Review Article

Access this article online

Quick Response Code:

Website: http://www.braincirculation.org

DOI: 10.4103/bc.bc_97_22

Localization of cerebral vasculopathy following bacterial meningitis: What can we learn about postinfective ischemic sequelae?

Vivig Shantha Kumar, Vignarth Shantha Kumar

Abstract:

Cerebrovascular complications of bacterial meningitis account for a high incidence of mortality and postinfective neurologic sequelae. Cerebrovascular complications occurring during acute bacterial meningitis are evident from angiographic evidence demonstrating arterial occlusion and vessel wall narrowing, histopathological studies demonstrating vessel wall changes, and radiographic studies demonstrating the presence of brain infarcts. Cerebrovascular disease during bacterial meningitis has been demonstrated in of *Haemophilus influenzae*, *Streptococcus pneumonia*, Group B *Streptococcus,* and *Mycobacterium tuberculosis* models of meningitis. Despite models of bacterial meningitis showing variable patterns of cerebral vasculopathy as a contributor to different aspects of postinfectious neurological decline, very few studies describe the predominant localization of cerebral vasculopathy with different meningitis causing pathogens. Thus, this review attempts to analyze the different locations of cerebral vasculopathic changes occuring in response to different microbial pathogens and provide a pathophysiologic basis for such an observation.

Keywords:

Bacterial Meningitis, *Haemophilus influenza*, *Mycobacterium tuberculosis*, *Streptococcus pneumonia*, Group B *Streptococcus*, Vasculopathy

Introduction

Bacterial meningitis is a life-threatening infection of the meninges, the brain's outer coverings, caused most commonly by *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumonia,* and *Mycobacterium tuberculosis,* with most cases resolving without the development of complications following the appropriate institution of antimicrobial agents. However, some cases do result in the development of complications, which significantly increases the associated morbidity and mortality. Although numerous complications arise during the course of bacterial meningitis, one particular consequence of concern stems from involvement of the cerebral vasculature. Cerebrovascular disease in bacterial meningitis is a well-established phenomenon. For example, cerebrovasculature complications of bacterial meningitis include arterial and venous thrombosis, aneurysms, and ischemic and hemorrhagic strokes. Given the clear involvement of the cerebrovascular system during bacterial meningitis, the pattern of cerebrovascular involvement is less clearly understood. With this being said, an insight into different localization patterns of cerebrovascular involvement during bacterial meningitis begins with an observation of arterial narrowing in different

Department of Internal Medicine, California Institute of Behavioral Neurosciences and Psychology, Fairfield, California, United States of America

Address for correspondence:
Dr. Vivig Shantha Kumar, Department of Internal Medicine, California Institute of Behavioral Neurosciences and Psychology, 4751 Mangels Blvd, Fairfield, California 94534, United States of America.
E-mail: vivigsk@gmail.com

Submission: 07-12-2022
Revised: 03-03-2023
Accepted: 21-03-2023
Published: 30-11-2023

How to cite this article: Kumar VS, Kumar VS. Localization of cerebral vasculopathy following bacterial meningitis: What can we learn about postinfective ischemic sequelae? Brain Circ 2023;9:205-13.

regions of the brain [Figure 1]. For instance, *Haemophilus influenza* models of bacterial meningitis commonly report a narrowing of large arteries. Specifically at a distinct region of the internal carotid artery (ICA), termed the supraclinoid portion. Contrastingly, *Group B streptococci/ Streptococcus pneumonia* models of meningitis commonly describe narrowing of small intracerebral arteries. Interestingly, *Mycobacterium tuberculosis* models of bacterial meningitis frequently demonstrate stenotic changes of large arteries at the base of the brain and accompanying small and medium sized vessels.

Discussion

Haemophilus influenzae meningitis: Involvement of the supraclinoid portion of the internal carotid artery

Haemophilus influenzae models of bacterial meningitis commonly describe a narrowing of large arteries. In particular, narrowing most often occurs at a discrete region of the internal carotid artery, termed the supraclinoid portion [Table 1].[1-5] In fact, cerebral angiographic studies provide evidence for involvement of the supraclinoid ICA in models of *Haemophilus influenzae* meningitis. For example, Lyons and Leeds *et al*. described altered regional cerebral blood flow patterns during the early phase of bacterial meningitis and attributed these hemodynamic changes to stenotic lesions most frequently affecting the supraclinoid region of the ICA.[4] Similarly, Gado *et al*., demonstrated a narrowing of multiple segments of arteries primarily located at the base of the brain, with the supraclinoid portion of the internal carotid artery most frequently and severely affected.[1] Along the same lines, Headings and Glasgow *et al*., observed that a majority of cerebral lesions primarily involved the supraclinoid ICA, with less frequent involvement of the anterior and middle cerebral arteries.[8] Furthermore, McMenamin *et al*. confirmed earlier observations of stenotic changes affecting the supraclinoid ICA by demonstrating the presence of a significant hemispheric hypodensitiy, corresponding to narrowing of the supraclinoid ICA.[11]

