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REVIEW

Effect of the factor V Leiden mutation on the incidence and outcome of severe infection and sepsis

M. Schouten[1,2,3], C. van 't Veer[1,2,3], T. van der Poll[1,2,3], M. Levi[1]*

[1]Department of Medicine, [2]Center for Infection and Immunity Amsterdam (CINIMA), [3]Center for Experimental and Molecular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, *corresponding author: tel. +31 (0)20-5662171, fax: +31 (0)20-6919658, e-mail. m.m.levi@amc.uva.nl

ABSTRACT

Activation of coagulation frequently occurs in severe infection and sepsis and may contribute to the development of multiple organ dysfunction. Factor V Leiden is a relatively common mutation resulting in a mild prohaemostatic state and consequently with an increased tendency to develop thrombosis. Hypothetically, patients with factor V Leiden may suffer from more severe coagulopathy in case of severe infection or sepsis. Aggravation of the procoagulant state in sepsis may subsequently result in more severe organ dysfunction and an increased risk of death. Here we discuss the experimental and clinical evidence regarding the relationship between the presence of a factor V Leiden mutation and the incidence and outcome of sepsis.

KEYWORDS

Factor V Leiden, thrombophilia, sepsis, infection, coagulation

INTRODUCTION

Virtually all patients with sepsis have coagulation abnormalities. These abnormalities range from subtle activation of the coagulation system that can only be detected by sensitive markers for coagulation factor activation to somewhat stronger coagulation activation detectable by a small decrease in the platelet count and subclinical prolongation of global clotting times to fulminant disseminated intravascular coagulation (DIC), which is characterised by simultaneous widespread microvascular thrombosis and profuse bleeding from various sites.[1] Septic patients with severe forms of DIC may present with manifest thromboembolic disease or clinically less apparent microvascular fibrin deposition, which predominantly presents as multiple organ dysfunction.[2-4] Clinically relevant coagulation abnormalities are present in 50 to 70% of patients with severe infection or sepsis, whereas about 35% of patients will actually meet the criteria for DIC.[5,6] There is ample evidence that activation of coagulation in concert with inflammatory activation can result in microvascular thrombosis and thereby contributes to multiple organ failure in patients with severe sepsis.[4,7,8] Firstly, there are several reports of post-mortem findings in septic patients with coagulation abnormalities and DIC.[9,10] These autopsy findings include diffuse bleeding at various sites, haemorrhagic necrosis of tissue, microthrombi in small blood vessels and thrombi in mid-size and larger arteries and veins.[11] The demonstration of ischaemia and necrosis has been associated with fibrin deposition in small and mid-size vessels of various organs.[12] Importantly, the presence of these intravascular thrombi appears to be clearly and specifically related to the development of organ dysfunction. Secondly, experimental animal studies of DIC show fibrin deposition in various organs. Experimental bacteraemia or endotoxaemia causes intra- and extravascular fibrin deposition in kidneys, lungs, liver, brain and various other organs.[13] Amelioration of the haemostatic defect by various interventions in these experimental models appears to improve organ failure and, in some but not all cases, mortality.[14-17] Interestingly, some studies indicate that amelioration of systemic coagulation activation will have a profound beneficial effect on resolution of local fibrin deposition and improvement of

organ failure.[18,19] Lastly, clinical studies support the notion of coagulation as an important determinant of clinical outcome. DIC has shown to be an independent predictor of organ failure and mortality.[2,20] In a consecutive series of patients with severe sepsis, the mortality of patients with DIC was 43%, as compared with 27% in those without DIC. In this study, mortality was also directly related to the severity of the coagulopathy in septic patients.[21]

Apart from microvascular thrombosis and organ dysfunction, coagulation abnormalities may also have other harmful consequences. For example, thrombocytopenia in patients with sepsis confers an increased risk of bleeding.[22] Indeed, in particular critically ill patients with a platelet count of <50 x 10^9/l have a four to fivefold higher risk for bleeding as compared with patients with a higher platelet count.[23,24] A low platelet count may be both the best indicator of thrombin generation and a sign of increased platelet-vessel wall interaction.[11]

