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CLINICAL ARTICLE

Genes influencing coagulation and the risk of aneurysmal subarachnoid hemorrhage, and subsequent complications of secondary cerebral ischemia and rebleeding

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Abstract
Background We investigated whether genes influencing coagulation are associated with the occurrence of aneurysmal subarachnoid hemorrhage (SAH) and with secondary cerebral ischemia and rebleeding in patients with aneurysmal SAH.
Method Genotyping for factor V Leiden (G1691A), prothrombin G20210A, methylenetetetrahydrofolate reductase (MTHFR) C677T, factor XIII subunit A Val34Leu, Tyr204Phe and Pro564Leu, and factor XIII subunit B His95Arg was performed in 208 patients with aneurysmal SAH and in 925 controls. Secondary cerebral ischemia occurred in 49 (24%) patients and rebleeding in 28 (14%) during their clinical course of 3 months after the aneurysmal SAH. The risk of aneurysmal SAH was assessed as odds ratio (OR) with 95% confidence interval (95% CI). The risk of secondary cerebral ischemia and rebleeding was assessed as hazard ratio (HR) with 95% CI using Cox regression.
Findings Carriers of the subunit B His95Arg factor XIII polymorphism had an increased risk of aneurysmal SAH with 23% of the patients homozygous or heterozygous for the variant allele compared to 17% of control subjects (OR 1.5, 95% CI 1.0–2.2). For the remaining genetic variants no effect on the risk of aneurysmal SAH could be demonstrated. A clear relation with the risk of secondary cerebral ischemia and of rebleeding could not be established for any of the genetic variants.
Conclusions We found that aneurysmal SAH patients are more often carriers of the subunit B His95Arg factor XIII polymorphism compared to controls. This suggests that carriers of the subunit B His95Arg factor XIII polymorphism have an increased risk of aneurysmal SAH. Larger studies should confirm our results. As aneurysmal SAH patients who died soon after admission could not be included in the present study, our results only apply to a population of patients who survived the initial hours after the hemorrhage. For the other studied genetic factors involved in coagulation, no association with the occurrence of aneurysmal SAH or with the occurrence of secondary cerebral ischemia or rebleeding after aneurysmal SAH could be demonstrated.

Keywords Intracranial aneurysm · Subarachnoid hemorrhage · Genes · Coagulation

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Introduction

Spontaneous subarachnoid hemorrhage (SAH) from rupture of an intracranial saccular aneurysm has an incidence of approximately 8 per 100,000 [20]. The prognosis after

aneurysmal SAH is poor with a case fatality rate of 32 to 67% [15]. In patients who survive the initial hours after aneurysmal SAH, secondary cerebral ischemia and rebleeding are major causes of death and disability [4, 6, 25]. Secondary cerebral ischemia occurs in approximately 25% to 35% of patients [4, 6, 25] during the clinical course. Rebleeding within the first 4 weeks occurs in 40% if the aneurysm is not treated [6] and remains an important cause of death, even if the aim is to occlude the aneurysm early after the bleeding [27].

Coagulation factors may be involved in aneurysmal SAH and its subsequent complications. The causes of SAH without a detectable aneurysm include bleeding disorders, but the role of coagulation disorders in the occurrence of aneurysmal SAH is not yet known [26]. A possible higher risk of aneurysmal SAH has been suggested for a coagulation factor XIII subunit A Tyr204Phe polymorphism [24]. Studies with antifibrinolytic drugs in patients with SAH found that this treatment reduces the occurrence of rebleeding but increases the risk of secondary cerebral ischemia [14, 28]. Thus, antifibrinolytic drugs have an opposite effect on the risks of rebleeding and secondary cerebral ischemia.

