Biochemical and genetic markers after subarachnoid haemorrhage

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Avhandlingen baseras på följande delarbeten:

I.   Csajbok, L. Z., Nylen, K., Ost, M., Sonander, H., & Nellgard, B. (2015). **In-hospital C-reactive protein predicts outcome after aneurysmal subarachnoid haemorrhage treated by endovascular coiling**. *Acta Anaesthesiol Scand, 59*(2), 255-264. doi: 10.1111/aas.12441

II. Csajbok, L. Z., Nylen, K., Ost, M., Blennow, K., Zetterberg, H., Nellgard, P., & Nellgard, B. (2015). ***Apolipoprotein E* polymorphism in aneurysmal subarachnoid haemorrhage in West-Sweden**. *Acta Neurol Scand, Epub. Ahaed of publication. doi: 10.1111/ane.12487*

III. Olsson, S., Csajbok, L. Z., Jood, K., Nylen, K., Nellgard, B., & Jern, C. (2011). **Association between genetic variation on chromosome 9p21 and aneurysmal subarachnoid haemorrhage**. *J Neurol Neurosurg Psychiatry, 82*(4), 384-388. doi: 10.1136/jnnp.2009.187427

IV. Csajbok, L. Z., Nylen, K., Ost, M., Blennow, K., Zetterberg, H., Nellgard, P., & Nellgard, B. (2015). **Biochip Neuromarker Array, a possible monitoring and prognostic tool after subarachnoid hemorrhage.** *Manuscript.*

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ABSTRACT

Background: Subarachnoid haemorrhage is a devastating disease with high morbidity and mortality despite novel treatment options are available. There are no established methods to measure the brain damage occurring due to the bleed and its complications and to predict early neurological outcome of the disease. Genetic predisposition is suggested as one of the determinants of outcome.

Aim: The aim of this thesis was to investigate nine biochemical neuromarkers' course and development in the early phase of aneurysmal subarachnoid haemorrhage (aSAH) with special emphasis on C-reactive protein (CRP) and to test if they could be used as markers of disease progression and possibly long-term outcome. As a tool, we aimed to test a novel multiple biochip array for simultaneous monitoring these markers. Finally, we intended to elucidate the effect of two chromosomes with different genetical polymorphisms on the incidence and development of the disease. (Apolipoprotein E and region 9p21)

Patients and methods: We have consecutively included patients admitted to the Sahlgrenska University Hospital for SAH, where the causative reason was a ruptured intracranial aneurysm. We have recorded the patients' admission status with neurological scales and radiological scores for the severity of the haemorrhage. We collected blood sample for determining genetics and continued to collect serum-samples for biochemical marker detection on day0-4, 6, 8, and finally once on days 11-14. We noted the complication cerebral vasospasm (CVS). A long-term follow-up was performed after one year with detailed neurological examinations. For the genetic studies matching controls were recruited among healthy individuals.

Results: In 98 endovascularly treated patients, we described the pattern of CRP increase after aSAH. It peaked on day3 with a mean value of 53 mg/l and decreased successively without normalising. This pattern was not dependent of infectious status. We noted a difference in increase between the patients with favourable and unfavourable disease development (*i.e.* CVS) and long-term outcome, focal neurology and need of assistance with daily activities (ADL) after one year. In a multivariate regression model with initial neurology, radiological severity, CRP was the only parameter showing significant OR. (OR: 1.25/10 units). We could present a predictive curve for poor outcome in relation to CRP values. Furthermore, we tested a 9 potential neuromarker-containing panel in a test series of 41 patients. Six of these markers, TNFR1, IL-6, hs-CRP, DDMR, NGAL and FABP showed significant correlation to CVS development and different outcome results. Four of the markers (TNFR1, hs-CRP, NGAL & FABP) had moderate or good predictive qualities. In a genetic study, ApoE polymorphism on the 19th chromosome, did not present any effect either on the incidence of aneurysm rupture or CVS development and outcome parameters after aSAH in 154 patients and 221 controls. However we have found a single nucleotide polymorphism (SNP) rs10757278 on the 9th chromosome p21 region, which even after controlling for hypertension and smoking showed a significant negative effect on aneurysm rupture in 183 patient and 366 controls

Conclusion: CRP proved to be a useful marker for following the course of aSAH and may be applicable for predicting complication or outcome. The tested biochip-neuropanel could be a valuable addition to neuro-monitoring during the initial phase of the aSAH. Finally, not *APOE* polymorphism, but a genetic variant on 9p21 chromosome region affected negatively the risk of aneurysm rupture in West Sweden.

Keywords: subarachnoid haemorrhage, biochemical marker genetic marker, outcome