococcal disease, beginning with increased adhesiveness of leukocytes to the vascular endothelium [Figure 2]. Initially, Tuomanen *et al*. proposed an alteration of normal endothelial cell phenotype by suggesting that early in the course of bacterial meningitis, increased leukocyte-endothelial cell interaction was observed.[59] Similarly, meningococci-derived cutaneous vasculitic lesions when cultured *in vivo* have been demonstrated to adhere to and subsequently invade the vascular endothelium.[60] In the same study, increased meningococci adherence to the vascular endothelium was associated with an increased prevalence of infiltrating neutrophils, lending support to the idea that meningococci facilitate leukocyte attachment to the vascular endothelium.[60] Further, histological specimens of cutaneous lesions caused by meningococci demonstrate an increased number of meningococci adherent to the vascular endothelium.[61] Meningococci are able to adhere to and invade the vascular endothelium through interactions with specific receptor ligands on the endothelial cell surface.[62-65] Subsequently, meningococci, alone or in combination with neutrophils, may lead to endothelial injury.[63,65] Meningococci adherent to the vascular endothelium may initiate endothelial damage by stimulating the margination and adherence of neutrophils from the circulating blood.[64] At this point, leukocytes initially mediate tissue injury and initiate vessel wall remodeling through the infiltration of the vessel wall with pro-inflammatory cytokines, polymorphonuclear neutrophils, and degradative enzymes. In particular, during bacterial meningitis, granulocytes trigger destructive vessel wall changes by releasing cytotoxic cellular proteases, reactive oxygen-derived species, nitric oxide, and polyunsaturated fatty acids.[66] These cytotoxic molecules exert different pathologic effects on the vessel wall resulting in the destruction of the layers of the vessel wall with the eventual weakening of the mechanical properties of the cerebral vasculature ultimately turning into a friable, matrix-devoid vascular wall.

The early pathological cascade of destructive vascular remodeling following leukocyte tissue influx proceeds with macrophage tissue trafficking and predominance as the dominant inflammatory cell type. Localization and trafficking of macrophages within the vascular wall sets into motion the sequential process of vessel wall weakening through the production of cytokines, proteases, and soluble protein mediators capable of regulating a number of processes related to cell survival and production of ECM. Of note, the prime target of macrophages following states of vascular wall inflammation is the smooth muscle cell.[67,68] Due to the fact that VSMCs maintain the integrity of the vascular wall through the synthesis of collagen and elastin, damage to these cells by macrophages leads to a marked weakening of the mechanical integrity of the arterial wall. The primary mechanism by which macrophages initiate smooth muscle cell damage is by triggering apoptosis of these cells.[69,70] Apoptosis of vascular smooth muscles, in response to vascular injury, is mediated by several different mechanisms including activation of proapoptotic Fas signaling pathways and release of cytotoxic pro-apoptotic signals such as nitric oxide and TNF-alpha.[68,71] In addition to facilitating the destruction of these cells, macrophages also reduce collagen synthesis by the remaining surrounding smooth muscle cells through the secretion of transforming growth factor-beta, effectively rendering the functional VSMCs unable to synthesize collagen leading to significant impairments in the structural integrity of the vascular wall.[72,73] Apart from indirectly modifying the composition of the ECM by influencing the synthetic properties of VSMCs, macrophages also directly influence the course of ECM remodeling through the release of matrix metalloproteinases (MMPs).[74] MMP release from infiltrating macrophages plays an ever-so-important role in vascular wall remodeling during bacterial meningitis. In line with this suggestion, several experimental studies highlight a critical inductive influence of matrix-metalloproteinases in the vascular wall remodeling process of bacterial meningitis.[75-80] MMPs, zinc-containing peptidases intracellularly located as inactive zymogens within leukocytes and brain cells, are responsible for the degradation of the ECM.[81-83] Within the cerebral vasculature, MPPS initiate a pathological cascade of destructive vascular remodeling through a series of sequential steps culminating in the eventual increase in leukocyte migration across the endothelial cell barrier. Upon activation, zymogens release MMPs leading to the degradation of the subendothelial basement membrane, a critical barrier to leukocyte transcellular migration into the tissue, in the cerebral vasculature by the degrading ECM proteins-collagen IV and V, the main constituents of the subendothelial basal lamina situated

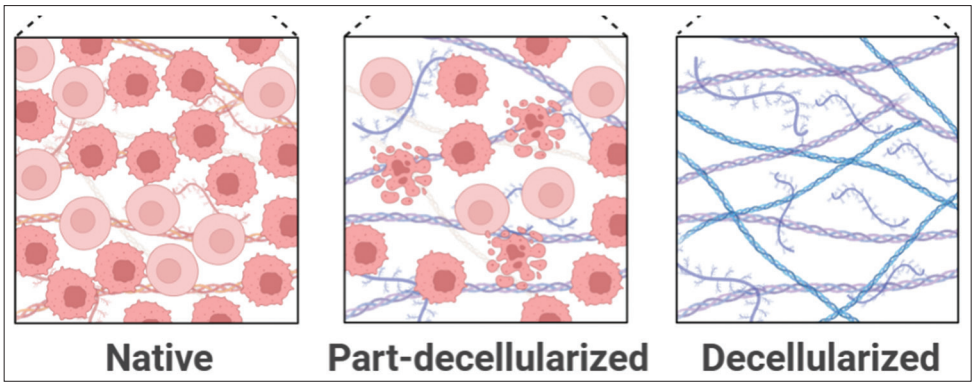

Figure 3: Soon after the onset of arterial inflammation, the tunica media is overloaded with an abundance of macrophages (native) that initially contribute to the remodeling of the media through the release of degradative proteases. Subsequently, macrophages and smooth muscle cells progressively under apoptosis, leading to a gradual resolution of acute inflammation and adaptation of a synthetic phenotype (part-decellularized). Ultimately, smooth muscle cells are replaced by a synthetic fibrotic matrix characterized by increased collagen deposition (decellularized)[121]

around the cerebral capillaries. Increased leukocyte and subsequent macrophage tissue trafficking propagate a cycle of continuous inflammatory cell trafficking, release of cytotoxic proteases further enhancing the already present inflammatory infiltrate, eventually leading to vessel wall necrosis and a weakening of the mechanical properties of the cerebral vasculature, inching towards the development of vasodilation from a loss of muscular integrity.