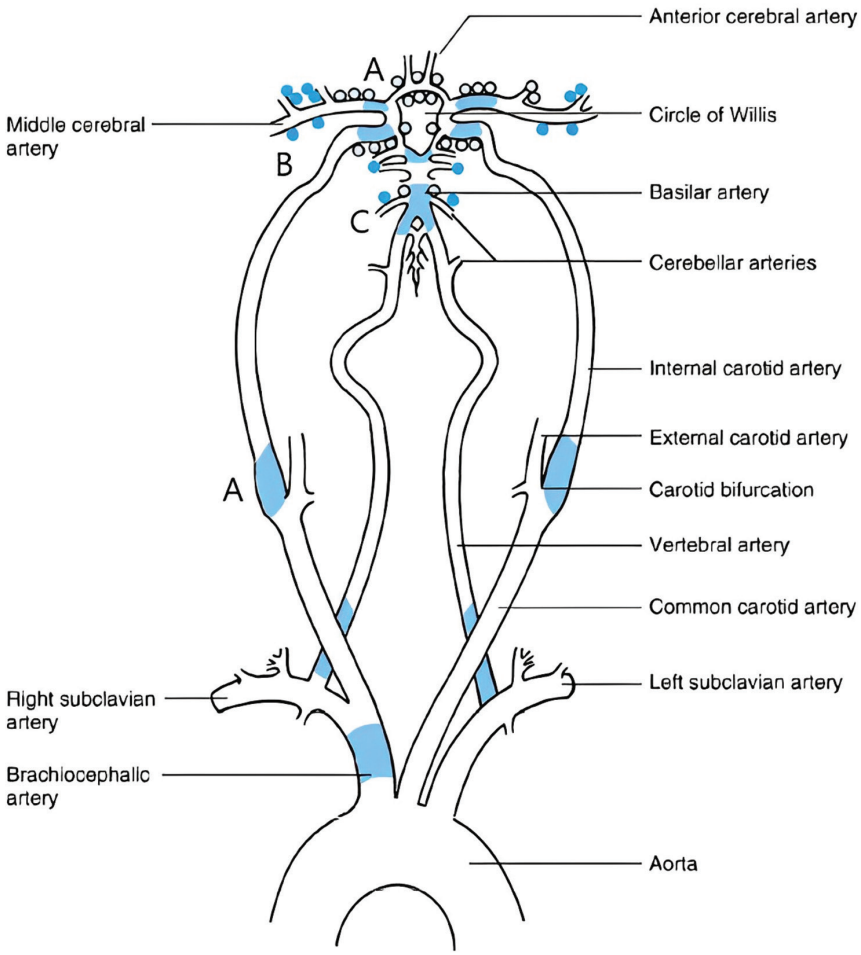

Figure 1: Areas of cerebrovascular stenosis (blue) in different models of bacterial meningitis. In *Hemophilus influenzae meningitis*, the internal carotid artery and its cranial regions, particularly the supraclinoid portion, are affected. (A) Conversely, during *Streptococcus pneumonia or Group B Streptococcal* meningitis, the middle cerebral artery and its penetrating intracerebral branches are involved. (B) Finally, In *Mycobacterium tuberculosis* meningitis, the basilar artery and other arteries at the base of the brain are affected[67].

A discussion about the preferential involvement of the supraclinoid ICA in Hemophilus influenza models of meningitis begins with a deep dive into the anatomical and morphological characteristics of the subarachnoid space and the meningeal layers. Initially, following the onset of bacterial meningitis, invading microorganisms and purulent exudate are strictly localized within the cerebrospinal fluid, being limited by the pia and arachnoid membrane layers of the meninges. Such a containment of the inflammatory process within the cerebrospinal fluid provides a demarcation between the cerebral parenchyma and the inflamed leptomeninges, initially preventing the extension of infection into the cerebral vasculature.[12] From the cerebrospinal fluid, the infectious process spreads to the subarachnoid space through ultrastructural modifications of the arachnoid layer of the meninges. Normally, the arachnoid layer consists of several layers of interlocking elongated cellular elements intertwined with one another by way of intercellular tight junctions. As such, the outer layer of the arachnoid meningeal layer is characterized by a single continous row of cells.[12] In contrast to the outer arachnoid layer, the inner parenchyma layer of the arachnoid is devoid of a continuous barrier, with the pia-arachnoid membrane rather demonstrating a discontinuous, nonadherent unicellular basal lamina, conducive to the diffusion of soluble mediators from the subarachnoid space. Furthermore, the thin basal lamina, by virtue of its disorganized arrangement, hardly poses a barrier to solute diffusion from the subarachnoid space into the extracellular spaces of the cerebral parenchyma, thus representing a contiguous pathway for spread of infection from the subarachnoid space into the cerebral parenchyma in close proximity to the cerebral vasculature.[12] Precisely, the cerebral extracellular area, a region of cerebral vasculature localization, is in continuity with the subarachnoid space through a series of perivascular extensions of the subarachnoid spaces, known as the Virchow-Robin spaces, possibly accounting for a direct route of spread from the subarachnoid space into the cerebral parenchyma. As the internal and external layers of the Virchow-Robin spaces correspond to the adventitia of cerebral blood vessels and a fine layer of collagen and reticular fibers, the spread of infection through the Virchow-Robin spaces invariably affects the cerebral vasculature. Thus, this anatomical relationship lends support to the spread of an infectious process from the subarachnoid space into the cerebral vasculature, with the Virchow-Robin spaces acting as an intermediate medium.[13]

In addition to the anatomical continuity of the cerebral vasculature with the subarachnoid space, cerebral arteries in the subarachnoid space are primed for the development of cerebrovascular complications owing to distinct modifications of the arterial wall. The internal carotid, basilar, and vertebral arteries – the dominant cerebral vasculature of the subarachnoid space – like other peripheral arteries elsewhere in the body, share a common structural organization of an outer tunica

Table 1: Cerebrovascular involvement in *Haemophilus influenzae* models of bacterial meningitis

Author	Patients	Cerebral blood vessel/vascular area affected
Thomas and Hopkins *et al.*[1]	5	Left supraclinoid internal carotid artery (1) Bilateral supraclinoid internal carotid artery, right middle cerebral artery (2) Bilateral supraclinoid internal carotid artery (3) Bilateral supraclinoid internal carotid artery, right middle cerebral artery (4) Intracranial arteries (5)
Lyons and Leeds *et al.*[4]	1	Bilateral supraclinoid internal carotid artery (1)
James *et al.*[6]	2	Bilateral supraclinoid internal carotid artery (1); Right supraclinoid internal carotid artery (2)
Gado *et al.*[7]	3	Right supraclinoid internal carotid artery, Proximal anterior and middle cerebral arteries (1); Right supraclinoid internal carotid artery (2); Right supraclinoid internal carotid artery, Proximal anterior cerebral artery (3)
Headings and Glasgow *et al.*[8]	1	Left supraclinoid internal carotid artery (1)
McMenamin *et al.*[11]	1	Bilateral supraclinoid internal carotid artery (1)