Since the prohaemostatic state in severe infection and sepsis seems to be relevant for the pathogenesis of organ dysfunction and mortality, it may be hypothesised that even a mild pre-existent prothrombotic state in patients, such as that caused by thrombophilia for example due to a factor V Leiden mutation, would aggravate the coagulation derangement during infection and sepsis and thereby affect outcome. Interestingly, experimental and clinical studies point to an interaction between a factor V Leiden mutation and the outcome of severe infection or sepsis, although the results are sometimes conflicting. In this article, we will briefly review experimental and clinical evidence on the relationship between factor V Leiden and the outcome of severe infection and sepsis.

THROMBOPHILIA AND OUTCOME IN INFECTION AND SEPSIS

Congenital thrombophilia is usually due to a genetic variation in a gene encoding a coagulation factor or – in general clinically less relevant – a fibrinolytic protein.[25] Such gene polymorphisms have been described for the coagulation factors prothrombin, factor V, fibrinogen and factor XIII and for the coagulation inhibitors antithrombin, protein C and protein S. In the last-mentioned, these mutations cause a deficiency of these natural anticoagulant factors. In the fibrinolytic system the most relevant polymorphism is the 4G/5G variation in the gene encoding plasminogen activator inhibitor type I (PAI-1). This polymorphism results in mildly elevated levels of PAI-1 and is related to an increased risk of myocardial infarction and ischaemic stroke.

Anecdotal reports have indicated that the presence of congenital thrombophilia may exacerbate the coagulopathy associated with severe infection and may even result in purpura fulminans.[26-30] Indeed, various coagulation defects seem to be associated with an aggravated coagulation response to infectious agents or sepsis, although a systematic overview is missing.[31,32] Prospective studies on the incidence or outcome of severe infections and sepsis in patients with a prothrombotic polymorphism or coagulation inhibitor deficiency are not available. However, some case-control studies have reported on the prevalence of thrombophilic abnormalities in cohorts of patients with severe sepsis. Moreover, a substantial number of animal studies have been performed. These studies have particularly focussed on deficiencies in the protein C and antithrombin pathways, the factor V Leiden mutation and genetic polymorphisms in the fibrinolytic system.

Antithrombin is the cardinal inhibitor of thrombin and factor Xa activity and, like the protein C pathway, a central regulator of coagulation activation *in vivo*. There is ample evidence that antithrombin is unable to adequately regulate these coagulation proteases in case of sepsis. Clinical studies show mean levels of antithrombin as low as 30% of normal values in patients with severe sepsis, whereas in selected individuals these levels may be even lower.[20,33,34] Low levels of antithrombin have been shown to be associated with a higher mortality in septic patients in several prospective studies.[20] Restoration of antithrombin levels in experimental DIC in animals has been demonstrated to adequately block the systemic activation of coagulation and in these studies was also associated with improved outcome in terms of less organ failure and a reduction in mortality.[15,35] In mice a heterozygous deficiency of antithrombin endotoxaemia leads to much more deposition of fibrin in various organs, including the kidneys, liver and heart, as compared with endotoxaemic wild-type mice.[36] There are no clinical data that point to a role of antithrombin deficiency in the outcome of sepsis or severe infection in humans.