A direct analysis of coagulation factors in SAH patients is hampered by early activation of the coagulation and fibrinolytic system following the hemorrhage [21]. Therefore, studying genetic factors may be a better approach to investigate the role of coagulation factors in the development of complications after SAH. A genetic study in SAH patients already suggested that the plasminogen activator inhibitor-1 (PAI-1) gene influencing coagulation is indeed involved in the occurrence of secondary cerebral ischemia [30]. The role of polymorphisms in coagulation factor V [5], prothrombin [22], methylenetetetrahydrofolate reductase (MTHFR, 9), coagulation factor XIII subunit A [2, 3] and subunit B [18] genes is currently unclear. The factor V Leiden and prothrombin G20210A polymorphisms are associated with an increased risk of thrombosis [5, 22], and for the factor V Leiden a decreased risk of bleeding has also been demonstrated [7, 19]. The factor V Leiden and prothrombin G20210A polymorphisms may therefore be associated with a possible decreased risk of SAH, an increased risk of secondary cerebral ischemia and possibly a decreased risk of rebleeding in SAH patients. In contrast, subunit A Val34Leu, Tyr204Phe and Pro564Leu factor XIII polymorphisms are associated with an increased risk of bleeding [2, 3] and may increase the risk for aneurysmal SAH and its subsequent rebleeding, and possibly show a decreased risk of secondary cerebral ischemia in SAH patients. The role of the MTHFR C677T polymorphism and subunit B His95Arg factor XIII polymorphism in coagulation is not (yet) clear [9, 18], but some studies have found an increased risk of thrombosis for both variants [17, 18].

The aim of this study was to investigate whether the above-mentioned polymorphisms are associated with the occurrence of aneurysmal SAH and with secondary cerebral ischemia and rebleeding in patients with aneurysmal SAH.

Methods and materials

Patient and control recruitment

Two hundred eight Dutch patients with aneurysmal SAH admitted to the University Medical Centre Utrecht were included. Aneurysmal SAH was defined by symptoms suggestive of SAH combined with evidence of subarachnoid blood on CT and a proven aneurysm on CT angiography or conventional angiography. A population-based control group was used including 925 women aged 18-49 years without a history of coronary heart disease, cerebrovascular event or peripheral vascular disease, as described in detail elsewhere [29]. The ethical review board of the University Medical Centre Utrecht approved our study protocol.

Data collection

The patient's age at the time of SAH, sex, clinical condition on admission, amount of blood on initial CT scan, and any episodes of rebleeding or secondary cerebral ischemia were recorded. For the clinical condition on admission the World Federation of Neurological Surgeons' (WFNS) scale was used [8]. The amount of blood on the CT scan on admission (within 72 h after the initial symptoms) was graded on a scale of 0 to 30 as defined by Hijdra et al. [11]. Rebleeding was defined as a sudden deterioration in the level of consciousness or a sudden increase in headache, combined with an increase of blood on CT compared with the previous CT. Secondary cerebral ischemia was defined as a gradual decline in the level of consciousness or a gradual development of new focal deficits or both, with confirmation of a new hypodensity on CT. The patients were followed up for 3 months.

Laboratory analyses

DNA was isolated from whole venous blood. Genotyping was performed using polymerase chain reaction (PCR) using previously described primers and assay conditions for the factor V Leiden (factor V G1691A) [5], prothrombin G20210A [22], MTHFR C677T [9], subunit A Val34Leu [16], Tyr204Phe and Pro564Leu factor XIII [24] and subunit B His95Arg factor XIII [18] polymorphisms. Genotyping of the variants was performed on coded DNA samples so that the patients' characteristics remained unknown to the technician.

