Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: the role of coagulation and fibrinolysis

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Summary (English)
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Patients with aneurysmal subarachnoid hemorrhage (SAH) are at risk to develop complications, especially within the first two weeks after the hemorrhage. Delayed cerebral ischemia (DCI) is a complication which occurs in about 30% of SAH patients, leading to symptoms such as aphasia, hemiparesis, or impaired level of consciousness. The cause of DCI remains unknown, however many clinicians still are convinced that DCI is caused by vasospasm. Indeed, several studies found a strong association between radiologically confirmed spasm and clinical signs of DCI, but an association is not a causal relation. In this thesis it is shown that microthrombosis, as a result of activation of the coagulation cascade and impairment of fibrinolytic activity, plays a role in the development of DCI.

Part 1. Pathogenesis of delayed cerebral ischemia

An overview of clinical and autopsy studies (Chapter 2) showed that DCI cannot always be attributed to vasospasm. For example, therapies aiming at radiologic vasospasm, such as endothelin receptor antagonists, were not successful since no clear effect on DCI was observed. In contrast, drugs not aiming at vasospasm, such as antifibrinolytic agents, influenced the incidence of DCI. Apparently, other factors besides vasospasm also play an important role, for example microthrombosis, resulting from increased coagulation activity (as a result of platelet activation and fibrin formation), impairment of the fibrinolytic cascade, inflammatory processes, and endothelium dysfunction. Interestingly, clinical studies show that DCI is associated with activation of the coagulation cascade within a few days after SAH, preceding the time window during which vasospasm occurs. Not only results of clinical studies are suggestive for the presence of microthrombi, since the presence of microthrombi has been confirmed by several autopsy studies. Patients with SAH who die from cerebral ischemic complications have significantly more microthrombi than patients who die from rebleeding or acute hydrocephalus, suggesting that microthrombi indeed play an important role in the pathogenesis of DCI.

Presently, several factors are known to predict the occurrence of DCI, such as loss of consciousness during the ictus of SAH, a low Glasgow Coma Score on admission in hospital, and a large amount of subarachnoid and intraventricular blood on CT imaging of the brain on admission. Despite these predictors, the question remains why some patients develop DCI and others not. A possible explanation might be that genetic factors are involved. Chapter 3 showed that patients with a genetic predisposition for impaired fibrinolytic activity, namely patients with the 4G allele in the plasminogen activator inhibitor (PAI)-1 polymorphism, are at increased risk to develop DCI compared to patients homozygous for the 5G allele (relative risk 3.3; 95% confidence interval 1.1-10.0). A trend was noted toward an increased incidence of poor outcome in patients with the 4G allele (relative risk 1.2; 95% confidence interval 0.7-2.2).
Elevated PAI-1 levels have also been associated with poor outcome in other acute life-threatening diseases, such as severe (head) trauma, meningococcal sepsis, meningitis, preeclampsia, malaria, and burns. In acute stressful events PAI-1 seems to act as an acute-phase reactant. In these circumstances, PAI-1 concentrations in patients with the 4G/4G genotype are approximately 2- to 4-times higher than in patients with the 5G/5G genotype, resulting in impaired fibrinolysis. During the acute illness the formation of microthrombi, resulting in disseminated intravascular coagulation, is no longer counteracted by the fibrinolytic system, finally leading to multiorgan failure. In patients with aneurysmal SAH, elevated PAI-1 levels may be decisive in the development of microthrombi. Since not all patients with vasospasm have DCI, the development of microthrombi in patients with vasospasm may determine whether or not DCI will occur.

Since acute stressful events might lead to microthrombosis as a result of higher PAI-1 levels and thereby impaired fibrinolytic activity, Chapter 4 investigated the association between the stress response after aneurysmal SAH and the occurrence of DCI. The extent of stress response was measured by plasma levels of cortisol, which is a glucocorticoid hormone secreted during the stress response. The hypothesis was that increased cortisol levels could play a pivotal role in the development of DCI, even more because in patients with aneurysmal SAH, high glucose levels, elevated blood pressure, and endothelium dysfunction are associated with the occurrence of DCI. High glucose levels, elevated blood pressure, and endothelium dysfunction all are physiological reactions of increased cortisol secretion. Indeed, increased cortisol levels early after SAH were found to be of prognostic value for the occurrence of DCI. The association between cortisol and DCI remained significant after adjusting in separate models for other known predictors of DCI occurrence, namely the amount of cisternal and ventricular blood on admission CT scan, loss of consciousness during ictus, and a low Glasgow Coma Score on admission. The increased stress response probably not only results in DCI as a result of impaired fibrinolytic activity, but also as a result of endothelium dysfunction.

