Variation in plasminogen-activator-inhibitor-1 gene and risk of meningococcal septic shock

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Summary

Background Some patients infected with Neisseria meningitidis develop septic shock accompanied by fibrin deposition and microthrombus formation in various organs, whereas others develop bacteraemia or meningitis without septic shock. We investigated whether genetic differences in the fibrinolytic system influence the development of meningococcal septic shock.

Methods We investigated 50 patients who survived meningococcal infection, and 131 controls from the same geographical region. Because we had no information on genotypes of patients who died, we also genotyped 183 first-degree relatives of a consecutive series of patients with meningococcal infection for the 4G/5G deletion/insertion polymorphism in the promoter region of the plasminogen-activator-inhibitor-1 gene (PAI-1). The 4G allele is associated with increased gene transcription in cell lines in vitro and with increased PAI-1 concentrations in carriers in vivo.

Findings The allele frequencies of 4G and 5G were similar between patients and controls. However, the 4G/4G genotype was present in only 9% of relatives of patients with meningitis compared with 36% of relatives of patients with septic shock. The 5G/5G genotype was more common among relatives of patients with meningitis (31 vs 11%, p=0·001). Patients whose relatives were carriers of the 4G/4G genotype had a six-fold higher risk of developing septic shock than meningitis (odds ratio 5·9 [95% CI 1·9–18·0]) compared with all other genotypes.

Interpretation Variation in the PAI-1 gene does not affect the probability of contracting meningococcal infection, but does influence the development of septic shock.

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Introduction

Intravascular fibrin deposition and formation of microthrombi in various organs are hallmarks of meningococcal septic shock. Despite antibiotic treatment and advanced life support, up to 50% of patients with this clinical picture die from refractory shock and multiorgan failure. Other patients infected with Neisseria meningitidis develop bacteraemia or meningitis but not septic shock. Meningococcal meningitis is not complicated by disseminated intravascular coagulation and has a benign course with a mortality rate below 5%.

Circulating endotoxin activates the extrinsic route of the coagulation system that underlies intravascular coagulation. The release of endotoxin varies between bacterial strains and may thus contribute to the different manifestations of the disease. Alternatively, the balance between procoagulant and anticoagulant properties of the host response may determine whether disseminated intravascular coagulation occurs and septic shock and multiorgan failure ensue. We have shown that inherited disorders in the protein C, protein S, and antithrombin pathways are not likely to be related to the development of meningococcal septic shock.

The fibrinolytic system counteracts the formation of microthrombi by the release of tissue plasminogen-activator and plasmin. Inhibition of fibrinolysis through circulating concentrations of plasminogen-activator-inhibitor-1 (PAI-1) may lead to a procoagulant state. High plasma concentrations of PAI-1 have been associated with an adverse outcome in patients with sepsis and meningococcal septic shock.

The 4G allele of a deletion/insertion (4G/5G) polymorphism in the promoter region of the PAI-1 gene has been associated with higher plasma concentrations of PAI-1. The presence of a guanine base at position –675 on the 5G allele, is essential for the binding of a repressor of transcriptase to the PAI-1 promoter in vitro. Gene transcription in transfected HepG2 cell lines with the 4G deletion allele increased six-fold when stimulated with interleukin-1.

We questioned whether genetic variation in the fibrinolytic system could explain why some patients with meningococcal infection develop septic shock whereas others develop only bacteraemia or meningitis. Therefore, we studied the gene frequencies of the 4G/5G deletion/insertion polymorphism in the promoter of the PAI-1 gene in patients and controls. Because patients who did not survive meningococcal infection were under-represented in this sample, we also investigated gene frequencies in families of a consecutive series of patients with meningococcal disease.

Patients and methods

Between January, 1989 and February, 1994, 80 patients with meningococcal infection were admitted to the Leiden University Medical Center, Netherlands. The diagnosis was based on clinical presentation and bacterial cultures from blood and...
had petechiae only, without signs of disseminated intravascular pressure controls were in Hardy-Weinberg equilibrium and did not involve in the susceptibility of patients to meningococcal infection. However, patients whose relatives were carriers of the 4G/4G genotype had a fivefold increased risk of developing septic shock rather than meningitis. A similar risk estimate was obtained when only the parents were included in the analysis, the gene frequencies in the various groups (n=103, p=0.04) and risk estimates (5-9 [1.2–28]) were similar.