Table 1 Patients' baseline characteristics

Characteristics	All patients (n=208)
Mean age ± SD	59.5±14.9
Women	149 (71.6%)
Poor clinical condition on admission	41 (19.7%)
Amount of cisternal blood > median of the Hijdra score	74 (35.6%)
Rebleeding	28 (13.5%)
Secondary cerebral ischemia	49 (23.6%)

SD = standard deviation

risk of secondary cerebral ischemia patients were censored in case they had a rebleeding or in case they died. Patients were censored in the analysis on the risk of rebleeding in case the aneurysm was treated by means of clipping or coiling or in case they died. The clinical condition on admission was determined as 'good' (WFNS I-III) or 'poor' (WFNS IV-V). For the amount of cisternal blood, the scores were dichotomized at the median of the Hijdra scores. As a poor clinical condition on admission and a large amount of extravasated blood increase the risk of secondary cerebral ischemia [1, 12, 23], we adjusted for these prognostic factors using their dichotomized values.

Data analyses

The risk of aneurysmal SAH was assessed as an odds ratio (OR) with corresponding 95% confidence intervals (CI). The risk of secondary cerebral ischemia and rebleeding was assessed as a hazard ratio (HR) with 95% confidence intervals (CI) using Cox regression. For both analyses, patients homozygous for the wild-type allele were compared with patients homozygous and heterozygous for the variant allele. Only for the MTHFR C677T polymorphism patients homozygous for the variant allele were compared with patients homozygous for the wild-type allele and heterozygous for the variant allele, as customary. For the assessment of the

Results

The patients' characteristics are summarized in Table 1. The mean age was 59.5 years (SD 14.9 years), and 71.6% were women. Secondary cerebral ischemia occurred in 49 (24%) patients and rebleeding in 28 (14%).

The ORs for the risk of aneurysmal SAH according to genotype are shown in Table 2. For carriers of the subunit B His95Arg factor XIII polymorphism, an increased risk of aneurysmal SAH was found with 23% of the patients homozygous and heterozygous for the variant allele compared to 17% of control subjects (OR 1.5, 95% CI 1.0–2.2, p-value 0.04). Also, carriers of the prothrombin

Table 2 Odds ratios for risk of aneurysmal subarachnoid hemorrhage according to genotype

Genotype	Patients*	Controls**	Odds ratio (95% CI)
FV Leiden	n=207	n=763	
GG	196 (94.7%)	721 (94.5%)	1 (reference)
GA and AA	11 (5.3%)	42 (5.5%)	0.9 (0.5–1.8)
Prothrombin G20210A	n=207	n=763	
GG	200 (96.6%)	745 (97.6%)	1 (reference)
GA and AA	7 (3.4%)	18 (2.4%)	1.5 (0.6–3.5)
MTHFR C677T	n=207	n=764	
CC and CT	185 (89.4%)	695 (91.0%)	1 (reference)
TT	22 (10.6%)	69 (9.0%)	1.2 (0.3–2.0)
FXIII A Val34Leu	n=208	n=747	
ValVal	122 (58.7%)	419 (56.1%)	1 (reference)
ValLeu and LeuLeu	86 (41.3%)	328 (43.9%)	0.9 (0.7–1.2)
FXIII A Tyr204Phe	n=207	n=754	
TyrTyr	188 (90.8%)	711 (94.3%)	1 (reference)
TyrPhe and PhePhe	19 (9.2%)	43 (5.7%)	1.7 (0.9–2.9)
FXIII A Pro564Leu	n=194	n=751	
ProPro	114 (58.8%)	466 (62.0%)	1 (reference)
ProLeu and LeuLeu	80 (41.2%)	285 (38.0%)	1.2 (0.8–1.6)
FXIII B His95Arg	n=196	n=730	
HisHis	151 (77.0%)	609 (83.4%)	1 (reference)
HisArg and ArgArg	45 (23.0%)	121 (16.6%)	1.5 (1.0–2.2)

*For the genotype analysis of the patients the percentage of missing genotypes is 2%

**For the genotype analysis of the controls the percentage of missing genotypes is 18%

CI = confidence interval

Table 3 Hazard ratios for risk of secondary cerebral ischemia and rebleeding after aneurysmal subarachnoid hemorrhage according to genotype

