The pathogenesis of cerebral vasospasm in bacterial meningitis

M Eisenhut*

Abstract

Introduction
Cerebral inflammation in bacterial meningitis has been associated with vasospasms of cerebral arteries and arterioles. Vasospasm has been associated with permanent neurological deficits and death. The objective of the review was to summarise evidence for the involvement of inflammatory mediators in the pathogenesis of cerebral vasospasm.

Materials and methods
Databases Pubmed, EMBASE and the Cochrane Library were searched and reference list of retrieved articles was taken using keywords, including cerebral vasospasm, meningitis and inflammation.

Results
Increased levels of interleukin-1 may be involved in vasospasm through the release of vasoconstrictor endothelin-1. Another key factor in the pathogenesis of cerebral arterial vasospasm may be the reduced bioavailability of the vasodilator nitric oxide. Therapeutic trials in vasospasm related to inflammation showed a reduction of vasospasm through calcium antagonists. The importance of inflammation in causing vasospasm has been highlighted by the successful reduction of features of vasospasm and morbidity by anti-inflammatory agents, including steroids and acetylsalicylic acid, which merit further study in all conditions with cerebral inflammation in double blind placebo controlled randomised trials.

Conclusion
Key factors in the pathogenesis of cerebral vasospasm in bacterial meningitis are the depletion of nitric oxide and effects of endothelin and interleukin-1. Auxiliary treatment increasing nitric oxide levels and antagonising the other inflammatory mediators may be able to reduce ischaemic brain injury associated with neurological deficits and increased mortality in bacterial meningitis.

Introduction
Cerebral vasospasm has been defined as ‘the reversible reduction in calibre of the lumen of a conducting artery in the subarachnoid space’. If it is severe enough, vasospasm can lead to cessation of distal blood flow and if it is present for a sufficient duration and extent, it can cause cerebral infarction. The risk of infarction depends on the adequacy of collateral blood supply, cardiac output, blood pressure and intracranial pressure. In the context of cerebral inflammation, many different factors influence cerebral blood flow. They include inflammatory hyperaemia, mean cerebral blood flow velocity, increased intracranial pressure, arterial CO₂, body temperature, mean arterial pressure, the use of mechanical ventilation and whether the patient is sedated during procedures. Transcranial doppler sonography is currently the most important tool in non-invasive diagnosis of cerebral vasospasm. Vasospasm is hereby characterised by a cerebral blood flow (CBF) velocity of greater than 120 cm/s. An increased ratio of CBF velocity between intracranial vessels and an extracranial internal carotid artery (> 3:1) can be used to define cerebral vasospasm and constitutes the Lindgaard index. The most extensively investigated form of cerebral vasospasm is the one associated with subarachnoid haemorrhage and can be used as a model to understand the influence of cerebral inflammation on cerebral vascular tone. Positron emission tomographic studies showed that ischaemic deficits from vasospasm related to subarachnoid haemorrhages were associated with regions of reduced blood flow. Cerebral vasospasm is a potentially treatable cause of ischaemic cerebral damage. A current lack of established supportive treatment options to reduce neurological sequelae in bacterial meningitis was the motivation for this review of cerebral vasospasm in cerebral inflammation during bacterial meningitis. The objectives were:

• To summarise the evidence for cerebral vasospasm in the pathophysiology of bacterial meningitis.

• To summarise the results of studies in the role of inflammation in cerebral vasospasm.

• To summarise the experimental evidence for the effects of interventions to reduce vasospasm in cerebral inflammation.

Materials and methods
In this narrative review, Pubmed, EMBASE and Cochrane library databases were searched using the keywords, cerebral vasospasm, meningitis and inflammation. Reference lists of retrieved articles were searched. The review summarised experimental studies investigating vasospasm as detected on radiological imaging as well as clinical manifestations attributable to vasospasm in bacterial meningitis such as focal neurological deficits. Evidence from studies...
investigating the pathogenesis and treatment of vasospasm in subarachnoid haemorrhage was also discussed as it was regarded as a model of inflammation induced vasospasm partially applicable to bacterial meningitis.