During the early phase of the inflammatory process affecting the vascular media, a dominant inflammatory cell constituency is established. Following the creation of a dense inflammatory zone, infiltrating acute inflammatory cells are gradually replaced by chronic inflammatory cells, which degrade the structural components of the vascular wall. Ultimately, a decellularized media persists characterized by a replacement of VSMCs by fibrotic elements [Figure 3].

The vasculopathic effects of MMPs are corroborated with histological evidence of vessel wall necrosis, particularly in small- and medium-sized blood vessel walls. In lieu of the suggestion that inflammatory cells and inflammatory cell products mediate destructive vessel wall changes in bacterial meningitis, vessel wall necrosis may be a consequence of vessel wall infiltration.[35,42,84,85] In studies of *tuberculous* bacterial meningitis, following the occurrence of vasospasm, the smooth muscle cells of the tunica media commonly demonstrate signs of cytoplasmic vacuolization, a early sign of VSMC apoptosis.[86] Similarly, in a separate study, the tunica media of cerebral arteries was observed to be deficient in VSMCs and accompanied by a corresponding increase in VSMC devoid amorphous regions in the tunica media. These amorphous areas, characterized by a loss of VSMCs, were replaced by dense fibrotic tissue similar in appearance to the adjacent adventitia.[87] Moreover, fragmentation and dissolution of the internal elastic lamina in the tunica intima and smooth muscle cell atrophy in the tunica media were observed before the onset of late-stage tunica intimal thickening.[87] This disruption of the internal elastic lamina and VSMCs emphasizes the occurrence of vessel wall necrosis in bacterial meningitis, forming the basis for myonecrosis and subsequent vasodilation that is commonly observed. Ultimately, initial necrotic inflammatory lesions affecting the tunica adventitia and media of the cerebrovasculature progress to the intimal layer, where they evolve into stenotic, occlusive lesions as a result of proliferative vessel wall changes coinciding with the thickening and organization of the surrounding purulent inflammatory exudate.[34,42,44]

Late intimal thickening and luminal stenosis

Vasodilation and myonecrosis of the cerebral arteries are subsequently followed up by an increase in intimal thickening and luminal narrowing of the cerebral vasculature in bacterial meningitis. Initial vasospasm, occurring due to either purulent exudate-induced pressure effects or vasoconstrictive actions of pro-inflammatory cytokines, damages the intima as a consequence of arterial narrowing-reduced blood flow leading to anoxic injury of the intima. In response to ischemic injury, the intima undergoes intimal proliferation and thickening resulting in myointimal hyperplasia and sequential ischemic cerebrovascular sequelae. For example, secondary intimal proliferation is most commonly observed in cerebral arteries affected by the greatest degree of vasospasm, highlighting a role of vasospasm in ischemia-induced intimal remodeling.[88] Histopathological studies more closely elucidate this transformation emphasizing that following hypoxic endothelial injury, breakdown of the endothelial cell barrier and leakage of intravascular fluid into the subendothelial space leads to the development of subendothelial edema. With the progression of bacterial meningitis, subsequently, breakdown of the internal elastic lamina and subsequent migration

of smooth muscle cells to the intima results in vascular reorganization of the subendothelial edema and eventual intimal thickening.[26] Lehrer, using a *tuberculous* model of meningitis, observed luminal narrowing of arteries at the base of the brain, and attributed vasculo-occlusive changes in the small- and medium-sized vessels as a plausible factor.[21] Likewise, Abraham, Mathew, and Chandy observed stenotic lesions principally affecting the supraclinoid portion of the ICA in the vicinity of the carotid siphon and in the proximal portions of the middle and anterior cerebral arteries. These stenotic lesions in the form of either distinct beadlike or completely occluded segments may very well represent an adverse consequence of early vasospasm, but histological evidence more closely points to an inflammatory process mediated vessel wall remodeling due to the presence of arteritic lesional changes suggestive of stenosis.[89] In *tubercular* bacterial meningitis, stenotic changes of the cerebral vasculature in the form of occlusive intimal thickening represent a deleterious late-occurring cerebrovascular complication.[36,42,85,90,91] In fact, occlusive cerebral vasculopathy in bacterial meningitis appears to occur either in the setting of vessel wall infiltration by inflammatory cells or following inflammatory cell-induced vascular remodeling.[42,87,91] Before the advent of intimal thickening, histological studies highlight the presence of adventitial fibrosis, medial atrophy, and internal elastic lamina fragmentation as important precursors.[87] The progression of histological changes from early adventitial fibrosis to subsequent medial atrophy and eventual internal elastic lamina breakdown emphasizes the inward migration of the vasculopathic inflammatory process from the adventitia towards the intima. The end result of the inflammatory process centered on the cerebral vessel intima is a segmental, concentric or crescentic appearance of the cerebral vasculature,[34,36,38,42] coinciding with intimal proliferation and myointimal hyperplasia.