( ): patient number in study

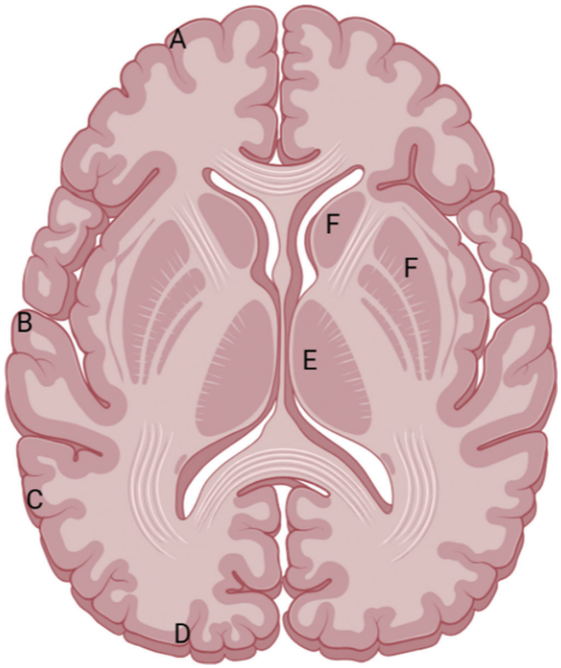

Figure 2: Preferential sites of cerebral vessel involvement in *Streptococcus pneumonia/Group B streptococcus* meningitis[67]
A: Frontal Cortex, B: Temporal Cortex, C: Frontal Cortex, D: Occipital Cortex; E: Thalamus; F: Basal Ganglia

adventitia, middle tunica media, and inner tunica intima.[14,15] In contrast to peripheral arteries, however these cerebral arteries display a thin, sparse layer of tunica media and adventitia, an absence of vasa vasorum, and are situated within a dense collection of cerebrospinal fluid within the subarachnoid and cistern spaces. Since *influenzal* meningitis commonly displays dense fibrinopurulent exudates with loculated pockets of pus predominantly located at the basilar cisterns, an accumulation of purulent exudate at this site may account for the commonly observed narrrowing of the supraclinoid ICA, particularly when the infection has been prolonged.[15] The supraclinoid ICA is situated at the base of the brain, usually distal to the ICA's S-shaped course through the meninges. Hence, this anatomical configurment of the supraclinoid ICA may render it more receptive to the pro-inflammatory effects of influenzal meningitis. Specifically, the tortuous S-shape, disorganized turbulent flow, and location at the base of the brain are contributory.[8] Slow turbulent blood flow, for instance, increases contact time between the microbial pathogen and the vessel wall, leading to increased residence time in the vascular channel and a greater opportunity to interact with the vessel wall. Therefore, disturbed flow within the supraclinoid ICA may be responsible for an increased incidence of arterial thrombi, accounting for a possible role of thrombotic phenomena in the formation of ischemic cerebrovascular disease in these patients. In keeping with this, the occurrence of arterial thrombi in the cerebral vasculature depends on three factors: structural alterations of the vessel wall, alterations of local blood flow patterns, and perturbations in the constituents of the circulating blood. For example, in models of *influenzal* meningitis, two or more of these determinants can be implicated in the development of arterial thrombosis. Histopathological studies of structural alterations affecting the cerebral vasculature further advance the proposition for an occurrence of arterial thrombi during the course of bacterial meningitis. As such, arterial occlusion of the supraclinoid ICA has been frequently observed during the course of *influenzal* meningitis.[1,4,6,7,16-18] Given persuasive evidence for the development of arterial thrombi in *influenzal* meningitis, thrombi are not readily observed in the cerebral vasculature. Instead, focal alterations of the vessel wall appear to be more commonly implicated in

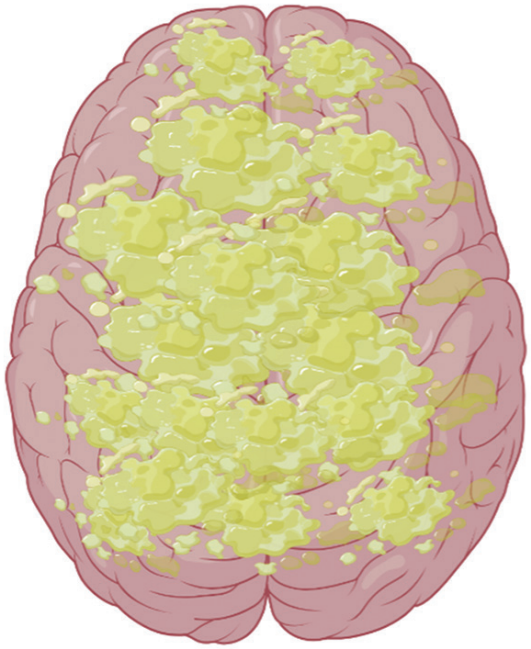

Figure 3: Distribution of dense purulent exudate over the cerebral convexities in Group B Streptococci/Streptococcus pneumococci meningitis[67]

Table 2: Cerebrovascular involvement in *Streptococcus Pneumonia* and *Group B Streptococcus* models of bacterial meningitis

Author	Patients	Cerebral blood vessel/vascular area affected
Pryde *et al.*[24]	8	Bilateral basal ganglia (1); Bilateral basal ganglia and cerebellum (2); Left cerebral cortex and cerebellum (3); Left cerebral cortex and cerebellum (4); Left parietal cortex (5); Left parietal cortex (6); Left thalamus (7); Left frontal cortex and subcortex (8)
Hernández *et al.*[32]	8	Bilateral basal ganglia and occipital cortex (1); Bilateral basal ganglia and left thalamus (2); Left parietal, occipital cortex and right atrial white matter (3); Left and right frontal cortex, right occipital cortex (4); Bilateral frontal, occipital, parietal cortex and thalamus (5); Bilateral basal ganglia (6); Bilateral basal ganglia, thalamus, temporal and parietal cortex (7); Right thalamus, bilateral occipital and frontal lobes (8)
Iijima *et al.*[33]	1	Bilateral medial basal ganglia and anterior thalamus (1)
Tibussek *et al.*[34]	13	Right anterior cerebral artery, cerebral cortex and cerebellum (1); Right middle cerebral artery (2); Bilateral cerebral cortex (3); Left frontal and occipital cortex (4); Right caudate and medial parietal lobe (5); Right occipital lobe (6); Bilateral frontal and temporal lobe (7); Right inferior frontal lobe (8); Left precentral gyrus and occipital lobe (9); Left posterior inferior temporal and occipital lobe (10); Right parietal operculum (11) Bilateral parietal lobe (12) Bilateral frontal and temporal lobe (13)
Rice *et al.* [35]	1	Bilateral thalamus, posterior limb of internal capsule, left caudate head, lentiform nucleus, Subcortical frontal and temporal white matter, occipital and horn of right ventricle (1)
Schut *et al.*[36]	6	Left parietal lobe, bilateral thalamus and brainstem (1); Bilateral thalamus (2); Bilateral basal ganglia and brainstem (3); Left frontal lobe and brainstem (4); Left corona radiata, right thalamus, brain stem (5); Left basal ganglia, medulla and cerebellum (6)