In patients with thrombotic thrombocytopenic purpura (TTP), microthrombosis is caused by a deficiency in a protease called A Disintegrin and Metalloprotease with ThromboSpondin motif (ADAMTS13). Under normal conditions ADAMTS13 cleaves UltraLarge von Willebrand Factor (ULvWF) multimers after its secretion from Weibel-Palade bodies in the vascular endothelium and from α-granules of platelets. Von Willebrand factor (vWF) is a glycoprotein which induces platelet adhesion and aggregation at sites of vascular injury or under stress conditions. Since large vWF multimers are more potent mediators of platelet thrombus formation than small vWF multimers, cleavage of ULvWF by ADAMTS13 results in lower-molecular weight vWF forms with reduced adhesive potential. In contrast, an ADAMTS13 deficiency, such as in patients with TTP, leads to higher concentrations of ULvWF, which ultimately results in microthrombosis and hereby ischemic complications, such as ischemic stroke.

The question is whether a similar pathogenesis of microthrombi as described in TTP is also responsible for microthrombi in SAH (Chapter 5). Patients with DCI after aneurysmal SAH
were shown to develop significantly higher von Willebrand factor antigen levels and decreased ADAMTS13 activity within 10 days after the hemorrhage compared to patients without DCI. Since vWF is a measure of endothelium function and an indicator of early activation of the coagulation pathway, these results suggest that microthrombosis plays a role in the pathogenesis of DCI after aneurysmal SAH.

The mechanism by which ADAMTS13 activity decreases in patients with DCI remains to be elucidated. A plausible explanation for the decreased ADAMTS13 activity is an increased use of ADAMTS13 as a result of higher von Willebrand factor antigen levels. However, no correlation was found between ADAMTS13 activity and vWF antigen. Furthermore, the decreased ADAMTS13 activity might be caused by thrombin or plasmin, present in the subarachnoid space after the hemorrhage. However, no correlation was found between ADAMTS13 activity and prothrombin fragment 1+2, and therefore it is unlikely that the decrease of ADAMTS13 activity in DCI is caused by thrombin. ADAMTS13 activity might also be suppressed by IL-6, since IL-6 inhibits the cleavage of ULvWF by ADAMTS13 under flow conditions. In patients with aneurysmal SAH increased levels of IL-6 are associated with DCI. However, no correlation was found between ADAMTS13 activity and IL-6. Finally, decreased ADAMTS13 activity might be caused by locally present neutralizing antibodies against ADAMTS13, however ADAMTS13 antibodies have never been studied in patients with SAH.

Part 2. Treatment options for delayed cerebral ischemia

TREATMENT WITH CALCIUM ANTAGONISTS

Presently, the only drug that decreases the incidence of DCI and poor outcome after SAH is the dihydropyridine calcium antagonist nimodipine. This beneficial effect was considered to be caused by an effect on vasospasm, but a systematic review showed that nimodipine did not affect vasospasm. Later it was shown that nimodipine increases fibrinolytic activity after SAH.

In a systematic review described in Chapter 6 other dihydropyridine calcium antagonists also appeared to increase fibrinolytic activity. The magnitude of fibrinolytic activity of dihydropyridine calcium antagonists is only modest compared with the fibrinolytic activity exerted by well-known fibrinolytics such as urokinase and recombinant tissue plasminogen activator. In a sensitivity analysis dihydropyridine calcium antagonists had no fibrinolytic activity in healthy individuals. Probably, the magnitude of fibrinolytic activity of dihydropyridines is limited to an improvement of impaired fibrinolysis in acute disorders such as aneurysmal SAH. By improving the impaired fibrinolytic system, treatment with dihydropyridine calcium antagonists may lead to a decreased incidence of DCI in patients with SAH. The results of this systematic review may also implicate that patients with SAH treated with nimodipine have an increased rebleeding rate. However, a Cochrane analysis studying the effect of calcium antagonists in SAH showed a tendency toward a reduced
The incidence of rebleeding.20 The authors suggested this might be a confounding effect as a result of protection against ischemia, which allows earlier intervention to secure the aneurysm by clipping or coiling, and consequently eliminate the risk of rebleeding.