There are several indications that the protein C system plays an important role in sepsis and also that defects in the protein C system may influence the outcome in sepsis. An impaired function of the protein C system is directly related to the severity and outcome of sepsis.[37] The most compelling evidence comes from experimental studies showing that administration of activated protein C to septic animals resulted in amelioration of DIC and an improved survival.[17] Clinical studies confirm the beneficial effect of activated protein C in sepsis.[38] Severe (congenital) protein C deficiency in mice results in thrombophilia as well as a proinflammatory phenotype with higher total white blood cell counts and higher basal IL-6 levels as compared with wild-type mice.[39] Further protein C deficiency was shown to affect endotoxaemia in a mouse model. In these experiments mice with a one-allele targeted deletion of the protein C, resulting in heterozygous protein C

deficiency,[40] were subjected to endotoxaemia.[41] Mice with a heterozygous deficiency of protein C had more severe DIC, as evidenced by a greater decrease in fibrinogen level and a larger reduction in platelet count. Also thrombin-antithrombin complex levels were 3.4-fold higher in protein $C^{+/-}$ mice as compared with wild-type mice and histological examination showed more fibrin deposition in lungs and kidneys in these mice. Survival at 12 hours after the endotoxin injection was diminished in the protein $C^{+/-}$ group. Interestingly, protein $C^{+/-}$ mice had significantly higher levels of the pro-inflammatory cytokines TNF-α, IL-6 and IL-1β, indicating an interaction between the protein C system and the inflammatory response. This last observation is consistent with many other studies indicating cross-talk between effects of protein C on coagulation and inflammatory modulation.[42] Similar findings were reported in studies in mice genetically predisposed to a severe protein C deficiency.[43] Interestingly, reconstitution of protein C levels in these mice with recombinant human activated protein C resulted in less severe inflammatory responses and an improved survival. In a model of severe abdominal infection through caecal ligation and puncture mice with a heterozygous deficiency of protein C had more profound organ dysfunction and an enhanced mortality in comparison with wild-type mice.[44] Taken together, these data suggest that preexistent protein C deficiency aggravates the coagulopathic response to severe infection and sepsis and is related to a worse outcome. It is not clear whether this observation may be extended to the clinical situation, mostly due to the fact that deficiency of protein C in humans is relatively rare. Therefore it is hard to establish a relationship between this condition and the incidence or outcome of sepsis.

FACTOR V LEIDEN IN MODELS OF EXPERIMENTAL INFECTION AND SEPSIS

In view of the central role of the protein C pathway in sepsis, a lot of attention has been given to the presence of factor V Leiden mutation, which leads to resistance to activated protein C, and the severity and outcome of sepsis or severe infection. In a clinical study in 259 children with meningococcal sepsis, factor V Leiden carriers had more profound coagulopathy and purpura fulminans, but their carrier status did not have a significant effect on survival.[45] Unfortunately, so far neither experimental or clinical studies in sepsis have shown unequivocal results regarding the presence of the factor V Leiden mutation. In one study, endotoxaemic mice carrying a heterozygous factor V Leiden mutation had a surprisingly lower mortality (19%) compared with their wild-type controls (57%).[46] In these experiments, factor V Leiden mice produced more thrombin than normal controls, indicating a more profound activation of coagulation. In contrast, in another study of experimental pneumococcal pneumonia in mice no major protective effect of the factor V Leiden mutation was seen.[47] Also, markers of coagulation activation, both systemically and in the bronchoalveolar compartment, were not different between factor V Leiden mice and wild-type littermates. Remarkably, homozygosity for the factor V Leiden mutation protected against lethality in mice that were treated with ceftriaxone. Also, factor V Leiden mice did not differ significantly in their response compared with wild-type mice in a model of septic peritonitis, as reflected by similar degrees of activation of coagulation, inflammation, organ dysfunction and survival.[48] In another experimental study the effect of the presence of one or two alleles of the factor V Leiden mutation was investigated in lethal H1N1 influenza.[49] Factor V Leiden mutation did not influence the procoagulant response, lung histopathology, or survival in this study. Lastly, however, in a more subtle model of endotoxin-induced coagulation activation in humans it was demonstrated that heterozygous carriers of factor V Leiden had a more pronounced increase in markers of thrombin generation and fibrinogen to fibrin conversion.[50] The authors also found an increase in fibrinolytic activity in factor V Leiden affected individuals, which they attributed to the facilitating role of soluble fibrin for endogenous fibrinolysis.