( ): patient number in study

arterial occlusions associated with *influenzal* meningitis. Accordingly, cerebral arteritis not arterial thrombosis is commonly observed during autopsy of *influenzal* meningitis. Inevitably, autopsy studies of advanced *influenzal* meningitis fail to demonstrate the presence of thrombi in the ICA but rather document the presence of vasculitis and coincident infarction, suggesting that vasculitis is more commonly responsible for arterial occlusion predisposing to infarction compared to arterial thrombi.[1,4,19] Interestingly, the commonly observed bilateral involvement of the ICA in *influenza meningitis* can be attributed to the proximity of the two ICAs to each other in the region of the supraclinoid portion, a region of the vessel that is heavily surrounded by a dense purulent subarachnoid exudate.

Group B *Streptococcus/Streptococcus pneumonia* meningitis: Involvement of small intracerebral arteries

Bacterial meningitis caused by Group B *Streptococcus/ Streptococcus pneumonia* is characterized by a higher mortality rate and a more likely clinical course associated with adverse neurologic complications complications.[20,21] In fact, the high fatality rate following streptococcal meningitis stems from the development of cerebral complications, such as cerebral infarctions.[22] As such, cerebrovascular sequelae are a common complication in patients with pneumococcal meningitis, with the occurrence of ischemic stroke observed in approximately 25% of patients.[22-24] For example, in a study of 24 children with pneumococcal meningitis, nearly half of the children were shown to have evidence of cerebrovascular disease.[25] Similarly, Igarashi *et al*. observed that nearly one-third of pediatric patients with childhood bacterial meningitis were prone to develop cerebral infarction, with the most frequently identified microorganism being *Streptococcus pneumonia* and less commonly Group B *Streptococci* as the causative pathogen.[26] The innate ability of *Streptococcus pneumoniae* to initiate cerebral vasculitis may stem from specific virulence factors that promote local invasion of the microorganism and persistence in the cerebrospinal fluid, permitting prolonged contact of the microorganism with penetrating intracerebral vessels.[26,27] In line with this suggestion, postmortem analysis of the involved cerebral vasculature commonly demonstrates the occurrence of necrotic and vasculitic vessel wall degenerations. Although very few studies highlight the occurrence of cerebrovascular disease in streptococcal models of bacterial meningitis, few studies attempt to delineate a possible pattern of cerebrovascular involvement. For instance, deep, small, penetrating intracerebral arteries, particularly in the gray matter, are predominantly affected by vasculitis resulting in the culminating in the development of ischemic stroke. As such, ischemic deficits involving the basal ganglia, thalamus and cerebral cortex in acute streptococcal central nervous system infections such as bacterial meningitis have frequently been reported [Figure 2].[29-31] For example, Vernino *et al*. demonstrated the presence of extensive infarcts primarily affecting the thalamus but with only scattered and sparse infarcts involving the basal ganglia and medial temporal lobes.[29] Similarly, Johkura *et al*. observed bilateral basal ganglia infarcts invariably associated, with a marked impairment in movement leading to a permanently bedridden state, in spite of appropriate antimicrobial treatment.[30] Likewise, Pugin *et al*. described radiographic evidence of parenchymal ischemia in the form of frontal lobe hypodensities in both cerebral hemispheres and multiple small hypodensities principally affecting the white matter of the cerebral hemisphere and basal ganglia. Further, the ischemic damage here coincided with basal ganglia infarcts, wherein associated impaired movements of the right arm and left leg persisted for nearly 1.5 months following infection, after which motor impairment gradually subsided.[31] Additionally, Kim *et al*., described, ischemic deficits involving the basal ganglia and postulated that these deficits may be explained by a vasculitic process, possibly affecting distal branches of large cerebral arteries.[28]

Given these studies, the anatomic basis for observed cerebrovascular involvement in streptococcal meningitis may be attributable to the course of large cerebral arteries passing through the subarachnoid space, where they give rise to small perforating arteries such as the lenticulostriate and thalamostriate small arteries, which supply the thalamus and basal ganglia [Table 2]. Due to the fact that these arteries originate from large arteries bathed in a thick purulent exudate located in the subarachnoid space and subsequently travel through the markedly inflammed meninges to distribute throughout the cerebral parenchyma, involvement of these small vessels may be a consequence of large vessel encroachement by purulent exudate and secondary vasculitic changes in downstream vessels. Furthermore, the preferential involvement of the basal ganglia may be due to its flow vulnerability during states of local and global hypoxia.[37] Consistent with this assumption is the observation that the basal ganglia is sparsely supported by a collateral circulatory system from adjacent surrounding terminal arteries, predisposing to an increasingly likely occurrence of ischemic deficits due to failure of a compensatory collateral flow system. As previously stated, the inflammatory response in pneumococcal meningitis does not cause direct injury to the basal ganglia.[38] Instead, basal ganglia injury represents a downstream consequence of large artery involvement. In accordance with this suggestion, during severe pneumococcal meningitis, purulent exudate is abundantly prominent in the basal cisterns and the associated perivascular Virchow-Robin spaces, which wrap around the penetrating branches of the middle cerebral artery.[39]