For a long time it was also believed that nimodipine could be an effective treatment option to improve outcome in patients with traumatic subarachnoid hemorrhage. Since the results of the largest study investigating this drug for this indication were only partly presented at a conference and were not completely published, considerable debate existed for a long time whether or not nimodipine was effective for this indication. We managed to obtain additional data from several trials, including unpublished data from the largest trial. These data were incorporated in a systematic review, of which the results are described in Chapter 7. The results of this systematic review showed that nimodipine does not improve outcome in this group of patients. The different effects of nimodipine in patients with aneurysmal and traumatic SAH can be explained by several factors. First, aneurysmal and traumatic SAH are different entities. In patients with aneurysmal SAH, DCI may occur in the weeks after the hemorrhage. This complication is associated with an increased risk of poor outcome. However, DCI is less common in patients with traumatic SAH. Nimodipine is probably only effective for DCI and might therefore be effective only in patients with aneurysmal SAH. Furthermore, since nimodipine exerts a profibrinolytic effect in patients with aneurysmal SAH, it could be that this drug has a deleterious effect in patients with traumatic SAH, by inducing cerebral and systemic hemorrhages.

**Treatment with statins**

This thesis showed that the pathogenesis of DCI after aneurysmal SAH is multifactorial, with several pathways ultimately leading to DCI. Therefore, since the coagulation pathway, fibrinolysis, endothelium dysfunction, and inflammation all seem to play a role in the pathogenesis of DCI, the hypothesis is that only drugs with pleiotropic effects, influencing all pathways, will have a major beneficial effect in the prevention and treatment of DCI. Since statins are supposed to be drugs with pleiotropic effects, an exploratory, randomized, double-blind placebo-controlled study was designed in which the biological effects of statins were investigated (Chapter 8). Interestingly, no evidence of acute pleiotropic effects by statins was shown in patients with aneurysmal SAH. An explanation for this finding might be that a treatment period of 14 days is too short to exert pleiotropic effects. On the other hand, biological effects of statins may not have been detected because systemic levels of biomarkers were measured, instead of local cerebral levels. It is possible that statins exert pleiotropic effects in cerebral blood vessels, but that this effect was diluted because of systemic biomarker measurements. The results may be different when blood withdrawals are taken from the jugular vein. When our study protocol was developed, jugular vein blood withdrawals were not planned, because this may lead to potentially dangerous complications. Nevertheless, this study could not confirm the previously described effects on the occurrence of DCI and poor outcome. A phase III randomized placebo-controlled trial, which now is in progress, will probably answer the question whether or not statins are beneficial in patients with aneurysmal SAH.
To broaden the focus in the investigation of possible pleiotropic effects of statins, a systematic review was performed (Chapter 9) on the incidence of hemorrhagic stroke in patients with a history of cerebrovascular disease treated with statins. The results of this systematic review showed that statin use in this group of patients is associated with an increased risk of future hemorrhagic strokes. These results seem to be in contrast with the observation that there are no acute biological effects of statins in patients with aneurysmal SAH. This can be explained as follows: first, patients with aneurysmal SAH were treated during a maximum of 14 days, which is much shorter than in the studies that investigated the effect of statins for secondary stroke prevention. It might be that it takes at least several weeks to months before statins have a profibrinolytic or anticoagulant profile. Second, cholesterol might be important in vessel wall integrity, and that statin treatment therefore leads to hemorrhagic stroke in the long term in patients with a history of cerebrovascular disease. Other systematic reviews investigating the effect of statins on hemorrhagic stroke mainly included patients without a history of cerebrovascular disease and found no increased risk of hemorrhagic stroke.23,24 Since patients with a prior stroke or transient ischemic attack often have lacunar strokes from cerebral small vessel disease, the hypothesis is that especially this group of patients is vulnerable to hemorrhagic stroke as a result of statin treatment. Indeed, in a post-hoc subgroup analysis of the ‘Stroke Prevention by Aggressive Reduction in Cholesterol Levels’ (SPARCL) study, an increased risk of hemorrhagic stroke was observed in patients with cerebral small vessel disease (hazard ratio 4.99, 95% CI 1.71 to 14.61) treated with statins.25
References