As stated earlier, luminal stenosis in the late stages of bacterial meningitis is a consequence of intimal proliferation and hyperplasia leading to vasculitis.[26] Vasculitis, the pathogenic manifestation of intimal hyperplasia, is accompanied by neither a breakdown of the endothelial cell layer nor intravascular thrombi formation leading to stenotic narrowing, accounting for vasculitic tissue ischemia.[3] Instead, stenotic narrowing, in the context of bacterial meningitis, revolves around the role of VSMCs in the tunica media following injury to the arterial wall. A standard response of the arterial vasculature to injury is the migration of VSMCs from the tunica media into the intima, followed by hyperproliferation in response to soluble mediators.[88] Possible mediators affecting migratory and proliferative capabilities of the VSMC include MMPs, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF).[92] First, VSMC migration requires the mechanical disruption of the endothelial cell basement membrane.[93] MMPs, proteolytic enzymes derived from macrophages, initiate endothelial cell basement membrane proteolysis, thereby decreasing endothelial cell-basement membrane adhesive interactions through the removal of adhesion sites or upregulation of VSMC binding sites, both of which facilitate VSMC intimal migration. Simultaneously, endothelial cell and VSMC adhesion junctions composed of VE-cadherin and N-cadherin, respectively, are proteolytically degraded by MMPs, promoting disintegration of these cells from their cellular attachment and preparing VSMC for migration.[94,95] In addition, MMPS trigger the fragmentation and dissolution of type 1 collagen, procuring the formation of new integrin binding sites.[96,97] The disruption of the endothelial basement membrane with decreased endothelial and VSMC cell-cell adherence, along with the upregulation of new integrin binding sites, increases cellular interactions between integrins and ECM components, leading to heightened activation of molecular pathways responsible for VSMC migration. Although several MMPS are responsible for mediating different components of vasculopathic derangement in bacterial meningitis following vascular injury, MMP-2 and MMP-9 have been most prominently observed to mediate VSMC migration.[98,99]

Upon migration into the intimal layer, VSMCs proliferate under the influence of diverse proliferative stimuli, including growth factors and pro-inflammatory cytokines. As such, two notable growth factors capable of modulating VSMC behavior in response to vascular injury are vascular endothelial-derived growth factor and PDGF. Vascular endothelial-derived growth factor, a soluble growth factor, initiates increases in vascular endothelial cell permeability, angiogenesis, and most importantly, migratory capabilities of the VSMC [Figure 4]. A putative role of VEGF in mediating stenotic changes of the arterial intima arises from the observation of increased levels of VEGF in the serum and CSF of patients with *tuberculous* meningitis.[100] Further, indirect evidence for the role of VEGF in initiating vasculitic changes in bacterial meningitis arises secondary to the pro-inflammatory properties of TNF-alpha. In a rabbit model of *tuberculous* bacterial meningitis, the occurrence of cerebral vasculitis coincides with CSF levels of TNF, suggesting that the production of TNF-alpha by the inflammatory process induces synthesis of VEGF.[101] VEGF, a soluble growth factor, is normally expressed by the VSMC but is rapidly upregulated during states of vascular injury leading to VEGF overexpression.[92,102] VEGF overexpression by VSMCs has been observed to occur during the presence of several noxious stimuli, including mechanical injury, ischemia, reactive oxygen species, and pro-inflammatory

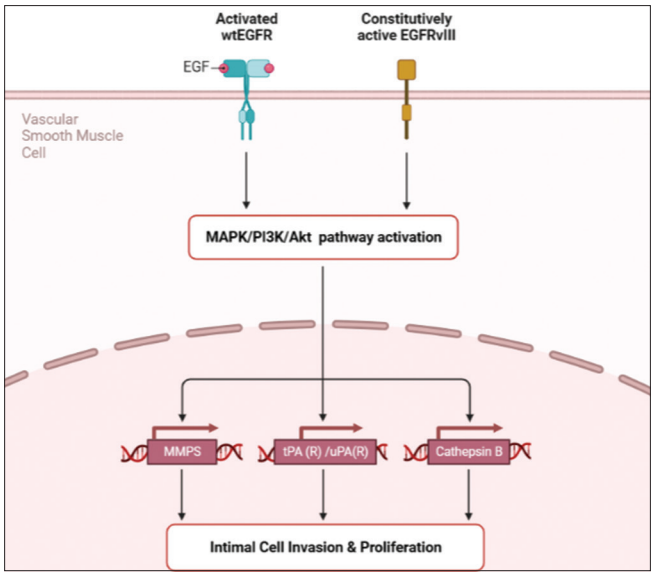

Figure 4: Focal increases in VEGF concentration within the tunica media interact with cell surface receptors on smooth muscle cells to stimulate transcription of genes responsible for matrix metalloproteinase, cathepsin B and tissue/urokinase plasminogen activator production. Initially, matrix metalloproteinase and cathepsin B degrade the subendothelial basement membrane and intervening extracellular matrix proteins such as collagen and fibrinogen to facilitate smooth muscle migration. Subsequently, urokinase plasminogen activator promotes smooth muscle cell migration from the media to the intima as well as stimulates smooth muscle cell proliferation to eventually contribute to the development of a stenotic intimal lesion[121]

cytokines (IL-1) and growth factors (basic fibroblast growth factor and PDGF).[103,104] Once induced, VEGF promotes migration of SMCs, thereby underling chemotactic stimuli of VEGF on VSMCs.[102] In addition, VEGF indirectly stimulates VSMC migration and subsequent intimal thickening by participating in the vascular response to injury through the production of MMPs by VSMCs.[105] Based on these studies, it is reasonable to speculate that during bacterial meningitis, hypoxia-induced endothelial injury contributes to intimal thickening and luminal stenosis through the upregulation of VEGF, which may act in a autocrine manner to facilitate the migration of VSMCs from the tunica media into the tunica intima, setting the stage for subsequent interactions with proliferative mediators such as PDGF.