Table 3: Cerebrovascular involvement in *Mycobacterium tuberculosis* models of bacterial meningitis

Author	Patients	Cerebral blood vessel/vascular area affected
Lan *et al.* [41]	17	Basal ganglia (4); Internal capsule (2); Cerebellum (1); Thalamus (1); Not reported (9)
Hsieh *et al.* [47]	-	Head of caudate nuclei; Anteromedial thalami; Posterolateral thalamus; Anterior limb/genu of internal capsule; Posterior Limb of internal capsule; Lenticular nuclei; Cortical white matter; Brain stem; Cerebellum
Kalita and Misra *et al.*[48]	55	Basal ganglia (14); Thalamus (4); Cortex or subcortex (16); Brain stem (5); Cerebellum (2) Not reported (14)
Andronikou *et al.* [49]	67	Basal ganglia; Caudate nucleus; Lentiform nucleus; Thalamus; Internal capsule; Cortex or subcortex
Leiguarda *et al.* [50]	25	Basal ganglia (16); Thalamus (1); Cortex or subcortex (3); Brainstem (1); Not reported (4)
Schoeman *et al.* [51]	26	Basal ganglia (19); Cortex or subcortex (4); Not reported (34)
Bhargava *et al.* [52]	61	Basal ganglia (10); Not reported (7)

( ): patient number in study

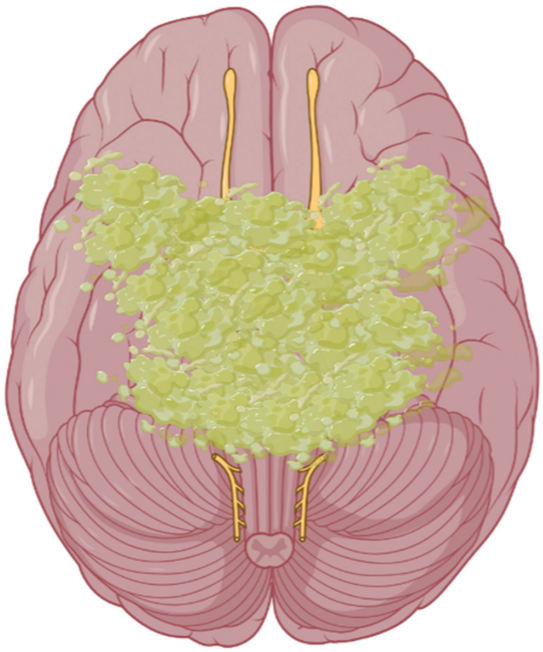

Figure 4: Distribution of very dense purulent exudate over the base of the brain in *Mycobacterium tuberculosis* meningitis[67]

Since, purulent exudate tracks down the subarachnoid space through the Virchow-Robin spaces before reaching the cerebral parenchyma, the penetrating deep branches of the gray matter are invariably affected, accounting for the occurrence of ischemic deficits of the thalamus and basal ganglia, which are regions of the cerebral parenchyma supplied by small penetrating branches of the middle cerebral artery.

In contrast to other causative pathogens, vessel wall modifications of streptococcal meningitis are remarkably sparse; however, a localized inflammatory vasculopathy in the vicinity of a thick purulent exudate accompanied by the development of an arterial thrombus is frequently observed. The formation of thrombi in these vessels may be the final event responsible for the advent of focal ischemic deficits amongst these patients. For example, Schut *et al*. demonstrated that patients with pneumococcal meningitis were observed to develop a late occuring cerebral thrombosis following an initial good clinical recovery.[36] Nearly 1-3 weeks later, these patients experienced an abrupt neurological deterioration and with several infarcts predominantly involving the posterior circulation.[36] Consistent with this suggestion, involvement of the cortex in Group B Streptococcal models of ischemic stroke may be attributable to involvement of the small pial arteries by the inflammatory process with subsequent thrombi formation.[40] Accordingly, Schut *et al*. demonstrated that small penetrating arteries supplying the thalamus and brain stem were observed to display evidence of thrombus formation, suggesting that an inflammatory reaction involving these cerebral vessels was causative. However, much to contrary, the vessel wall layers were devoid of any inflammatory cells, emphasizing that the formation of cerebral thrombosis stems more from a hypercoagulable state rather than from structural modifications of the arterial wall.[36] Interestingly, thrombi were not solely localized to regions of involved cerebral vessels nor could observed focal neurological deficits be attributed to particular blood vessels demonstrating the presence of inflammatory infiltrates. The seemingly random pattern of thrombi distribution inconsistent with the presence of focal ischemic deficits could not be explained by the occurrence of DIC either, as this too was not readily observed. Instead, a large number of fibrin-based clots were localized to the subpial regions of the cerebral hemisphere, whereas smaller number of fibrin-based clots were confined to the deeper regions of the cerebral parenchyma such as the thalamus and basal ganglia.[36] From this observation, it seems likely that a hypercoagulative process is initiated at the surface of the cerebral hemisphere, consequently leading to the development of diffuse thrombi affecting the pial and subpial arteries, which ultimately leads to ischemic deficits of downstream small intracerebral arteries that account for thalamic or basal ganglia damage in streptococcal meningitis models. Such a process may be plausible considering that dense purulent exudate in pneumococcal meningitis is extensively distributed over the cerebral convexities, wherein the thick exudate may interact with surface vessels to result in local thrombi formation [Figure 3]. Ultimately, this route of involvement seems likely to account for the occurrence of both cortical and subcortical infarctions, regions of

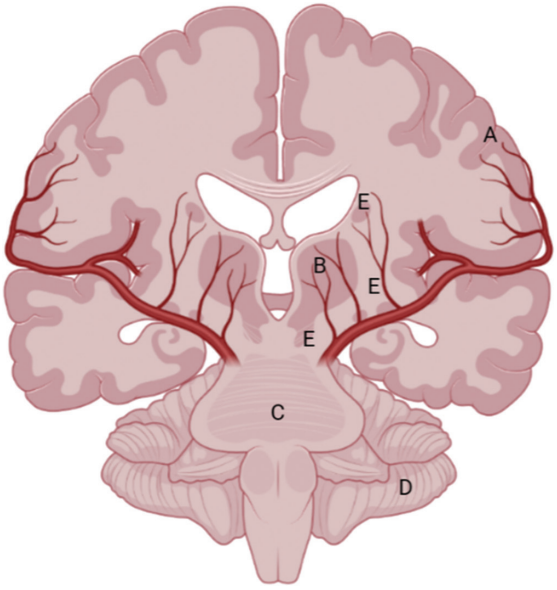

Figure 5: Preferential sites of cerebral vessel involvement in *Mycobacterium tuberculosis meningitis*.[67]
A: Cerebral Cortex, B: Thalamus, C: Pons, D: Cerebellum, E: Basal Ganglia

the cerebral parenchyma supplied by different caliber cerebral arteries, commonly observed in Streptococcus pneumonia or Group B streptococci models of meningitis.

