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Alteration of Hemostatic Coagulative Balance in Bacterial Meningitis: Activation of Coagulation & Inhibition of Fibrinolysis

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Abstract

Bacterial Meningitis is an acute purulent infection of the leptomeninges in the subarachnoid space, most commonly caused by *Streptococcus pneumonia, Neisseria meningitidis*, and *Haemophilus influenzae*. A variety of complications originate from a primary focus of bacterial meningitis, but none as severe as cerebrovascular complications. The basis for the development of post-infective cerebrovascular sequelae following an attack of bacterial meningitis remains largely speculative; however several studies suggest a derangement of the coagulative system in evoking such an outcome. A primary derangement of the coagulative status stems from an unbalance between the activation of coagulative processes and an inhibition of anticoagulant processes, resulting in a net heightened activation of coagulation. Multiple pieces of experimental evidence suggest a net overall procoagulant status is achieved by heightened activation of coagulation and inhibition of fibrinolysis. In our analysis of perturbations of coagulative status following acute bacterial meningitis, we begin our discussion by describing structural and functional properties of normal anticoagulant proteins in the circulation that normally function to limit excess coagulation, reducing the development of a procoagulant status in the blood. Next, we continue our discussion, by analyzing the various factors that contribute to a suppression/down regulation of normal anticoagulant pathways, thereby increasing procoagulative status of the blood. Subsequently, we analyze the initiators of activation of coagulation and their implications following an injury with an insight into molecular mechanisms capable of initiating such changes. Finally, we end the discussion by describing the initial short-lived acute fibrinolytic response to bacterial infection and inflammation followed by a late-rising sustained anti-fibrinolytic response capable of inhibiting fibrinolysis and enhancing procoagulant status. Our main objective in this study is to more closely understand possible perturbations in the coagulative profile of the blood that may contribute to the development of cerebrovascular sequelae following an post-infective meningitis infection.

Introduction

Acute bacterial meningitis is a life treating purulent infection of the leptomeninges, characterized by the influx of inflammatory cells into the subarachnoid space with the attendant development of a purulent exudate most commonly due to Streptococcus pneumonia, Haemophilus influenzae, and Neisseria meningitidis [1]. In spite of improvements in the antimicrobial treatment of bacterial meningitis over the last few decades, mortality and post-infective complications continue to present heavily to disease burden [2,3]. Intracerebral complications such as seizures, cerebral edema, cranial nerve palsies (CN 3, 4, 6, 7), hydrocephalus, and cerebrovascular events increase the clinical consequences of bacterial meningitis leading to an unfavorable clinical outcome [2,4]. A particularly disturbing complication of acute bacterial meningitis is the involvement of the cerebral vasculature with the attendant development of post-infective cerebrovascular sequelae [5-16]. Post-infective cerebrovascular sequelae are a predictable consequence of nearly one-fifth of adults with community acquired bacterial meningitis [3]. In most cases, cerebrovascular complications of bacterial meningitis are manifested by the development of arterial or venous thrombi, ischemic or hemorrhagic stroke, and cerebral venous sinus thrombosis.

Although numerous pathophysiological alterations are in play to evoke changes in the cerebral vasculature, a particularly

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important alteration is the alteration of coagulation [17]. The role of the coagulation system in bacterial meningitis plays an important role in understanding the cerebrovascular sequelae of bacterial meningitis. In bacterial meningitis, the normal hemostatic balance between a coagulative and an anticoagulative profile is perturbed, with a shifting towards a more procoagulant profile [18,19]. This is accomplished by derangements in several coagulation factors. For example, patients with bacterial meningitis have higher levels of tissue factor, an initiator of coagulation. Increased levels of tissue factor result in higher than normal activation of the extrinsic pathway of coagulation generating increased amounts of thrombin. A heightened coagulative profile is further enhanced by the attenuation of fibrinolysis due to increased levels of plasminogen-activator inhibitor 1. Increased levels of PAI-1 contributed to the hypercoagulability by blocking the conversion of inactive plasminogen into active plasmin, thereby reducing the breakdown of fibrin based blood clots.