Following the migration of VSMCs into the intima, PDGF is a signaling mediator involved in mediating subsequent smooth muscle cell responses to endothelial cell injury. Although the action of different subtypes of PDGF on VSMCs is multifarious, the PDGF-BB subtype has been consistently demonstrated to initiate VSMC migration in response to arterial injury.[106-109] PDGF-BB expression, in bacterial meningitis, contributes to ischemic stroke through a perturbation in normal endothelial cell barrier function.[110] Further, in *E. coli* models of bacterial meningitis, PDGF expression is upregulated by the vascular endothelium. Following insults to the vascular wall, PDGF is derived from both platelets adherent to the denuded endothelium as well as infiltrating macrophages in the vascular wall. Since inflammation of the cerebral vasculature in bacterial meningitis begins from the adventitia and spreads inward towards the intima, infiltrating macrophages may be a dominant source of PDGF release into the vascular wall. Consistent with this suggestion, recent studies have identified infiltrating macrophages as a cellular source of PDGF release, a mitogen capable of directly influencing smooth muscle cell proliferation in the intima leading to growth of a stenotic lesion.[111,112] In atherosclerotic models, macrophages have been demonstrated as an initial source of PDGF serving to bind to Platelet-derived growth factor receptor-expressing smooth muscle cells in the vascular media to promote the development of a neointimal stenotic lesion.[53,113] All in all, these studies suggest that heightened activation of PDGF expression during bacterial meningitis mediates intimal migration, proliferation, and secretion of ECM leading to the formation of a hyperplastic intima-the pathophysiological mechanism for luminal stenosis during the late stages of bacterial meningitis. Given the role of PDGF in promoting vascular remodeling through migratory and proliferative properties on quiescent VSMCs, high levels of PDGF level strongly correlate with significant impairments of the functionality of the vascular endothelium and are predictive of a poor overall prognosis.[114-116] In support of this viewpoint, deleterious neurologic sequelae persisted in many patients with increases in VEGF/PDGF, and a positive correlation was noted between CSF VEGF and PDGF and patients with bacterial meningitis, which may serve as a useful index to evaluate the prognosis of bacterial meningitis.[117] Ultimately, given the roles of VEGF and PDGF in inating a structural vasculopathy of the cerebral vasculature, the CSF levels of these mediators serve as reliable predictors of cerebrovascular sequelae in patients with bacterial meningitis. Eventually, VSMC migration and proliferation in the intimal layer, elicits a fibrotic reaction leading to a dense collagen fibril network in the ECM [Figure 5].

The cerebral arteriopathy coinciding with the recovery phase of bacterial meningitis is responsible for the late-occurring severe clinical outcome and fatal complications.[117,118] In line with this, Kerr and Filloux observed the occurrence of cerebral infarction in a child nearly 6 years following *Haemophilus influenzae* meningitis.[119] Upon cerebral arteriography, the anterior cerebral artery and proximal portion of the middle cerebral artery were found to have stenotic changes. Although the sequential evolution of vasculopathy here is not available, it is reasonable to assume that the stenotic changes noted were a consequence of permanent long-standing progressive vasculitis evolving over time

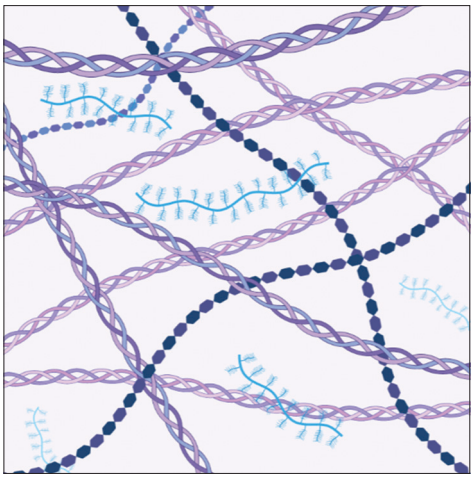

Figure 5: During the late stage of cerebral arteriopathy, the intima is transformed into a fibrotic layer with a predominance of smooth muscle cells and abundant collagen synthesis and deposition, consequently contributing to a stenotic/obliterative lesion[121]

from vasospasm. Similarly, Bullock and Welchman documented a significant deterioration in general health approximately 10 days after the onset of *tuberculous* meningitis.[120] In the same study, deterioration was linked to basal regions of low-density intensity on computed tomography scan performed 2 weeks after the onset of infection. Ultimately, with the development of intimal stenosis during the late/recovery stages of cererbal arteriopathy, ischemic deficits may complicate bacterial meningitis leading to a poor neurological recovery and disability.

Conclusion

Cerebrovascular complications are a dreaded sequelae of bacterial meningitis. Bacterial meningitis results in a structural narrowing of the cerebral vasculature accounting for the increased occurrence of ischemic events, including stroke. Although the development of cerebrovascular sequelae in bacterial meningitis is commonly described, the structural vascular wall modifications that take place are less clearly elucidated. From this review, it is clear that initial response of the cerebral vasculature in bacterial meningitis is a reversible narrowing of the vessel, representing either a reflexive vasospasm in response to the surrounding purulent exudate or the vasoconstrictive actions of pro-inflammatory cytokines and vasoactive mediators such as ET-1. Subsequently, cerebral vasospasm is closely followed by a hypoxic injury with the development of a dysfunctional endothelium characterized by a pro-inflammatory and proatherogenic phenotype, leading to inflammatory cell infiltration into the vessel wall, destruction of the media and intimal smooth muscle cell migration and proliferation setting into motion a pathological cascade of vessel wall remodeling that culminates in intimal fibrosis and organic stenosis.

Ethical approval and patient content

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Conflicts of interest

There are no conflicts of interest.