Genotype	Complication	No complication	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
FV Leiden	Secondary cerebral ischemia	No secondary cerebral ischemia		
GG	45 (23.0%)	151 (77.0%)	1 (reference)	1 (reference)
GA and AA	4 (36.4%)	7 (63.6%)	1.8 (0.6–4.9)	1.8 (0.6–5.0)
	Rebleeding	No rebleeding		
GG	26 (13.2%)	171 (86.8%)	1 (reference)	
GA and AA	1 (9.1%)	10 (90.9%)	0.6 (0.1–4.5)	NA
Prothrombin G20210A	Secondary cerebral ischemia	No secondary cerebral ischemia		
GG	48 (24.0%)	152 (76.0%)	1 (reference)	1 (reference)
GA and AA	1 (14.3%)	6 (85.7%)	0.5 (0.1–3.9)	0.5 (0.1–3.9)
	Rebleeding	No rebleeding		
GG	27 (13.4%)	174 (86.6%)	1 (reference)	
GA and AA	0 (0%)	7 (100%)	0.7 (0.1–5.4)	NA
MTHFR C677T	Secondary cerebral ischemia	No secondary cerebral ischemia		
CC and CT	47 (25.4%)	138 (74.6%)	1 (reference)	1 (reference)
TT	2 (9.1%)	20 (90.9%)	0.4 (0.1–1.5)	0.4 (0.1–1.5)
	Rebleeding	No rebleeding		
CC and CT	22 (11.9%)	163 (88.1%)	1 (reference)	
TT	4 (18.2%)	18 (81.8%)	0.6 (0.2–1.7)	NA
FXIII A Val34Leu	Secondary cerebral ischemia	No secondary cerebral ischemia		
ValVal	30 (24.62%)	92 (75.4%)	1 (reference)	1 (reference)
ValLeu and LeuLeu	18 (20.9%)	68 (79.1%)	0.9 (0.5–1.6)	0.9 (0.5–1.6)
	Rebleeding	No rebleeding		
ValVal	14 (11.4%)	109 (88.6%)	1 (reference)	
ValLeu and LeuLeu	14 (16.3%)	72 (83.7%)	1.2 (0.5–2.6)	NA
FXIII A Tyr204Phe	Secondary cerebral ischemia	No secondary cerebral ischemia		
TyrTyr	44 (23.4%)	144 (76.6%)	1 (reference)	1 (reference)
TyrPhe and PhePhe	4 (21.1%)	15 (78.9%)	0.9 (0.3–2.4)	0.9 (0.3–2.4)
	Rebleeding	No rebleeding		
TyrTyr	27 (14.3%)	162 (85.7%)	1 (reference)	
TyrPhe and PhePhe	1 (5.3%)	18 (94.7%)	0.3 (0.0–2.5)	NA
FXIII A Pro564Leu	Secondary cerebral ischemia	No secondary cerebral ischemia		
ProPro	31 (27.2%)	83 (72.8%)	1 (reference)	1 (reference)
ProLeu and LeuLeu	17 (21.3%)	63 (78.8%)	0.8 (0.4–1.4)	0.8 (0.4–1.4)
	Rebleeding	No rebleeding		
ProPro	12 (10.5%)	102 (89.5%)	1 (reference)	
ProLeu and LeuLeu	14 (17.5%)	66 (82.5%)	1.8 (0.8–4.2)	NA
FXIII B His95Arg	Secondary cerebral ischemia	No secondary cerebral ischemia		
HisHis	33 (21.9%)	118 (78.1%)	1 (reference)	
HisArg and ArgArg	14 (31.1%)	31 (68.9%)	1.5 (0.8–2.8)	1.6 (0.8–2.9)
	Rebleeding	No rebleeding		
HisHis	18 (11.8%)	134 (88.2%)	1 (reference)	
HisArg and ArgArg	8 (17.8%)	37 (82.2%)	1.1 (0.4–2.9)	NA

*Adjusted for clinical condition on admission and amount of blood on initial CT scan.