Mycobacterium tuberculosis meningitis: Involvement of basal arteries

Cerebrovascular disease is a well established phenomenon in tuberculous models of bacterial meningitis. For example, Lan *et al*. observed that nearly half of Taiwanese patients with tuberculous meningitis developed cerebral infarctions.[41] Similarly, Chan *et al*. demonstrated the occurence of cerebral infarction in 30% of patients with tuberculous meningitis.[42] Additionally, Koh *et al*. reported the occurrence of cerebral infarction in nearly a quarter of patients with tuberculous meningitis.[43] Keeping this in mind, tuberculous models of bacterial meningitis frequently demonstrate stenotic changes of large arteries at the base of the brain [Table 3]. In children, models of tuberculous meningitis frequently demonstrate vasculitis and consequent infarcts involving perforating basal arteries and arteries of the Circle of willis.[44] As such, Fugate *et al*. observed that arteries at the base of the brain displayed a greater prominence of wall vessel remodeling- fibrinoid necrosis and intimal proliferation- compared to other vessels, and amongst these vessels smaller sized arteries were more readily occluded than larger sized arteries.[45] Additionally, Patkar *et al*. observed that vessels passing through the base of the brain at the Sylvian fissure are most susceptible to developing vasculitis, with nearly half of these patients subsequently developing infarctions.[46]

The anatomic basis for the involvement of arteries at the base of the brain in tuberculous meningitis revolves around the distribution of inflammatory exudate. During tuberculous meningitis, purulent exudate, generated by the inflammatory process, settles predominantly at the base of the brain by virtue of gravity, where it induces vasculitic changes of the surrounding cerebral vasculature.[43] A closer analysis of the distribution of purulent exudate in tuberculous meningitis suggests that the initial exudate extends from the primary foci of infection into the subarachnoid spaces surrounding the cerebral sulci and basal cisterns along the inner surface of the skull as well as along the dural folds of the falx and tentorium.[53] Following this descent, the exudate particularly localizes to a distinct region of the basal cistern and the sylvian fissure and gradually accumulates.[54,55] Inevitably, the basal meningeal layer demonstrates a region of rich enhancement coinciding with the development of a thick purulent exudate here.[56] These regions, characterized by a peculiar affinity for the accumulation of a thick purulent exudate, include the interpeduncular fossa, sylvian fissures, and the pontine, ambient, and suprasellar cistern regions.[57] In contrast to the dense localization of purulent exudate at the base of the brain, the convexities corresponding to the apical surfaces of the cerebral hemispheres are less frequently affected, confirming only a predominant basal localization of the inflammatory process in tuberculous bacterial meningitis.[57-59] In keeping with the prevailing idea of a predominant localization of purulent exudate in the basal regions of the cerebral hemisphere, Andronikou *et al*. demonstrated that the occurrence of high-density signals, corresponding to regions of abnormal meningeal enhancement due to purulent exudate deposition, in the vicinity of the basal cisterns strongly correlates with infarcts associated with tuberculous meningitis in the pediatric population. More specifically, histological studies describe the presence of a dense gelatinous fibrino-cellular exudate originating from the leptomeningeal layers and predominantly localized to the interpeduncular fossa, a rhomboid-shaped area at the base of the brain.[46] From this location, the exudate can extend in different directions to involve different regions of the brain and the corresponding blood vessels: anteriorly wrapping around optic chiasma and anterior cerebral vessels; laterally penetrating into the Sylvian fissure and encircling the carotid and middle cerebral arteries and their branch vessels; caudally to cover the medullary, pontomesencephalic, and cerebellar cisterns [Figure 4].[43,49,60] As the exudate courses along the various routes of spread, it coats intervening arteries and their perforating branches at the base of the brain, initiating gradual structural modifications of the arterial wall.[48] Consequently, vasculitis progressively develops as different arterial segments of the Circle of Willis pass through the thick, dense basilar purulent exudate and get strangulated, leading to prolonged contact time with the vessel wall and the resultant vessel wall cascade

of vasospasm, inflammation and consequent luminal narrowing.[61,62] Consistent with such an observation, exudate extension along the basal cistern into the Sylvian fissure involves the middle cerebral artery and its corresponding perforating branches resulting in infarcts of the subthalamic nuclei and inferior internal capsule with associated motor impairment.[63]

In addition to involving large vessels at the base of the brain, *Mycobacterium tuberculosis* may also involve small and medium-sized vessels. Most commonly, these vessels include the posterior cerebral, thalamo-perforating arteries and lenticulostriate arteries, which may result in infarctions involving the basal ganglia.[46] For example, Donald PR and Thwaites *et al*. discovered that cerebral infarctions most frequently occur in a discrete region of the brain known as the "TB zone."[64,65] Within this zone, commonly involved vessels include the medial striate, thalamo-tuberal, and thalamo-perforating arteries corresponding to infarcts localized to the caudate nuclei, anteromedial thalamus, and anterior limbs and genu of the internal capsule [Figure 5]. Interestingly, predominant involvement of medial arteries compared to lateral arteries in the circle of Willis provides an interesting parallel that medial arteries are most commonly involved by the basal inflammatory exudate in tuberculous meningitis, an observation consistent with an accumulation of thick purulent exudate in medial regions of the brain stem such as the, interpeduncular fossa and the pons. Building on this, Hsieh *et al*. described the extension of cerebrovascular disease from the base of the brain to the brain stem in approximately 3% of cases.[47] Ultimately, the specific regions of the cerebral parenchyma most vulnerable to ischemic deficits in tuberculous meningitis are the basal ganglia, internal capsule, cerebral cortex, thalamus, cerebellum, and pons.[66]

Conclusion

Cerebrovascular complications of bacterial meningitis are a dreaded consequence, accounting for a high incidence of mortality and morbidity in these patients. Of note, a particularly devastating postinfective sequelae is occurrence of focal ischemic deficits. Although the underlying mechanism underlying the development of cerebral ischemia in bacterial meningitis remains largely unclear, localization of the pattern of cerebral vessel involvement may help provide insight into the frequency of stenotic lesions in particular forms of bacterial meningitis, ultimately leading to reduced morbidity and mortality through more appropriate target therapies.