**Results**

**Evidence for vasospasm in bacterial meningitis**

Tuberculous meningitis is a form of bacterial meningitis in which the link between cerebral inflammation and vasculopathy has been the subject of most detailed studies starting in the 19th century. Stroke is common in tuberculous meningitis with an incidence rate of 15% to 60%. Three main pathologies have been proposed: vasculitis is most prominent in vessels passing through the basilar exudate, proliferative changes with intimal thickening with resultant stenosis or occlusion and necrotizing vascular lesions. The fibrinoid necrosis of the affected brain tissue, which was found in the absence of infiltration, raised the possibility of vasospasm as an additional feature of vasculopathy. In some instances, infarction was found to have occurred without vasculitic changes or thrombosis compatible with vasospasm. The poor correlation between angiographic findings and infarction was also supportive of an important role of vasospasm in the pathology of tuberculous meningitis.

The first direct evidence for vasospasm in bacterial meningitis was established in a case of ‘haemophilus influenza’ meningitis. A prospective investigation of 22 adults with bacterial meningitis by transcranial doppler sonography related the degree of arterial narrowing to outcome: Low Glasgow Coma Scales (<7) on admission, focal cerebral ischaemic deficits and seizures that were more frequent in patients with cerebral blood flow velocity >210 cm/s compatible with vasospasm and fatal outcome only found with this high velocity. Patients with minor or no vascular involvement had less prominent initial impairment of consciousness. Other investigations confirmed features of cerebral vasospasm in bacterial meningitis.

**Lessons from observations of the microcirculation in sepsis**

The role of inflammation in vasospasm has also been evident from in vivo observation of microcirculation in sepsis, which may reflect processes present in cerebral microcirculation in bacterial meningitis. Assessment of changes in peripheral microcirculation may be an accessible tool for observation of processes also occurring in the brain and for observation of response to interventions.

Strategies to improve microvascular recruitment, which have been explored in models of sepsis in rats, have been applied to cerebral vasospasm. The influence of severe systemic inflammation as observed in sepsis on peripheral vasospasm may also apply to the influence of cerebral inflammation on cerebral vasospasm. Distal shock, such as one that occurs during sepsis and septic shock, is associated with an abnormal distribution of microvascular blood flow and metabolic distress in the presence of normal or even supranormal levels of cardiac output. Vasospasm of part of the arterioles supplying the capillary is a mechanism involved in this maldistribution. The introduction of new microcirculatory imaging techniques, such as orthogonal polarization spectral and sidestream dark-field imaging (OPS/SDF), has allowed direct observation of the microcirculation at the bedside. Images of the sublingual microcirculation during septic shock and resuscitation have revealed that the distributive defect of blood flow occurs at the capillary level. In rat models of cecal ligation and puncture, investigators have used intravital video microscopy to demonstrate that sepsis is characterised by decreased microcirculatory flow velocity, an abundance of stopped-flow microvessels, increased heterogeneity of microcirculatory flow and low density of perfused capillaries. As these microcirculatory flow alterations can occur in the absence of global hemodynamic derangements (e.g. absence of arterial hypotension), microcirculatory dysfunction largely reflects intrinsic events occurring in the microvessels, such as localised vasospasm. The ensuing microcirculatory ‘failure’ can cause marked impairment of tissue oxygen transport resulting in tissue hypoxia. In septic patients, microcirculatory failure appears to be a major perturbation with prognostic significance. Severe derangements of microcirculatory flow, including the severity of initial derangements in the early resuscitation phase of therapy as well as the persistence of microcirculatory derangements over time, have been associated with lower survival.

Application of microcirculatory recruitment manoeuvre procedures has been shown to be effective in promoting microcirculatory blood flow and correct metabolic distress in clinical studies using OPS/SDF imaging. Fluids in combination with the nitric oxide donor nitroglycerin were shown to recruit disturbed microcirculation following pressure guided resuscitation in septic shock patients, suggesting a role for vasodilator therapy in the treatment of microcirculatory failure associated with vasospasm. Support of pump function by dobutamine therapy has been shown to improve microcirculatory flow independent of improvement of global hemodynamic parameters.