References

1. Swartz MN. Bacterial meningitis: More involved than just the meninges. N Engl J Med 1984;311:912-4.
2. Pfister HW, Borasio GD, Dirnagl U, Bauer M, Einhäupl KM. Cerebrovascular complications of bacterial meningitis in adults. Neurology 1992;42:1497-504.
3. Igarashi M, Gilmartin RC, Gerald B, Wilburn F, Jabbour JT. Cerebral arteritis and bacterial meningitis. Arch Neurol 1984;41:531-5.
4. Paulson OB, Brodersen P, Hansen EL, Kristensen HS. Regional cerebral blood flow, cerebral metabolic rate of oxygen, and cerebrospinal fluid acid-base variables in patients with acute meningitis and with acute encephalitis. Acta Med Scand 1974;196:191-8.
5. Ashwal S, Stringer W, Tomasi L, Schneider S, Thompson J, Perkin R. Cerebral blood flow and carbon dioxide reactivity in children with bacterial meningitis. J Pediatr 1990;117:523-30.
6. Gordon I, Orton M, Hughes T, Dinwiddie R. Evaluation of regional cerebral perfusion (rCBF) in acute neurological disorders in childhood. J Nucl Med 1991;32:943.
7. McMenamin JB, Volpe JJ. Bacterial meningitis in infancy: Effects on intracranial pressure and cerebral blood flow velocity. Neurology 1984;34:500-4.
8. Snyder RD, Stovring J, Cushing AH, Davis LE, Hardy TL. Cerebral infarction in childhood bacterial meningitis. J Neurol Neurosurg Psychiatry 1981;44:581-5.
9. Weisberg LA. Cerebral computerized tomography in intracranial inflammatory disorders. Arch Neurol 1980;37:137-42.
10. Packer RJ, Bilaniuk LT, Zimmerman RA. CT parenchymal abnormalities in bacterial meningitis: Clinical significance. J Comput Assist Tomogr 1982;6:1064-8.
11. Dunn DW, Daum RS, Weisberg L, Vargas R. Ischemic cerebrovascular complications of Haemophilus influenzae meningitis. The value of computed tomography. Arch Neurol 1982;39:650-2.
12. Cabral DA, Flodmark O, Farrell K, Speert DP. Prospective study of computed tomography in acute bacterial meningitis. J Pediatr 1987;111:201-5.
13. Taft TA, Chusid MJ, Sty JR. Cerebral infarction in Haemophilus influenzae type B meningitis. Clin Pediatr (Phila) 1986;25:177-80.
14. Pugin D, Copin JC, Goodyear MC, Landis T, Gasche Y. Persisting vasculitis after pneumococcal meningitis. Neurocrit Care 2006;4:237-40.
15. Fugate S, Roos KL. Stroke associated with infections including immunizations. Semin Cerebrovasc Dis Stroke 2001;1:240-8.
16. Schut ES, Lucas MJ, Brouwer MC, Vergouwen MD, van der Ende A, van de Beek D. Cerebral infarction in adults with bacterial meningitis. Neurocrit Care 2012;16:421-7.
17. Wertham F. The cerebral lesions in purulent meningitis. Arch Neurol Psychiatry 1931;26:549.
18. Klobassa DS, Zoehrer B, Paulke-Korinek M, Gruber-Sedlmayr U, Pfurtscheller K, Strenger V, *et al.* The burden of pneumococcal meningitis in Austrian children between 2001 and 2008. Eur J Pediatr 2014;173:871-8.