Ethical approval and patient content
Not applicable.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Thomas VH, Hopkins IJ. Arteriographic demonstration of vascular lesions in the study of neurologic deficit in advanced meningitis. Dev Med Child Neurol 1972;14:783-7.
2. Raimondi AJ, Di Rocco C. Cerebral angiography in meningocerbral inflammatory diseases in infancy and childhood: A study of thirty-five cases. Neurosurgery 1978;3:37-44.
3. Igarashi M, Gilmartin RC, Gerald B, Wilburn F, Jabbour JT. Cerebral arteritis and bacterial meningitis. Arch Neurol 1984;41:531-5.
4. Lyons EL, Leeds NE. The angiographic demonstration of arterial vascular disease in purulent meningitis. Report of a case. Radiology 1967;88:935-8.
5. 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.
6. James AE Jr., Hodges FJ 3rd, Jordan CE, Mathews EH, Heller R Jr. Angiography and cisternography in acute meningitis due to *Hemophilus influenzae*. Radiology 1972;103:601-6.
7. Gado M, Axley J, Appleton DB, Prensky AL. Angiography in the acute and post-treatment phases of *Hemophilus influenzae* meningitis. Radiology 1974;110:439-44.
8. Headings DL, Glasgow LA. Occlusion of the internal carotid artery complicating *Haemophilus influenzae* meningitis. Am J Dis Child 1977;131:854-6.
9. Wertham F. The cerebral lesions in purulent meningitis. Arch Neurol Psychi 1980;26:549-82.
10. Eicke WJ. Changes in meningitis and their significance for the pathogenesis of early childhood brain damage. Virchow's Archives of Pathological Anatomy and Physiology and of Clinical Medicine 1947;14:88–124.
11. McMenamin JB. Internal carotid therapy occlusion in *Haemophilus influenzae* meningitis. J Pediatr 1982;101:723-5.
12. Waggener JD. The pathophysiology of bacterial meningitis and cerebral abscesses: An anatomical interpretation. Adv Neurol 1974;6:1-17.
13. Greenfield JG. Infectious Diseases of the Central Nervous System. Neuropathology. Baltimore: Williams & Wilkins; 1963. p. 138-56.
14. Dahl E. The fine structure of intracerebral vessels. Z Zellforsch Mikrosk Anat 1973;145:577-86.
15. Yaşargil MG. Microsurgery: Applied to Neurosurgery. New York: Academic Press; 1969.
16. Levinson A, Hartenstein H. Intracranial calcification following pneumococcic meningitis. J Pediatr 1951;38:624-9.
17. Mathew NT, Abraham J, Chandy J. Cerebral angiographic features in tuberculous meningitis. Neurology 1970;20:1015-23.
18. Gibson NF. Anterior fontanelle herniation. Pediatrics 1975;56:466-9.
19. Nyhan WL, Richardson F. Complications of meningitis. Annu Rev Med 1963;14:243-60.
20. de Gans J, van de Beek D, European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. N Engl J Med 2002;347:1549-56.
21. Shackley F, Knox K, Morris JB, Crook D, Griffiths D, Mayon-White R, *et al.* Outcome of invasive pneumococcal disease: A UK based study. Oxford Pneumococcal Surveillance Group. Arch Dis Child 2000;83:231-3.
22. Pfister HW, Borasio GD, Dirnagl U, Bauer M, Einhäupl KM. Cerebrovascular complications of bacterial meningitis in adults. Neurology 1992;42:1497-504.
23. Kastenbauer S, Pfister HW. Pneumococcal meningitis in adults:

Spectrum of complications and prognostic factors in a series of 87 cases. Brain 2003;126:1015-25.
24. Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS Jr., *et al.* Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J Med 1993;328:21-8.
25. Pryde K, Walker WT, Hollingsworth C, Haywood P, Baird J, Hussey M, *et al.* Stroke in paediatric pneumococcal meningitis: A cross-sectional population-based study. Arch Dis Child 2013;98:647-9.
26. Jorens PG, Parizel PM, Demey HE, Smets K, Jadoul K, Verbeek MM, *et al.* Meningoencephalitis caused by *Streptococcus pneumoniae*: A diagnostic and therapeutic challenge. Diagnosis with diffusion-weighted MRI leading to treatment with corticosteroids. Neuroradiology 2005;47:758-64.
27. Cabral DA, Flodmark O, Farrell K, Speert DP. Prospective study of computed tomography in acute bacterial meningitis. J Pediatr 1987;111:201-5.
28. Kim KS, Kaye KL, Itabashi HH, Yoshimori RN, Weil ML. Cerebritis due to group B streptococcus. Scand J Infect Dis 1982;14:305-8.
29. Vernino S, Wijdicks EF, McGough PF. Coma in fulminant pneumococcal meningitis: New MRI observations. Neurology 1998;51:1200-2.
30. Johkura K, Nishiyama T, Kuroiwa Y. Bilateral basal ganglia infarctions in a patient with *Streptococcus pneumoniae* meningitis. Eur Neurol 2002;48:123-4.
31. Pugin D, Copin JC, Goodyear MC, Landis T, Gasche Y. Persisting vasculitis after pneumococcal meningitis. Neurocrit Care 2006;4:237-40.
32. Hernández MI, Sandoval CC, Tapia JL, Mesa T, Escobar R, Huete I, *et al.* Stroke patterns in neonatal group B streptococcal meningitis. Pediatr Neurol 2011;44:282-8.
33. Iijima S, Shirai M, Ohzeki T. Severe, widespread vasculopathy in late-onset group B streptococcal meningitis. Pediatr Int 2007;49:1000-3.
34. Tibussek D, Sinclair A, Yau I, Teatero S, Fittipaldi N, Richardson SE, *et al.* Late-onset group B streptococcal meningitis has cerebrovascular complications. J Pediatr 2015;166:1187-92.e1.
35. Rice CM, Ramamoorthi M, Renowden SA, Heywood P, Whone AL, Scolding NJ. Cerebral ischaemia in the context of improving, steroid-treated pneumococcal meningitis. QJM 2012;105:473-5.
36. Schut ES, Brouwer MC, de Gans J, Florquin S, Troost D, van de Beek D. Delayed cerebral thrombosis after initial good recovery from pneumococcal meningitis. Neurology 2009;73:1988-95.
37. Kirton A, Busche K, Ross C, Wirrell E. Acute necrotizing encephalopathy in Caucasian children: Two cases and review of the literature. J Child Neurol 2005;20:527-32.
38. Brandt CT. Experimental studies of pneumococcal meningitis. Dan Med Bull 2010;57:B4119.
39. Shrier LA, Schopps JH, Feigin RD. Bacterial and fungal infections of the central nervous system. In: Principles of Child Neurology. 1st ed. New York: McGraw-Hill; 1996. p. 766-71.
40. 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.
41. Lan SH, Chang WN, Lu CH, Lui CC, Chang HW. Cerebral infarction in chronic meningitis: A comparison of tuberculous meningitis and cryptococcal meningitis. QJM 2001;94:247-53.
42. Chan KH, Cheung RT, Lee R, Mak W, Ho SL. Cerebral infarcts complicating tuberculous meningitis. Cerebrovasc Dis 2005;19:391-5.
43. Koh SB, Kim BJ, Park MH, Yu SW, Park KW, Lee DH. Clinical and laboratory characteristics of cerebral infarction in tuberculous meningitis: A comparative study. J Clin Neurosci 2007;14:1073-7.
44. Abdel Razek AA, Alvarez H, Bagg S, Refaat S, Castillo M. Imaging spectrum of CNS vasculitis. Radiographics 2014;34:873-94.
45. Fugate JE, Lyons JL, Thakur KT, Smith BR, Hedley-Whyte ET, Mateen FJ. Infectious causes of stroke. Lancet Infect Dis 2014;14:869-80.
46. Patkar D, Narang J, Yanamandala R, Lawande M, Shah GV. Central nervous system tuberculosis: Pathophysiology and imaging findings. Neuroimaging Clin N Am 2012;22:677-705.
47. Hsieh FY, Chia LG, Shen WC. Locations of cerebral infarctions in tuberculous meningitis. Neuroradiology 1992;34:197-9.
48. Kalita J, Misra UK. Outcome of tuberculous meningitis at 6 and 12 months: A multiple regression analysis. Int J Tuberc Lung Dis 1999;3:261-5.
49. Andronikou S, Wilmshurst J, Hatherill M, VanToorn R. Distribution of brain infarction in children with tuberculous meningitis and correlation with outcome score at 6 months. Pediatr Radiol 2006;36:1289-94.
50. Leiguarda R, Berthier M, Starkstein S, Nogués M, Lylyk P. Ischemic infarction in 25 children with tuberculous meningitis. Stroke 1988;19:200-4.
51. Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Serial CT scanning in childhood tuberculous meningitis: Prognostic features in 198 cases. J Child Neurol 1995;10:320-9.
52. Bhargava S, Gupta AK, Tandon PN. Tuberculous meningitis – A CT study. Br J Radiol 1982;55:189-96.
53. Garg RK. Tuberculous meningitis. Acta Neurol Scand 2010;122:75-90.
54. Smith HV, Daniel P. Some clinical and pathological aspects of tuberculosis of the central nervous system. Tubercle 1947;28:64-80.
55. Smith HV. Tuberculous meningitis. Int J Neurol 1964;4:134-57.
56. Doniach I. Changes in the meningeal vessels in acute and chronic (streptomycin-treated) tuberculous meningitis. J Pathol Bacteriol 1949;61:253-9, 4 pl.
57. 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.
58. Winkleman NW, Moore T. Meningeal blood vessels in tuberculous meningitis. Am Rev Tuberc 1940;42:315e33.
59. Horne NW. Tuberculous meningitis: Problems in pathogenesis and treatment. Edinb Med J 1951;58:413-29.
60. Snyder RD, Stovring J, Cushing AH, Davis LE, Hardy TL. Cerebral infarction in childhood bacterial meningitis. J Neurol Neurosurg Psychiatry 1981;44:581-5.
61. Hendin AS, Margolis MT, Glickman MG. Occlusion of the basilar artery in tuberculous meningitis. Neuroradiology 1973;6:193-5.
62. Peacock WJ, Deeny JE. Improving the outcome of tuberculous meningitis in childhood. S Afr Med J 1984;66:597-8.
63. Davis AG, Rohlwink UK, Proust A, Figaji AA, Wilkinson RJ. The pathogenesis of tuberculous meningitis. J Leukoc Biol 2019;105:267-80.
64. Donald PR, Schoeman JF. Tuberculous meningitis. N Engl J Med 2004;351:1719-20.
65. Thwaites GE, Macmullen-Price J, Tran TH, Pham PM, Nguyen TD, Simmons CP, *et al.* Serial MRI to determine the effect of dexamethasone on the cerebral pathology of tuberculous meningitis: An observational study. Lancet Neurol 2007;6:230-6.
66. Poltera AA, Templeton AC. Intracranial tuberculosis in Uganda: A post-mortem survey. Afr J Med Sci 1973;4:343-9.
67. Adapted from BioRender.com 2023. Available from: https://app.biorender.com/biorender-templates. [Last accessed on 2023 Jun 02].