CI = confidence interval; NA = not applicable

G20210A and the subunit Tyr204Phe factor XIII polymorphisms showed an increased risk of aneurysmal SAH, but these differences did not reach statistical significance. Carriers of the factor V Leiden (factor V G1691A), MTHFR C677T, subunit A Val34Leu and Pro564Leu factor XIII polymorphisms did not have a higher risk of aneurysmal SAH.

Table 3 shows the HR for the risk of secondary cerebral ischemia and rebleeding according to genotype. A clear relation with the risk of secondary cerebral ischemia and of rebleeding could not be established for any of these genetic variants. However, for some polymorphisms, an association was observed, although with wide confidence intervals. Notably, for the factor V Leiden polymorphism that has been proven to be associated with an increased risk of thrombosis in previous studies [5], we found a moderately increased risk of secondary cerebral ischemia (crude HR 1.8, 95% CI 0.6–4.9 and adjusted HR 1.8, 95% CI 0.6–5.0) and an opposite lower risk of rebleeding (HR 0.6, 95% CI 0.1–4.5), although this did not reach statistical significance.

Discussion

This study was performed to analyze whether genes influencing coagulation are associated with the occurrence of aneurysmal SAH and with the risk of secondary cerebral ischemia and rebleeding in patients with aneurysmal SAH. Polymorphisms in the factor V Leiden, prothrombin G20210A, MTHFR C677T, subunit A Val34Leu, Tyr204Phe and Pro564Leu factor XIII and subunit B His95Arg factor XIII were investigated.

With regard to the risk of aneurysmal SAH, we found that aneurysmal SAH patients are more often carriers of the subunit B His95Arg factor XIII polymorphism compared to controls. This suggests that carriers of the subunit B His95Arg factor XIII polymorphism have an increased risk of aneurysmal SAH. As yet not much is known about the His95Arg polymorphism in the factor XIII subunit B. One study suggested the Arg95 variant to be associated with an increased risk of thrombosis in combination with an increased factor XIII subunit B dissociation [18]. Our finding that the His95Arg factor XIII subunit B polymorphism is associated with an increased risk of aneurysmal SAH is not consistent with the previous observation of an increased risk of thrombosis [18]. Further studies investigating the influence of this variant on the risk of thrombosis and bleeding are needed. Ideally, we would have analyzed data on the coagulation system and the overall thrombosis and bleeding risk in our patient group and related those data to the polymorphisms studied. Unfortunately, we do not have these data for our studied patients.

On analyzing the association of genes influencing coagulation with the occurrence of secondary cerebral ischemia and rebleeding in patients with aneurysmal SAH, no unequivocal, large effects could be demonstrated. This may be explained by the fact that our study population was relatively small. However, larger studies are difficult to perform as these should include approximately over 1,000 patients to demonstrate the small effects (HR of 1.5 or smaller) of the coagulation factors.

Our findings do suggest that, consistent with the increased risk of thrombosis of the factor V Leiden polymorphism [5], factor V Leiden is associated with an increased risk of secondary ischemia and an opposite decreased risk of rebleeding in patients with aneurysmal SAH. These results should be interpreted with caution as the 95% CIs were wide for all the HR calculated in this study.

Aneurysmal SAH patients who died soon after admission could not be included in the present study because they could not be asked to participate. Our results therefore apply to a population of patients who survived the initial hours after the hemorrhage. Not including these patients may have biased our results as some of these patients may have died because of early rebleeding within hours of the initial hemorrhage [10, 13], leading to an under representation of patients with rebleeding in our study.

The results of this study suggest that genetic factors are involved in coagulation in the occurrence of aneurysmal SAH as we found evidence that carriers of the subunit B His95Arg factor XIII polymorphism are at increased risk. Larger studies should confirm our results. For the other studied polymorphisms involved in coagulation, no association with the occurrence of aneurysmal SAH or with the occurrence of secondary cerebral ischemia or rebleeding after aneurysmal SAH could be demonstrated.

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