With that being said, this review focuses on the alterations that take place in the cerebrospinal fluid following an attack of acute bacterial meningitis from heightened activation of coagulation to an attenuated fibrinolysis.

Normal Anticoagulant Pathways

Activation of coagulation following inflammation is kept balanced by 3 physiological anticoagulative hemostatic pathways. These coagulation pathway inhibitors function primarily to limit excessive coagulation and include heparin-antithrombin pathway, tissue factor pathway inhibitor, and the protein c and s pathways [20]. The first line of defense, Heparin-antithrombin pathway consists of individual anticoagulative contributions from heparin and antithrombin. Heparin, a sulfated mucopolysaccharide glycoprotein with a molecular weight of 6.5 kDA, binds to lysyl residues on antithrombin resulting in the formation of a heparin-antithrombin complex. The Heparin-Antithrombin complex limits coagulation by binding to and inactivating a number of different coagulation factors, including factors 2a, 9a, 10a, 11a, and 12a [21]. Amongst these, thrombin and factor 10a are most sensitive to inhibition with a tenfold greater inhibition of thrombin compared to factor 10a. Further, vascular heparin-like proteoglycans facilitate antithrombin mediated inhibition of factors 10a, 9a and thrombin [22]. Decreased activity of coagulation factors 10a and thrombin result in reduced conversion of inactive fibrinogen to active fibrin, Impairing development of fibrin-blood clots. Apart from directly modulating expression of coagulation factors, antithrombin inhibits endotoxin-induced interleukin 6-formation by inflammatory mononuclear cells and endothelium, preventing corresponding elevations in thrombin [23,24]. Moreover, antithrombin interaction with cell surfaces appears to block NFkb nuclear translocation with the subsequent release of cytokines and induction of adhesion molecules by the vascular endothelium [25,26] (Table 1).

Protein C and S pathways form the second line of defense. Protein C, a vitamin K dependent plasma protein, circulates in the plasma as an inactive zymogen. Under physiological conditions, the protein C pathway begins with the binding of thrombin to thrombomodulin present on the endothelial cell membrane [27]. Thrombomodulin, a cofactor constitutively expressed on endothelial cell surfaces, interacts with and modifies the activity of thrombin [28]. Thrombomodulin, following the binding of thrombin, results in a marked increase in the activation of protein C. Subsequent binding of protein C to the endothelial protein C receptor further increases the activation of protein C [20]. Ultimately, protein C exerts its anticoagulant effect by proteolytic inactivation of coagulation factors 5a and 7a and by promoting fibrinolysis by inhibiting plasminogen activator 1 [29].

Finally, the tissue factor pathway inhibitor forms the final line of defense. TFPI, the main inhibitor of tissue factor-factor 7 complex, similarly functions to limit thrombin generation [20] by binding to tissue factor-factor 7 complex, inhibiting activation of tissue factor-mediated coagulation.

Activation of Coagulation

In bacterial meningitis, coagulation begins with the activation of the tissue factor pathway. The procoagulant status noted in bacterial meningitis stems from increased thrombin generation, mediated by the tissue factor pathway [30-32]. In meningococcal sepsis, plasma from these patients demonstrates the presence of micro-particles consisting of CD14 and tissue factor. In the same study, an overabundance of thrombin was generated, noted by increased plasma levels of thrombin [33]. An attempt to elucidate the source of tissue factor during bacterial meningitis points towards

Table 1: Physiological Anticoagulant Pathways - Heparin - Antithrombin 3, Protein C - Thrombomodulin, Tissue Factor Pathway Inhibitor.

Normal anticoagulant pathway	Interactions	Physiological function
Heparin-Antithrombin	Heparin binds to Antithrombin 3 forming Heparin Antithrombin 3 Complex	• Inhibition of coagulation factors 2a, 9a, 10a, 11a, 12a • Inhibition of fibrinogen conversion into fibrin
Protein C	Protein C binds to Thrombomodulin forming Protein C-Thrombomodulin complex	• Inactivation of coagulation factors 5a and 7a • Promote fibrinolysis by inhibition of plasminogen activator 1
Tissue Factor Pathway Inhibitor	Tissue factor pathway inhibitor binds to tissue factor and factor 7 forming Tissue factor pathway inhibitor- factor 7- tissue factor complex	• Inhibits tissue factor-factor 7 complex • Reduced thrombin generation