19. Adams RD, Kubik CS, Bonner FJ. The clinical and pathological aspects of influenzal meningitis. Arch Pediatr (N Y) 1948;65:408-41.
20. Greitz T. Angiography in tuberculous meningitis. Acta Radiol Diagn (Stockh) 1964;2:369-78.
21. Lehrer H. The angiographic triad in tuberculous meningitis. A radiographic and clinicopathologic correlation. Radiology 1966;87:829-35.
22. Lyons EL, Leeds NE. The angiographic demonstration of arterial vascular disease in purulent meningitis. Report of a case. Radiology 1967;88:935-8.
23. Cairns H, Russell DS. Cerebral arteritis and phlebitis in pneumococcal meningitis. J Pathol Bacteriol 1946;58:649-65.
24. Pfister HW. Complicated purulent meningitis in the adult: Persisting high mortality caused by vasculitis and intracranial pressure. Nervenarzt 1989;60:249-54.
25. Raimondi AJ, Di Rocco C. Cerebral angiography in meningocerbral inflammatory diseases in infancy and childhood: A study of thiryt-five cases. Neurosurgery 1978;3:37-44.
26. Yamashima T, Kashihara K, Ikeda K, Kubota T, Yamamoto S. Three phases of cerebral arteriopathy in meningitis: Vasospasm and vasodilatation followed by organic stenosis. Neurosurgery 1985;16:546-53.
27. Ferris EJ, Rudikoff JC, Shapiro JH. Cerebral angiography of bacterial infection. Radiology 1968;90:727-34.
28. Hassin GB. Histologic studies in meningitis. Arch Neurol Psychiatry 1932;28:789.
29. Crompton MR. The pathogenesis of cerebral infarction following the rupture of cerebral berry aneurysms. Brain 1964;87:491-510.
30. Fassbender K, Ries S, Schminke U, Schneider S, Hennerici M. Inflammatory cytokines in CSF in bacterial meningitis: Association with altered blood flow velocities in basal cerebral arteries. J Neurol Neurosurg Psychiatry 1996;61:57-61.
31. Fassbender K, Schminke U, Ries S, Ragoschke A, Kischka U, Fatar M, *et al.* Endothelial-derived adhesion molecules in bacterial meningitis: Association to cytokine release and intrathecal leukocyte-recruitment. J Neuroimmunol 1997;74:130-4.
32. Rob CG, Eastcott HH. Aortic aneurysm due to tuberculous lymphadenitis. Br Med J 1955;1:378-9.
33. Friede RL. Cerebral infarcts complicating neonatal leptomeningitis. Acute and residual lesions. Acta Neuropathol 1973;23:245-53.
34. Winter WJ. The effect of streptomycin upon the pathology of tuberculous meningitis. Am Rev Tuberc 1950;61:171-84.
35. Smith HV. Tuberculous meningitis. Int J Neurol 1964;4:134-57.
36. Poltera AA. Thrombogenic intracranial vasculitis in tuberculous meningitis. A 20 year "post mortem" survey. Acta Neurol Belg 1977;77:12-24.
37. Goldzieher JW, Lisa JR. Gross cerebral hemorrhage and vascular lesions in acute tuberculous meningitis and meningo-encephalitis. Am J Pathol 1947;23:133-45.
38. Doniach I. Changes in the meningeal vessels in acute and chronic (streptomycin-treated) tuberculous meningitis. J Pathol Bacteriol 1949;61:253-9, 4 pl.
39. Auerbach O. Tuberculous meningitis: Correlation of therapeutic results with the pathogenesis and pathologic changes. II. Pathologic changes in untreated and treated cases. Am Rev Tuberc 1951;64:419-29.
40. Seidman MA, Mitchell RN. Surgical pathology of small- and medium-sized vessels. Surgical Pathology Clinics 2012;5:435–51.
41. Smith HV, Vollum RL, Cairns H. Treatment of tuberculous meningitis with streptomycin. Lancet 1948;1:627-36.
42. Winkelman WN, Moore MT. Meningeal blood vessels in tuberculous, meningitis. J Nerv Ment Dis 1942;95:230.
43. Horne NW. Tuberculous meningitis: Problems in pathogenesis and treatment. Edinb Med J 1951;58:413-29.
44. Daniel PM. Gross morbid anatomy of the central nervous system of cases of tuberculous meningitis treated with streptomycin. Proc R Soc Med 1949;42:169-74.
45. Thwaites GE, Simmons CP, Than Ha Quyen N, Thi Hong Chau T, Phuong Mai P, Thi Dung N, *et al.* Pathophysiology and prognosis in vietnamese adults with tuberculous meningitis. J Infect Dis 2003;188:1105-15.
46. Rich AR, McCordock HA. Pathogenesis of tubercular meningitis. Bull Johns Hopkins Hosp 1933;52:5-13.
47. Zervas NT, Liszczak TM, Mayberg MR, Black PM. Cerebrospinal fluid may nourish cerebral vessels through pathways in the adventitia that may be analogous to systemic vasa vasorum. J Neurosurg 1982;56:475-81.
48. Endo T, Uchida Y, Matsumoto H, Suzuki N, Nomura A, Hirata F, *et al.* Regulation of endothelin-1 synthesis in cultured guinea pig airway epithelial cells by various cytokines. Biochem Biophys Res Commun 1992;186:1594-9.
49. Katabami T, Shimizu M, Okano K, Yano Y, Nemoto K, Ogura M, *et al.* Intracellular signal transduction for interleukin-1 beta-induced endothelin production in human umbilical vein endothelial cells. Biochem Biophys Res Commun 1992;188:565-70.
50. Mima T, Yanagisawa M, Shigeno T, Saito A, Goto K, Takakura K, *et al.* Endothelin acts in feline and canine cerebral arteries from the adventitial side. Stroke 1989;20:1553-6.
51. McMeans JW. The occurrence of arteritis in meningitis. Am J Med Sci 1916b; 151:249-56.
52. Schwartz SM, deBlois D, O'Brien ER. The intima. Soil for atherosclerosis and restenosis. Circ Res 1995;77:445-65.
53. Pfister LA, Tureen JH, Shaw S, Christen S, Ferriero DM, Täuber MG, *et al.* Endothelin inhibition improves cerebral blood flow and is neuroprotective in pneumococcal meningitis. Ann Neurol 2000;47:329-35.
54. McAllister CK, O'Donoghue JM, Beaty HN. Experimental pneumococcal meningitis. II. Characterization and quantitation of the inflammatory process. J Infect Dis 1975;132:355-60.
55. Lu CH, Chang HW, Lui CC, Huang CR, Chang WN. Cerebral haemodynamics in acute bacterial meningitis in adults. QJM 2006;99:863-9.
56. Müller M, Merkelbach S, Huss GP, Schimrigk K. Clinical relevance and frequency of transient stenoses of the middle and anterior cerebral arteries in bacterial meningitis. Stroke 1995;26:1399-403.
57. Davis DO, Dilenge D, Schlaepfer W. Arterial dilatation in purulent meningitis. Case report. J Neurosurg 1970;32:112-5.
58. Oberc MA, Engel WK. Ultrastructural localization of calcium in normal and abnormal skeletal muscle. Lab Invest 1977;36:566-77.
59. Tuomanen EI, Saukkonen K, Sande S, Cioffe C, Wright SD. Reduction of inflammation, tissue damage, and mortality in bacterial meningitis in rabbits treated with monoclonal antibodies against adhesion-promoting receptors of leukocytes. J Exp Med 1989;170:959-69.
60. Sotto MN, Langer B, Hoshino-Shimizu S, de Brito T. Pathogenesis of cutaneous lesions in acute meningococcemia in humans: Light, immunofluorescent, and electron microscopic studies of skin biopsy specimens. J Infect Dis 1976;133:506-14.
61. Hill WR, Kinney TD. The cutaneous lesions in acute meningococcemia; a clinical and pathologic study. J Am Med Assoc 1947;134:513-8.
62. Virji M, Makepeace K, Peak I, Payne G, Saunders JR, Ferguson DJ, *et al.* Functional implications of the expression of PilC proteins in meningococci. Mol Microbiol 1995;16:1087-97.
63. Virji M, Kayhty H, Ferguson DJ, Alexandrescu C, Heckels JE, Moxon ER. The role of pili in the interactions of pathogenic Neisseria with cultured human endothelial cells. Mol Microbiol 1991;5:1831-41.
64. Virji M, Makepeace K, Moxon ER. Distinct mechanisms of interactions of Opc-expressing meningococci at apical and basolateral surfaces of human endothelial cells; the role of integrins in apical interactions. Mol Microbiol 1994;14:173-84.
65. Dunn KL, Virji M, Moxon ER. Investigations into the molecular