**The role of inflammatory mediators in vasospasm**

**The role of nitric oxide**

Cerebral vasodilatation, in response to hypercapnia, depends on formation of nitric oxide, a mediator released in inflammation. After release by endothelium, NO stimulates...
soluble guanylate cyclase in vascular muscle, resulting in an increase in the intracellular concentration of guanosine 3', 5' -cyclic monophosphate (cGMP) resulting in relaxation (Figure 1). NO is generated from L-arginine by NO synthase. NO can be inactivated by reaction with superoxide anion, resulting in the formation of peroxynitrite. Inactivation of NO by superoxide anion may contribute to impaired NO-mediated dilatation of cerebral blood vessels under conditions in which reactive oxygen species are produced, as in meningitis. Endothelial NO synthase is down-regulated by tumour necrosis factor and NO by a negative-feedback mechanism. The inducible NO synthase is up-regulated by interleukin-1, interferon gamma and TNF and down-regulated by IL-4, IL-10 and TGF-beta.

Much of the work investigating the genetic predisposition to cerebral vasospasm focused on the endothelial isoform of nitric oxide synthase. In gene transfer experiments, eNOS overexpression in animal and human intracranial arteries is vasoprotective after aneurysmal subarachnoid haemorrhage (SAH). Several investigations have confirmed the association of the T-786C genotype of eNOS with vasospasm.

The role of interleukin-1
The etiological role of specific cytokines in vasospasm in bacterial meningitis in vivo was highlighted by a study which documented a significant increase in IL-1 beta and IL-6 concentrations in patients with elevated cerebrovascular blood flow indicative of vasospasm in humans. A similar effect on vasospasm of IL-1 and IL-6 was suggested by a study of cerebral blood flow in SAH: Development of CBFVs > 210 cm/s (n = 22) was associated with significantly increased CSF concentrations of IL-1, IL-6 and TNF compared with the presence of CBFV < 210 cm/s.

High concentrations of these immunomediators in cerebrospinal fluid (CSF) may exert vasoactive effects. For example, IL-1 (MW 17,000 Da) or IL-6 (MW 26,000 Da) could easily get access to the walls of contiguous basal arteries from their adventitial side, as even larger molecules (such as horseradish peroxidase, MW 40000 Da) pass from the cysterna magna through the vessel wall to the basal membrane within minutes. This is possible because, in contrast to other arteries, the surface of the major cerebral arteries is not confined by collagen or fibroblasts, but is in direct contact with the CSF. An investigation in patients with SAH, showed that the levels of IL-1 beta but not TNF alpha were increased and correlated with the later development of vasospasm.

IL-1 acts through G-protein coupled receptors by activation of protein kinase C (PKC) (Figure 2). Prolonged contraction in cerebral vasospasm for up to two weeks is mediated by PKC. This occurs by regulation of myogenic tone by sensitizing myofilaments to calcium. IL-1 may also act through activation of the myosine light chain kinase. Phosphorylation of myosin light chain (MLC) is one of the most important steps for vascular smooth muscle contraction. The classic concept of the mechanism of vascular smooth muscle contraction includes an activation of MLC kinase (MLCK) that leads to the phosphorylation of MLC and subsequent smooth muscle contraction.

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the intracellular Ca concentrations were not always proportional to the levels of MLC phosphorylation and smooth muscle contraction, an additional mechanism to regulate Ca sensitivity has been proposed. Recently, evidence for the involvement of the small GTPase Rho in Ca sensitivity in smooth muscle contraction was reported from several laboratories. The molecular mechanism of MLC phosphorylation regulated by Rho was largely unknown, but recent analyses revealed that Rho regulates MLC phosphorylation through its target protein, Rho-kinase and the myosin-binding subunit (MBS) of MLC phosphatase (MLCP). Indeed, studies in vitro suggested that Rho activates Rho-kinase, which phosphorylates MBS and results in the inhibition of MLCPh. Investigations in a porcine model with IL-1β revealed that MLC phosphorylation (on stimulation by serotonin) are enhanced at the spastic site and that hydroxyfasudil, a specific Rho-kinase inhibitor, exerted an inhibitory effect on the spasm, both in vivo and in vitro. Western blot analysis showed that during the serotonin-induced contractions, the extent of phosphorylation of the myosin-binding subunit (MBS) of myosin phosphatase one of the major substrates of Rho-kinase, was significantly greater in the spastic than in the control segment and that the increase in MBS phosphorylations was also markedly inhibited by Y27632. There was a highly significant correlation between the extent of MBS phosphorylations and that of contractions.