monocytes and endothelial cells. The role of TF expression by monocytes is supported from infant models of bacterial meningitis, where more than 60% of circulating monocytes were shown to express tissue factor on the cell surface [34]. Indeed, increased levels of tissue factor were noted on the surface of circulating monocytes in meningococcal infections. Monocytes with very high tissue factor levels, in excess of nearly 60-3000x fold higher compared to normal quiescent cells, displayed a greater propensity for fatal outcomes of bacterial meningitis [35-36]. In a comparative study of tissue factor expression in circulating monocytes of patients with meningococcal sepsis were noted to have higher levels of tissue factor in non-survivors compared to survivors, providing a correlation between tissue factor levels and disease severity of bacterial meningitis. (Østerud)

Tissue Factor is a 4.5 kDA protein constitutively expressed in different sites within the arterial vasculature, usually not in contact with the circulating blood [37,38]. The hidden expression of tissue factor renders it inactive unless it comes in contact with blood following either disruption of the vascular endothelium or through overproduction of TF by cells in the circulation [39-41]. In the setting of infections, more commonly, the overproduction of proinflammatory cytokines by the vascular endothelium provides a source of tissue factor rather than vascular wall disruption [42-44]. Tissue factor expression by the endothelial cells is mediated by endothelial cell activation [45-48]. Endothelial activation is induced by a number of mediators such as proinflammatory cytokines [49]. Upon endothelial activation by proinflammatory cytokines TNF-alpha and IL-1, tissue factor interacts with factor 7 forming a tissue factor-factor 7 complex [49,50]. Subsequently, the Tissue Factor-Factor 7 complex activates factor 7. Following generation of tissue factor, the intrinsic pathway is activated, thereby carrying out the procoagulant behavior of the blood. First, tissue factor binds to and activates factor 7; the tissue factor-factor 7 complex subsequently catalyzes the cleavage of inactive factor 10 to activate factor 10. Now, Activated factor 10, along with factor 5a, prothrombin and calcium forms thrombin. Next, thrombin proteolytically acts of fibrinogen to convert it to fibrin, resulting in the development of a blood clot. Inhibition of the common pathway of coagulation, in animal models, is observed following the use of antibodies directed against tissue factor. The cerebrospinal fluid of patients with pneumococcal meningitis demonstrates higher levels of soluble tissue factor [30,50] compared to normal subjects. Further, children with meningococcal septic shock were shown to have activation of the intrinsic pathway of coagulation, which is mediated by tissue factor-factor 7.

Expression of tissue factor by vascular endothelial cells, monocytes, and macrophages is driven by the influence of endotoxin and TNF-alpha released in response to an infectious/inflammatory stimuli [51,52]. In bacterial meningitis, apart from tissue factor expression on circulating monocytes, the vascular endothelium also upregulates expression of tissue factor [40,53]. Activation of endothelial cell procoagulant activity by Neisseria meningitis may follow exposure of the endothelium to certain bacterial structural proteins [54-56]. One such structural wall component of gram negative bacteria is lipopolysaccharide. Pathogenic strains of neisseria meningitidis when grown together with human monocytes lead to the production of tissue factor. However, the production of tissue factor between N.meningitidis colonies capable of producing endotoxin and colonies unable to produce endotoxin differed. Specifically, a 10,000 fold increase in tissue factor levels were observed in N.meningitidis colonies capable of producing endotoxin compared to colonies unable to produce endotoxin. (Prins). Further, human endothelial cells challenged with colony forming units of N.meningitidis were found to induce tissue factor expression. Additionally, bacterial culture filtrate experiments suggest that tissue factor expression on endothelial cells following N.meningitidis infection appears to be a function of shed lipopolysaccharide from the cell surface [57]. Experiments involving use of limulus amoebocyte lysate, present in bacterial culture filtrates and capable of reacting with the LPS membrane component of gram negative bacteria such as Neisseria Meningitidis, and polymyxin B provide supportive evidence for the role of LPS in procuring a procoagulant status of the blood [57]. Bacterial culture filtrate experiments pretreated with limulus amoebocyte lysate and polymyxin B demonstrated an overall decrease in procoagulant activity. Moreover, the decrease in procoagulant activity was correlated with a similar reduction of lipopolysaccharide levels in the blood. In addition, meningococcal strains treated with penicillin, gentamicin and functional serum (with active complement and antibody-mediated killing) resulted in cellular lysis and destruction [58-60]. Here also, loss of active meningococcal strains reduced procoagulant effect with a similar decrease in plasma lipopolysaccharide levels [60].