basis of meningococcal toxicity for human endothelial and epithelial cells: The synergistic effect of LPS and pili. Microb Pathog 1995;18:81-96.
66. Scheld WM, Koedel U, Nathan B, Pfister HW. Pathophysiology of bacterial meningitis: Mechanism (s) of neuronal injury. J Infect Dis 2002;186 Suppl 2:S225-33.
67. Clarke M, Bennett M. The emerging role of vascular smooth muscle cell apoptosis in atherosclerosis and plaque stability. Am J Nephrol 2006;26:531-5.
68. Boyle JJ, Weissberg PL, Bennett MR. Tumor necrosis factor-alpha promotes macrophage-induced vascular smooth muscle cell apoptosis by direct and autocrine mechanisms. Arterioscler Thromb Vasc Biol 2003;23:1553-8.
69. Stoneman VE, Bennett MR. Role of apoptosis in atherosclerosis and its therapeutic implications. Clin Sci (Lond) 2004;107:343-54.
70. Littlewood TD, Bennett MR. Apoptotic cell death in atherosclerosis. Curr Opin Lipidol 2003;14:469-75.
71. Kavurma MM, Bhindi R, Lowe HC, Chesterman C, Khachigian LM. Vessel wall apoptosis and atherosclerotic plaque instability. J Thromb Haemost 2005;3:465-72.
72. Fadok VA, Bratton DL, Konowal A, Freed PW, Westcott JY, Henson PM. Macrophages that have ingested apoptotic cells *in vitro* inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF-beta, PGE2, and PAF. J Clin Invest 1998;101:890-8.
73. Grainger DJ. Transforming growth factor beta and atherosclerosis: So far, so good for the protective cytokine hypothesis. Arterioscler Thromb Vasc Biol 2004;24:399-404.
74. Stamenkovic I. Extracellular matrix remodelling: The role of matrix metalloproteinases. J Pathol 2003;200:448-64.
75. Nau R, Brück W. Neuronal injury in bacterial meningitis: Mechanisms and implications for therapy. Trends Neurosci 2002;25:38-45.
76. Meli DN, Loeffler JM, Baumann P, Neumann U, Buhl T, Leppert D, *et al.* In pneumococcal meningitis a novel water-soluble inhibitor of matrix metalloproteinases and TNF-alpha converting enzyme attenuates seizures and injury of the cerebral cortex. J Neuroimmunol 2004;151:6-11.
77. Williams PL, Leib SL, Kamberi P, Leppert D, Sobel RA, Bifrare YD, *et al.* Levels of matrix metalloproteinase-9 within cerebrospinal fluid in a rabbit model of coccidioidal meningitis and vasculitis. J Infect Dis 2002;186:1692-5.
78. Leppert D, Leib SL, Grygar C, Miller KM, Schaad UB, Holländer GA. Matrix metalloproteinase (MMP)-8 and MMP-9 in cerebrospinal fluid during bacterial meningitis: Association with blood-brain barrier damage and neurological sequelae. Clin Infect Dis 2000;31:80-4.
79. Leib SL, Clements JM, Lindberg RL, Heimgartner C, Loeffler JM, Pfister LA, *et al.* Inhibition of matrix metalloproteinases and tumour necrosis factor alpha converting enzyme as adjuvant therapy in pneumococcal meningitis. Brain 2001;124:1734-42.
80. Leib SL, Leppert D, Clements J, Täuber MG. Matrix metalloproteinases contribute to brain damage in experimental pneumococcal meningitis. Infect Immun 2000;68:615-20.
81. Backstrom JR, Lim GP, Cullen MJ, Tökés ZA. Matrix metalloproteinase-9 (MMP-9) is synthesized in neurons of the human hippocampus and is capable of degrading the amyloid-beta peptide (1-40). J Neurosci 1996;16:7910-9.
82. Gottschall PE, Deb S. Regulation of matrix metalloproteinase expressions in astrocytes, microglia and neurons. Neuroimmunomodulation 1996;3:69-75.
83. Pagenstecher A, Stalder AK, Kincaid CL, Shapiro SD, Campbell IL. Differential expression of matrix metalloproteinase and tissue inhibitor of matrix metalloproteinase genes in the mouse central nervous system in normal and inflammatory states. Am J Pathol 1998;152:729-41.
84. Hektoen L. The vascular changes of tuberculous meningitis, especially the tuberculous endarterities. J Exp Med 1896;1:112-63.
85. Thomas MD, Chopra JS, Banerjee AK, Singh MS. Tuberculous meningitis (a clinico-pathological study). Neurol India 1977;25:26-34.
86. Shankar SK, Santosh V, Mahadevan A, Yasha TC, Satishchandra P. Pathology of cerebral vasculature in neurotuberculosis e some observations. Prog Clin Neurosci 2001;14:134e41.
87. Vasishta RK, Banerjee AK. CNS tuberculosis e pathology. In: Chapra JS, Sawhney IMS, editors. Neurology in tropics. Churchill Livingstone; 1999. p. 391–8
88. Dalal PM. Observations on the involvement of cerebral vessels in tuberculous meningitis in adults. Adv Neurol 1979;25:149-59.
89. Mathew NT, Abraham J, Chandy J. Cerebral angiographic features in tuberculous meningitis. Neurology 1970;20:1015-23.
90. Dastur DK, Lalitha VS. The many facets of neurotuberculosis: An epitome of neuropathology. Prog Neuropathol 1973;2:351e498.
91. Macgregor AR, Green CA. Tuberculosis of the central nervous system, with special reference to tuberculous meningitis. J Pathol Bacteriol 1937;45:613-45.
92. Louis SF, Zahradka P. Vascular smooth muscle cell motility: From migration to invasion. Exp Clin Cardiol 2010;15:e75-85.
93. Aguilera CM, George SJ, Johnson JL, Newby AC. Relationship between type IV collagen degradation, metalloproteinase activity and smooth muscle cell migration and proliferation in cultured human saphenous vein. Cardiovasc Res 2003;58:679-88.
94. Savani RC, Wang C, Yang B, Zhang S, Kinsella MG, Wight TN, *et al.* Migration of bovine aortic smooth muscle cells after wounding injury. The role of hyaluronan and RHAMM. J Clin Invest 1995;95:1158-68.
95. Uglow EB, Slater S, Sala-Newby GB, Aguilera-Garcia CM, Angelini GD, Newby AC, *et al.* Dismantling of cadherin-mediated cell-cell contacts modulates smooth muscle cell proliferation. Circ Res 2003;92:1314-21.
96. Carragher NO, Frame MC. Focal adhesion and actin dynamics: A place where kinases and proteases meet to promote invasion. Trends Cell Biol 2004;14:241-9.
97. Nelson WJ, Nusse R. Convergence of Wnt, beta-catenin, and cadherin pathways. Science 2004;303:1483-7.
98. Jin UH, Suh SJ, Chang HW, Son JK, Lee SH, Son KH, *et al.* Tanshinone IIA from Salvia miltiorrhiza BUNGE inhibits human aortic smooth muscle cell migration and MMP-9 activity through AKT signaling pathway. J Cell Biochem 2008;104:15-26.
99. Shi ZD, Ji XY, Berardi DE, Qazi H, Tarbell JM. Interstitial flow induces MMP-1 expression and vascular SMC migration in collagen I gels via an ERK1/2-dependent and c-Jun-mediated mechanism. Am J Physiol Heart Circ Physiol 2010;298:H127-35.
100. Matsuyama W, Hashiguchi T, Umehara F, Matsuura E, Kawabata M, Arimura K, *et al.* Expression of vascular endothelial growth factor in tuberculous meningitis. J Neurol Sci 2001;186:75-9.
101. Ryuto M, Ono M, Izumi H, Yoshida S, Weich HA, Kohno K, *et al.* Induction of vascular endothelial growth factor by tumor necrosis factor alpha in human glioma cells. Possible roles of SP-1. J Biol Chem 1996;271:28220-8.
102. Grosskreutz CL, Anand-Apte B, Duplàa C, Quinn TP, Terman BI, Zetter B, *et al.* Vascular endothelial growth factor-induced migration of vascular smooth muscle cells *in vitro*. Microvasc Res 1999;58:128-36.
103. Stavri GT, Hong Y, Zachary IC, Breier G, Baskerville PA, Ylä-Herttuala S, *et al.* Hypoxia and platelet-derived growth factor-BB synergistically upregulate the expression of vascular endothelial growth factor in vascular smooth muscle cells. FEBS Lett 1995;358:311-5.
104. Brogi E, Wu T, Namiki A, Isner JM. Indirect angiogenic cytokines upregulate VEGF and bFGF gene expression in vascular smooth muscle cells, whereas hypoxia upregulates VEGF expression only. Circulation 1994;90:649-52.
105. Celletti FL, Waugh JM, Amabile PG, Brendolan A, Hilfiker PR,