Another key mechanism by which IL-1 mediates vasospasm is through PDGF and bFGF. The receptors for these growth factors are also known to have tyrosine kinase activity and inhibition of tyrosine kinase is known to reduce vasospasm in a swine model.

Endothelin-1

The most important peptide leading to vasoconstriction in cerebral blood vessels is endothelin, a 21 amino acid peptide with three isopeptides produced by separate genes. Only endothelin-1 (ET-1) is produced in cerebral endothelium and mediates cerebral vasoconstriction via endothelin-A (ETA) receptors. ETA is localised in vascular smooth muscle cells, and stimulation leads to increase in intracellular calcium concentrations leading to vasoconstriction.

ET-1 expression is enhanced by transforming growth factor-beta, haemoglobin and TNF, and can be inhibited by nitric oxide, nitric oxide donor drugs, and dilator prostanoids via an increase in cellular cGMP, and natriuretic peptides via an increase in cAMP levels. The imbalance of nitric oxide and ET-1 could be an important cause of pathological arterial contraction. IL-1 and TNF have thereby been shown to induce the production of ET-1.

The effect of TNF on cerebral perfusion may be exerted through the stimulation of ET-1 release in a TNFR2 dependent pathway. In a rat model, cerebral blood flow – as measured by injection and recovery of microspheres from the brain tissue – was found to be reduced in pneumococcal meningitis. The cerebral blood flow could be restored by the ET-1 antagonist bosentan with a reduction in cortical cerebral injury. For an overview of substances mediating cerebral vasospasm, see Figure 3.

The effect of therapeutic interventions in vasospasm

In tuberculous meningitis, adjuvant treatment with corticosteroids has been indirectly associated with features of reduced vasculopathy, which may include vasospasm.

A large randomised controlled trial showed improved mortality in tuberculous meningitis with adjuvant corticosteroids, but did not show a reduction in severe disability; however, an observational MRI study did suggest a reduction in strokes in patients treated with corticosteroids.

An open-label study of aspirin in the prevention of stroke and mortality in tuberculous meningitis found a non-significant reduction in stroke and a significant reduction in mortality with a possible synergism with corticosteroids.

Discussion

The evidence for the importance of vasospasm in the pathogenesis of complications of bacterial meningitis underscores the importance of maximizing perfusion by aggressive treatment of hypovolemia and hypotension in the often associated sepsis. Support of pump function by dobutamine therapy has been shown to improve...
micro-circulatory flow independent of improvement of global haemodynamic parameters\(^\text{37}\) and should be investigated in its effect on morbidity and mortality in future randomised controlled trials of supportive treatment of bacterial meningitis, regardless of the presence of hypotension.

The nitric oxide donor intravenous sodium nitrite has been shown to prevent and reverse cerebrovascular spasm in primates and has been demonstrated to be safe for administration in humans\(^\text{38}\). This calls for double blind RCT’s in humans with cerebral inflammation associated with vasospasms in all forms of bacterial meningitis. NO is synthesised from L-arginine. The experience with L-arginine in investigations of cerebral malaria\(^\text{39}\) could form the basis for the development of this precursor as adjunctive treatment in children with bacterial meningitis in randomised controlled trials.

Aggressive maintenance of normothermia or mild hypothermia in patients with military blast injury resulted in a dramatic reduction in the incidence of PTV from 47.5% to 5%. Future studies need to confirm this finding and investigate whether hypothermia can reduce cerebral inflammation related ischaemic damage to the brain in other conditions like bacterial meningitis or cerebral malaria (CM)\(^\text{40}\).

High levels of erythropoietin, which has been shown to upregulate endothelial nitric oxide synthase were associated with protection against neurological sequelae in African children with CM\(^\text{41}\). Erythropoietin should be used in future investigations of agents to improve outcome in bacterial meningitis.

Important lessons for neurological morbidity reducing auxiliary treatment of bacterial meningitis can be drawn from experience in treatment of subarachnoid haemorrhage (SAH): The selective endothelin-1A receptor antagonist Clazosentan was assessed in randomised placebo controlled trials. A meta-analysis of 4 RCT’s with 2024 participants\(^\text{42}\) showed a reduction in delayed ischaemic neurological deficit with this endothelin-1A receptor antagonist.