In conclusion, coagulation in bacterial meningitis is initiated by several factors expressed in response to the infecting microorganism. Proinflammatory cytokines, TNF and IL-1, induced by the vascular endothelium in response to bacterial cell wall components and gram negative bacterial lipopolysaccharide endotoxin elicit tissue factor expression by the endothelium. The potent effect of proinflammatory cytokines & cell wall components on endothelial cells may be a contributory detrimental cause of cerebrovascular consequences in bacterial meningitis.

Suppression of Natural Anticoagulant Pathways

Several pieces of experimental evidence highlight perturbations in heparin-antithrombin pathway in bacterial meningitis. Decreased levels of antithrombin were noted in the serum of patients with acute meningococcal infections [59,60]. Upon exposure of meningococci and lipopolysaccharide endotoxin to the vascular endothelium, binding of antithrombin to the endothelium as well as functional activity of antithrombin is suppressed *in vitro* models [61]. Similarly, in a comparative study between patients with meningococcal septicemia and patients without localized meningococcal infections, patients with septicemia were observed to have lower serum concentrations of antithrombin 3. In the same study, within the meningococcal

septicemic group, patients with the lowest antithrombin 3 levels were observed to have a higher incidence of fatal outcomes [62]. In response to severe inflammatory responses, antithrombin levels may be decreased due to a combination of factors: Excessive consumption (due to continued thrombin generation), decreased synthesis (secondary to negative acute phase responses), or increased degradation (due to elastase release by activated neutrophils [63-65]. First, proinflammatory cytokines reduce the synthesis and expression of glycosaminoglycans by the endothelial cells [60]. Second, reduced glycosaminoglycans impair the inhibitory potential of AT due to a decreased availability of the cofactor [66]. Building on this, infusion of a very high concentration of recombinant antithrombin, markedly reduced plasma levels of IL-6 and IL-8. Consequently, decreased levels of IL-6 had an overall net favorable effect on the outcome of DIC [67]. Given that IL-6 expression appears to be a primary prerequisite responsible for markedly increased tissue factor expression and increased fibrin formation, decreased levels of IL-6 result in reduced tissue factor expression, decreased fibrin formation, and increased fibrinogen levels, all of which ultimately reduce the procoagulant status of the blood.

In acute meningococcal acute infections, unopposed upregulation of procoagulant pathways leads to increased procoagulant status by suppressing the protein C pathway [59,68]. Plasma levels of anticoagulant proteins-antithrombin, protein C and protein C, are reduced in meningococcal sepsis. Further, reduced amounts of activated protein C are produced due to a loss of thrombomodulin and endothelial protein C receptors from the endothelial surface. As noted above, protein C activation is markedly imparied in severe meningococcal sepsis, similarly correlated with a suppression of endothelial thrombomodulin-endothelial protein C receptor activity [69,70]. Protein C-dependent antithrombotic mechanisms- thrombin binding to thrombomodulin on the endothelial surface, thrombin-thrombomodulin complex binding to protein C, and protein C/S mediated inactivation of coagulation factors 5a, 8a and downregulation of plasminogen activator inhibitor, are defective in meningococcal sepsis [71,72]. Skin biopsy samples in patients with meningococcal sepsis highlight a repression of both thrombomodulin and endothelial protein C receptor expression [73,74]. In a comparative study between severely ill and moderately ill patients with meningococcal septicemia, lower plasma levels of protein C in were observed in severely ill patients at the time of admission, providing a correlation between more severe outcomes of bacterial meningitis in protein C deficient states [59]. Following endotoxin challenge, several animal studies show an increased susceptibility to fatal outcomes with protein C deficiency, but demonstrated favorable outcomes and improved mortality with protein C administration [70]. Along the same lines, immunohistochemistry studies performed in septic patients highlighted reduced production of activated protein C [59,75,76]. Perturbation of the protein C anticoagulant pathway begins with endothelial dysfunction. Proinflammatory cytokines and endotoxin released by the dysfunctional endothelium influence expression of components of the protein C anticoagulant pathway [70]. TNF-alpha and IL-1 Beta, released by the vascular endothelium, mediate downregulation of thrombomodulin expression by the vascular endothelium [77]. Similarly, LPS endotoxin elaborated by gram negative meningococci induces regression of thrombomodulin from the endothelial cell surface. Additionally, proinflammatory cytokines (TNF-alpha and IL-1 Beta) and endotoxin inhibit thrombomodulin and endothelial cell protein c receptor gene transcription by the vascular endothelium [72,78]. Further, neutrophil elastase, derived from infiltrating inflammatory cells, degrades thrombomodulin and initiates suppression of endothelial thrombomodulin expression (Table 2).