Taken together, it seems that factor V Leiden may have some effect on the coagulopathy associated with sepsis; however, the effect is so subtle that it does not seem to be relevant against the background of the profound derangement of coagulation that is seen in severe sepsis or overwhelming infection.

FACTOR V LEIDEN IN CLINICAL SEPSIS STUDIES

Clinical studies on the role of factor V Leiden in sepsis also show variable results. The presence of the factor V Leiden mutation was analysed in large cohorts of patients with severe sepsis that had been included in intervention studies with recombinant human activated protein C.[38,51] In this cohort of 3894 patients, the prevalence of factor V Leiden heterozygosity was 3.9%, which is slightly higher than the predicted allelic frequency of 2.5%.[52] The 28-day mortality in those with factor V Leiden was not significantly different from the control population (19.3 *vs* 26.2%, respectively; risk ratio 0.74; 95% confidence interval (CI) 0.53-1.03). Moreover there were no differences in the incidence of serious bleeding or thrombotic events between factor V Leiden carriers and non-factor V Leiden carriers. In another publication in which the data of only

one of these two studies were presented, patients with a heterozygous factor V Leiden mutation were shown to have a lower mortality (13.9%) than those without this mutation (27.9%; p=0.013).[46] The effect of treatment with recombinant human activated protein C did not differ between the two groups. In the Copenhagen City Heart study 9253 individuals were screened for the presence of the factor V Leiden mutation and followed for a period of more than seven years to establish the risk of hospitalisation for any infectious disease and the subsequent risk of progression of disease to death.[53] The relative risk of any infection in carriers of the factor V Leiden mutation was 1.08 (95% CI 0.87-1.35) as compared with noncarriers (after adjustment for age, sex, smoking, alcohol consumption, income and level of education). In contrast with the previously mentioned study, patients with the factor V Leiden mutation in this study had a higher risk of death from infection as compared with patients who did not have this mutation (adjusted relative risk 4.41; 95% CI 1.42-13.67). The same group of authors presented data from four case cohorts of patients with either Gram-negative sepsis, or invasive pneumococcal disease, or intensive care admission.[54] When they compared their 1249 patients with matched controls, they found in an adjusted logistic regression analysis that factor V Leiden carriers had a higher risk of intensive care admission (OR 1.62; 95% CI 1.08-2.42) and were at increased risk of death (relative risk 1.78; 95% CI 1.13-2.81) compared with controls. Factor V Leiden was not associated with susceptibility to or outcome from pneumococcal infection or sepsis. Similarly, in a prospective observational study in 73 patients admitted with severe sepsis, the presence of a factor V Leiden mutation had no effect on short- or long-term mortality or any other clinically significant outcome.[55] Lastly, and in contrast with previous studies, a small study in 106 patients with acute respiratory distress syndrome showed a survival benefit in factor V Leiden heterozygotes (30-day survival 7/7 = 100% compared with 57/99 = 58% in patients without the mutation).[56] Obviously, this observation needs confirmation in larger cohorts of patients.

CONCLUSION

Activation of coagulation seems to play a pivotal role in the pathogenesis and outcome of severe infection and sepsis. Hypothetically, a preexisting prohaemostatic state, as seen in congenital thrombophilia, may aggravate the severity of this coagulopathy and may thereby affect outcome. Both experimental and clinical studies show inconsistent results as to a difference in survival from sepsis or severe infection in carriers of the factor V Leiden mutation. Although it may be biologically plausible that the factor V Leiden mutation and the ensuing activated protein C resistance would aggravate the response to sepsis, the opposite may also be true as it has been speculated that a balanced and moderate increase in thrombin generation, as may be caused by a heterozygous factor V Leiden mutation, might be protective during severe infection and sepsis by means of generating slightly more activated protein C.[57] Additional analyses in larger cohorts of septic patients or long-term prospective studies in patients with a known factor V Leiden mutation will be required to clarify this issue.

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