The effect of calcium antagonists in SAH was reviewed in a systematic review including 16 trials involving 3361 patients\(^\text{43}\). Overall calcium antagonists reduced the risk of poor outcome and the corresponding number of patients needed to treat was 19. Calcium antagonists reduced the occurrence of secondary ischaemia and showed a favourable trend for case fatality. Table 1 shows a summary of agents which reduced vasospasm in animal and human studies. Vasospasm occurred in most of those experiments in the context of subarachnoid haemorrhage, a condition associated with inflammation of the subarachnoid space but also free haemoglobin which binds nitric oxide and may be a dominating mechanism of cerebral vasospasm in SAH not present in bacterial meningitis. The agents investigated should be investigated in studies of supportive treatment in humans with bacterial meningitis.

### Table 1. Agents associated with an in vivo reduction of vasospasm in experimental studies (modified from reference 44)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Parameter assessed</th>
<th>Model</th>
<th>Findings</th>
<th>Reference</th>
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<tr>
<td>Thromboxane A2 synthetase inhibition</td>
<td>Symptomatic vasospasm</td>
<td>Human</td>
<td>Decrease in symptomatic vasospasm</td>
<td>Tokiyoshi et al.1991(^\text{45})</td>
</tr>
<tr>
<td>Topical dexamethasone</td>
<td>Middle cerebral artery velocity</td>
<td>Human</td>
<td>Prevention of angiographic vasospasm</td>
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<tr>
<td>Sodium nitrite</td>
<td>Arterial diameter</td>
<td>Primates</td>
<td>i.v. sodium nitrite reverses cerebral vasospasm after subarachnoid haemorrhage</td>
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<tr>
<td>L-citrulline</td>
<td>Basilar artery diameter, nitric oxide synthase expression</td>
<td>Murine</td>
<td>Systemic L-citrulline prevents angiographic basilar artery vasospasm and nitric oxide synthase expression after subarachnoid haemorrhage</td>
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<tr>
<td>Janus kinase 2</td>
<td>Vasospasm, Janus kinase 2 activity</td>
<td>Lporine</td>
<td>Reduction in vasospasm and reduction in Janus kinase 2 activity</td>
<td>Chen et al. 2008(^\text{49})</td>
</tr>
<tr>
<td>Endothelin converting enzyme inhibitor</td>
<td>Basilar artery diameter</td>
<td>Lporine</td>
<td>Decrease in vasospasm</td>
<td>Lin et al. 2007(^\text{50})</td>
</tr>
<tr>
<td>Caspase inhibitor Z-VAD-FMK</td>
<td>Basilar artery diameter</td>
<td>Lporine</td>
<td>Decrease in angiographic vasospasm</td>
<td>Iseda et al. 2007(^\text{51})</td>
</tr>
<tr>
<td>Anti-E selectin monoclonal antibodies</td>
<td>Anterior cerebral artery diameter</td>
<td>Murine</td>
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<td>Lin et al. 2005(^\text{52})</td>
</tr>
<tr>
<td>Trehalose</td>
<td>Vasospasm</td>
<td>Lporine</td>
<td>Decrease in arachidonic acid release and vasospasm after subarachnoid haemorrhage</td>
<td>Echigo et al. 2012(^\text{53})</td>
</tr>
</tbody>
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Coma in conditions with and possibly even without cerebral inflammation may be if irreversible due to permanent or if reversible due to intermittent vasospasm. Investigations into features of vasospasm as well as therapeutic trials of vasospasm resolving agents in patients with coma are warranted.

**Conclusion**

Key factors in the pathogenesis of cerebral vasospasm in bacterial meningitis are depletion of nitric oxide and effects of endothelin-1 and interleukin-1. Auxiliary treatment increasing nitric oxide levels and antagonising the other inflammatory mediators may be able to reduce ischaemic brain injury associated with neurological deficits and increased mortality in bacterial meningitis.

**Abbreviations list**

CBE, cerebral blood flow; CSF, cerebrospinal fluid; ET-1, endothelin-1; ETA, endothelin-A; MBS, myosin phosphatase; MLCK, MLCK kinase; MLCP, MLCK phosphatase; PKC, protein kinase C; OPS/SDF, orthogonal polarization spectral and sidestream dark-field imaging; SAH, subarachnoid haemorrhage.

**References**


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