Suppression of natural anticoagulant pathways during the course of bacterial meningitis occurs in response to proinflammatory cytokines and lipopolysaccharide endotoxin. Downregulation of these pathways abborates protective anticoagulative mechanisms tipping the balance towards procoagulation, increasing the likelihood of subsequent thrombotic/embolic manifestations of the cerebral vasculature.

Blunting of the Fibrinolytic Response

Fibrinolysis is a protective enzymatic response mediated by the circulating proteases, helping to break down fibrin-based clots and reduce the risk of microthrombosis and thrombotic complications. Vascular endothelial cells participate in fibrinolysis through the synthesis and elaboration of plasminogen activators-tissue type and urokinase-type plasminogen activators. Plasminogen activators aid in the proteolytic cleavage of inactive plasminogen to active plasmin, which subsequently binds to the fibrin polymer and enzymatically degrades into smaller non functional monomers. The initial response of the fibrinolytic system to inflammation rests upon the activation of endothelial cells in response to proinflammatory cytokines TNF and IL-1 [79]. A healthy balance between TPA and PAI-1 are necessary prerequisites for the occurrence of fibrinolysis. Elevated levels of plasminogen activator inhibitor-1 in the cerebrospinal

Table 2: Suppression/down regulation of physiological anticoagulant pathways in bacterial meningitis.

References	Natural anticoagulant pathways	Perturbation in bacterial meningitis
[59-62]	Heparin-Antithrombin pathway	• Decreased levels of antithrombin • Decreased binding of antithrombin to the endothelium & decreased activity of antithrombin
[59,70,77]	Endothelium-Protein C	• Downregulation of endothelial thrombomodulin expression • Suppress thrombomodulin and endothelial protein C receptor gene transcription

fluid have been reported in various infectious/inflammatory neurological disorders [80-82].

Serum levels of tPA and PAI-1 are increased in patients with bacterial meningitis [70,83]. In response to acute meningococcal infections, proinflammatory stimuli induce release of tissue/urokinase plasminogen activator, to initiate coagulation, and plasminogen activator inhibitor 1, to inhibit coagulation [84]. Proinflammatory mediated activation of endothelial cells results in the release of tissue type and urokinase plasminogen activators from intercellular endothelial stores. However, the initial activation of plasminogen activators with subsequent generation of plasmin is short lived and replaced by the delayed but sustained release of plasminogen activator inhibitor 1. Indeed, in patients with bacterial meningitis, plasminogen activator inhibitor-1 levels show a deviation from the normal. Levels of plasminogen activator inhibitor-1, an inhibitor of the thrombotic pathway, are increased in acute meningococcal infections [85]. Likewise, a similar increase in the level of plasminogen activator 1 is observed in patients with meningococcal sepsis. In the same study, Kornelisse RF highlighted a direct correlation between the levels of PAI-1 and severity of the disease, suggesting a loss of fibrinolytic response is associated with a more severe disease state [86]. Further, Aiuto, et al., observed an improvement in hemodynamic profile and skin perfusion in patients with meningococcal purpura fulminans following the infusion of recombinant tPA [87]. As noted above, given the increase in PAI-1 levels in acute meningococcal infections/meningococcal sepsis, a heightened procoagulant activity is observed due to the depletion of plasminogen activators. Additionally, a genetic polymorphism in the plasminogen activator inhibitor type1 promoter site influences the expression of fibrinolysis in the human population. On exposure to Neisseria meningitidis inflection, patients with a functional polymorphism of the 4G/4G gene at the PAI-1 promoter site demonstrated significant increases in PAI-1 levels compared to patients without a functional polymorphism [88]. The same patients with the 4G/4G gene polymorphism were observed to develop meningococcal septicemia with a 2 fold greater increase in the mortality rate, thereby supporting the idea that a loss of fibrinolysis in bacterial meningitis correlated with a more adverse outcome [89]. Consequently, fibrinolysis is inhibited resulting in impaired clearance of fibrin from the plasma and a hypercoagulable state develops.