Dake MD. Vascular endothelial growth factor enhances atherosclerotic plaque progression. Nat Med 2001;7:425-9.
106. Shekhonin BV, Tararak EM, Samokhin GP, Mitkevich OV, Mazurov AV, Vinogradov DV, *et al.* Visualization of apo B, fibrinogen/fibrin, and fibronectin in the intima of normal human aorta and large arteries and during atherosclerosis. Atherosclerosis 1990;82:213-26.
107. Ferns GA, Sprugel KH, Seifert RA, Bowen-Pope DF, Kelly JD, Murray M, *et al.* Relative platelet-derived growth factor receptor subunit expression determines cell migration to different dimeric forms of PDGF. Growth Factors 1990;3:315-24.
108. Koyama N, Morisaki N, Saito Y, Yoshida S. Regulatory effects of platelet-derived growth factor-AA homodimer on migration of vascular smooth muscle cells. J Biol Chem 1992;267:22806-12.
109. Clunn GF, Refson JS, Schachter M, Hughes AD. Different effects of platelet derived growth factor isoforms on DNA synthesis and migration in human vascular smooth muscle cells. Biochem Soc Trans 1995;23:608S.
110. Su EJ, Fredriksson L, Geyer M, Folestad E, Cale J, Andrae J, *et al.* Activation of PDGF-CC by tissue plasminogen activator impairs blood-brain barrier integrity during ischemic stroke. Nat Med 2008;14:731-7.
111. Rudijanto A. The role of vascular smooth muscle cells on the pathogenesis of atherosclerosis. Acta Med Indones 2007;39:86-93.
112. Raines EW. PDGF and cardiovascular disease. Cytokine Growth Factor Rev 2004;15:237-54.
113. Koga J, Aikawa M. Crosstalk between macrophages and smooth muscle cells in atherosclerotic vascular diseases. Vascul Pharmacol 2012;57:24-8.
114. Ten Freyhaus H, Berghausen EM, Janssen W, Leuchs M, Zierden M, Murmann K, *et al.* Genetic ablation of PDGF-dependent signaling pathways abolishes vascular remodeling and experimental pulmonary hypertension. Arterioscler Thromb Vasc Biol 2015;35:1236-45.
115. Antoniu SA. Targeting PDGF pathway in pulmonary arterial hypertension. Expert Opin Ther Targets 2012;16:1055-63.
116. Wight TN. Arterial remodeling in vascular disease: A key role for hyaluronan and versican. Front Biosci 2008;13:4933-7.
117. Morichi S, Morishita N, Takeshita M, Ishida Y, Oana S, Yamanaka G, *et al.* Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) levels in the cerebrospinal fluid of children with influenza-associated encephalopathy. J Infect Chemother 2017;23:80-4.
118. Chang CJ, Chang WN, Huang LT, Chang YC, Huang SC, Hung PL, *et al.* Cerebral infarction in perinatal and childhood bacterial meningitis. QJM 2003;96:755-62.
119. Kerr L, Filloux FM. Cerebral infarction as a remote complication of childhood Haemophilus influenzae meningitis. West J Med 1992;157:179-82.
120. Bullock MR, Welchman JM. Diagnostic and prognostic features of tuberculous meningitis on CT scanning. J Neurol Neurosurg Psychiatry 1982;45:1098-101.
121. Adapted from BioRender.com 2023. Available from: https://app.biorender.com/biorender-templates. [Last accessed on 2023 Jun 02].