Among the 50 patients who survived meningococcal infection, the frequency of the 4G/4G genotype was 44% in the patients with septic shock and 14% in patients with meningitis only (p=0.08). On the basis of the genotypes of the patients, carriers of the 4G/4G genotype had a fivefold increased risk of developing septic shock instead of meningitis (4-8 [0.8–28]) compared with all other genotypes.

The gene frequencies of the PAI-1 promoter polymorphism did not differ between the relatives of the 45 patients who survived and those of the 16 patients who died from meningococcal disease. Mortality was associated almost exclusively with septic shock. The frequency of the 4G/4G genotype was 26% in the relatives of survivors, and 28% in the relatives of those who died.

Discussion
The advantage of using first-degree relatives of a consecutive series of patients is that the results of the study are not distorted by selection of patients on the basis of disease severity or outcome. The gene frequencies of the PAI-1 promoter polymorphisms in the relatives of patients with meningococcal infection were similar to the frequencies observed in the general population. This finding shows that the polymorphism is not involved in the susceptibility of patients to meningococcal infection. However, patients whose relatives were carriers of the 4G/4G genotype had a fivefold increased risk of developing septic shock rather than meningitis. A similar risk estimate was obtained when only the parents were analysed.

Previous studies in healthy volunteers have shown the regulatory mechanism of the fibrinolytic system after an endotoxin challenge. The earliest response to such a challenge is the release of tissue plasminogen-activator in the circulation. This onset of fibrinolysis may prevent microvascular thrombosis, which ensues when circulating endotoxin activates coagulation by the tissue pathway. A few hours later, PAI-1 concentrations increase, and concentrations of tissue plasminogen-activator decrease. Fibrinolytic activity thus ceases. In accordance with these experimental data in healthy volunteers, prospective time series in febrile patients have shown that the concentrations of tissue plasminogen activator and PAI-1 were an order of magnitude higher in those who developed septic shock than in those who developed sepsis only.

Carriers of the 4G allele may produce increased amounts of PAI-1 in response to N meningitidis infection. This accelerated inhibition of fibrinolysis may contribute to the formation of microthrombi, vascular disruption, and necrosis. These processes may favour further
outgrowth of meningococci and the development of septic shock and multiorgan failure. Viable meningococci can be detected in the thrombotic skin lesions of most patients with sepsis even after the start of antimicrobial treatment. In line with these observations, high plasma concentrations of PAI-1 early in the disease course have prognostic value for an adverse outcome. Furthermore, experimental evidence in animals shows that activation of the fibrinolytic system by the administration of tissue plasminogen-activator decreases intravascular fibrin deposits and mortality.

In our series, the PAI-1 promoter polymorphism was not related to mortality. The reason for this finding may be that the impact of the PAI-1 polymorphism varies during the different stages of the disease: the polymorphism may have deleterious effects in the early phase of the disease due to inhibition of fibrinolysis, but its effects may be reversed when septic shock has fully developed and consumption coagulopathy is present. Alternatively, the impact of the PAI-1 polymorphism may be overshadowed by other mechanisms that have a role in the mortality of septic shock. We have previously shown that polymorphisms in the production of inflammatory cytokines are closely associated with a fatal outcome. Our findings are another illustration of the genetically determined host response to infection. Moreover, this study has identified causal mechanisms that contribute to the outcome of infectious disease. Whether these findings can be extrapolated to disseminated intravascular coagulation in other manifestations of infection is not yet clear. There may be a genetic predisposition for the hypercoagulable state and complications of malaria. Once a genetic predisposition is ascertained, the search for an environmental modulator—eg, drug intervention, can be intensified.

Contributors
Rudi Westendorp designed the study and recruited the patients and their families, Jouke-Jan Hottenga and Eline Slagboom determined the PAI-1 genotypes. All investigators contributed to the interpretation of the data and to the writing of the paper.

References