The heightened procoagulant state induced by increased levels of PAI-1 and decreased levels of plasminogen activators is highlighted by experimental data involving mice following the administration of endotoxin, a potent inducer of fibrin formation. Mice abborated of PAI-1 expression, when challenged with endotoxin, displayed decreased formation of thrombi, compared to mice with normal PAI-1 expression, where significant thrombi were present following endotoxin administration. Further, mice with a deficiency of plasminogen activators were found to have more extensive fibrin deposition with macro thrombosis following exposure to endotoxins [90]. Moreover, endothelial cells cultures when co cultured with endotoxins and proinflammatory mediators (TNF-alpha and IL-1) induce synthesis and promote release of plasminogen activator-1 and suppress tissue plasminogen activator production. Similarly, exogenous infusion of interleukin 1B into baboons elicited a transient and early activation of fibrinolysis, which was subsequently rapidly suppressed by increased production of PAI-1, effectively blunting the fibrinolytic response to IL-6 [91,92].

The potent role of TNF in shutting off the fibrinolytic response to infection is demonstrated in limited studies; however the role of anti-TNF agents in thwarting such a response may provide further supportive evidence. Anti-TNF agents when exogenously administered in humans and chimpanzees fail to display a rise in the levels of tPA and PAI-1. Given the key regulatory role of PAI-1 in the fibrinolytic system, decreased levels of PAI-1 supports the role of TNF in contributing to the development of a blunted fibrinolytic response to infection.

Conclusion

Bacterial meningitis is a severe purulent infection of the subarachnoid leptomeninges caused primarily by Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae that has a deleterious effect on cerebrovascular structures. The exact cause of post-infective cerebrovascular sequelae following bacterial meningitis is unknown; however, several studies suggest that a coagulative system derangement is to blame. An imbalance between activation of coagulative processes and the inhibition of anticoagulant processes lead to a net increase in coagulation activation. Multiple lines of evidence suggest that in bacterial meningitis increased activation of coagulation activation and heightened inhibition of fibrinolysis inhibition procure a net procoagulant state. Coagulation in infections begins with the activation of the tissue factor pathway. Procoagulant status in inflammation is caused by increased thrombin generation, which is mediated by the tissue factor pathway in response to either vessel endothelial disruption or overproduction of tissue factor by circulating inflammatory cells. Normally, anticoagulant proteins in the bloodstream are responsible for limiting excessive coagulation and preventing the development of a procoagulant state in the blood. In bacterial meningitis, Three physiological anticoagulative hemostatic pathways acting to balance coagulation activation are suppressed: the heparin-antithrombin pathway, the tissue factor pathway inhibitor, and the protein c and s pathways. Finally, fibrinolysis is abborated through a short lived acute fibrinolytic response to bacterial infection and inflammation followed by a sustained late occurring anti-fibrinolytic response, abolishing off fibrinolysis and increasing the likelihood of developing post-infective cerebrovascular prothrombotic sequalue. The observation of heightened procoagulant activity relative to anticoagulant activity in patients with bacterial meningitis who develop cerebrovascular consequences highlights a vital role of the coagulation-anticoagulation system in bacterial meningitis.

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