ABSTRACT

The hemostatic pathway in ischemic stroke

Clinical studies of genetic variation and plasma protein measurements

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Although stroke is a common cause of death and disability in adults, there are few studies on stroke compared to other common diseases. A stroke could be either ischemic or hemorrhagic, but even within these two groups, disease etiology shows heterogeneity. In ischemic stroke, the different etiologic subtypes represent different underlying pathophysiologic mechanisms. However, the formation of a thrombus is a key mechanistic event in the majority of ischemic stroke events. Therefore, the aim of the present thesis was to test the hypothesis that hemostatic gene polymorphisms and/or plasma levels of hemostatic proteins are associated with ischemic stroke. A second aim was to investigate whether the associations differ between the etiologic subtypes of ischemic stroke.

The studies were based on the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS), which includes 844 patients with ischemic stroke and 668 controls, all younger than 70 years of age. Patients were classified into the major etiologic subtypes of ischemic stroke, *i.e.* large-vessel disease, small-vessel disease, cardioembolic stroke and cryptogenic stroke. Genotyping was carried out using both low- and high-throughput methods. Plasma levels of hemostatic proteins were determined by immunological methods.

The initial studies in this thesis focused the von Willebrand factor (VWF) as well as the VWF-cleaving protease ADAMTS13. We found that ADAMTS13 gene variation was associated with overall ischemic stroke and with the etiologic subtype of cryptogenic stroke. Regarding VWF, the plasma levels were increased in overall ischemic stroke, as well as in all four major etiologic subtypes, as compared to the controls. There were also significant differences in VWF levels between the subtypes, highlighting the importance of considering etiologic subtypes in ischemic stroke studies. ABO blood group strongly influences VWF plasma levels, but we found no association between ABO and ischemic stroke. We then went on by analyzing plasma levels and gene variants of the newly discovered factor VII-activating protease (FSAP). FSAP gene variation influenced the plasma levels, but was not associated with ischemic stroke. Plasma FSAP on the other hand, was independently associated with overall ischemic stroke and with all major etiologic subtypes, indicating that FSAP is involved in ischemic stroke independent of the underlying etiology. We also observed an association between coagulation factor XI (FXI) gene variants and overall ischemic stroke up to 70 years of age, suggesting that FXI might be involved in ischemic stroke with a relatively young age of onset.

In conclusion, these results support a role for prothrombotic mechanisms in the pathophysiology of ischemic stroke. These mechanisms appear to be of importance for all four major etiologic subtypes of ischemic stroke, while we also show that there are subtype-specific differences.

Keywords: ischemic stroke, etiologic subtypes of ischemic stroke, genetics, SNP, hemostasis, prothrombotic, ADAMTS13, VWF, ABO blood group, FSAP, FXI

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