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Biomarkers and risk of intracerebral hemorrhage
– Population-based studies in northern Sweden

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Akademisk avhandling

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Abstract
Background: Intracerebral hemorrhage (ICH) is associated with a high morbidity and mortality. Treatment options for the condition are limited. It is possible that individuals at increased risk of ICH could be identified using biomarkers, for example markers of hemostasis and fibrinolysis. Even if these biomarkers are not part of the causal chain, they could be used as risk indicators to better define high-risk groups. Another approach could be to measure already established risk markers for ICH, such as self-reported alcohol consumption, using a blood biomarker.
Aims: The aim of this thesis was to investigate potential biomarkers and risk of ICH. Specific aims were to evaluate the associations between factor XII (FXII), D-dimer, von Willebrand factor (VWF), ABO blood groups with focus on blood group O, phosphatidylethanol (PEth), and risk of ICH.
Methods: In our first study, aiming to investigate the association between FXII and risk of hemorrhagic stroke, we followed participants of the health examination northern Sweden MONItoring trends and determinants in CArdiovascular disease (MONICA) performed in 1994 as a cohort until 2011. FXII concentrations were measured in blood samples drawn at the baseline health examination where the participants also answered a questionnaire regarding lifestyle factors and medical history. Diagnosis codes from the National Patient Register and the Swedish Cause of Death Register were used to find cases of hemorrhagic stroke, defined as ICH or subarachnoid hemorrhage. In the subsequent studies, the associations between biomarkers (FXII, D-dimer, VWF, ABO blood groups, and PEth) and risk of ICH were investigated using a matched, nested case-referent design including individuals that had participated in the Västerbotten Intervention Programme, the MONICA and the Mammography Screening Project in 1985–2007. The participants donated blood samples at baseline for future research which were stored at -80 degrees C until biomarker analyses. The majority of the participants also underwent a baseline health examination including a questionnaire. First-ever ICH diagnoses during the study period 1985–2007 were validated using medical records and autopsy reports. To each case, two referents were matched for age, sex, geographical region, health examination date and health examination setting.
Results: In the cohort study of the association between FXII and risk of hemorrhagic stroke, 1,852 participants were included among which 30 experienced a hemorrhagic stroke event. There was an association between high FXII concentrations and risk of hemorrhagic stroke in a multivariable model (hazard ratio 1.51; 95% confidence interval [CI] 1.03–2.21 per standard deviation [SD] of FXII). In the case-referent study of the association between FXII and risk of ICH, 70 cases with ICH and 137 matched referents were included. We found no association between FXII and risk of ICH in a multivariable model (odds ratio [OR] 1.06; 95% CI 0.57–1.97 per SD of FXII). The study of the association between D-dimer and risk of ICH included 141 cases and 255 matched referents. We found an association between D-dimer and risk of ICH in a multivariable model (OR 1.36; 95% CI 1.05–1.77 per SD of D-dimer). When stratifying the analysis for time between blood sampling and ICH event in tertiles, the association remained significant in the cases with the shortest time between blood sampling and ICH event in a multivariable model (OR 1.78; 95% CI 1.05–3.05 per SD of D-dimer). The study investigating the association between VWF and risk of ICH included 139 cases and 276 referents. We found no association between VWF and risk of ICH in a multivariable model (OR 0.85; 95% CI 0.54–1.34 per SD of VWF). In the analysis investigating the associations between ABO blood groups and risk of ICH, 162 cases and 317 referents were included. We found no association between blood group O compared to non-O blood groups and risk of ICH (OR 0.96; 95% CI 0.65–1.42). In the study of the association between PEth concentrations and risk of ICH, 97 cases and 180 referents were included. There was an association between PEth concentrations > 0.30 μmol/L compared to < 0.01 μmol/L and risk of ICH in a multivariable model (OR 4.64; 95% CI 1.49–14.40).
Conclusions: High concentrations of D-dimer and PEth are associated with an increased risk of ICH. Our conclusion of the two studies investigating the association between FXII and risk of hemorrhagic stroke and ICH respectively is that there is no association between FXII and risk of ICH. We found no association between VWF or blood group O and risk of ICH.

Keywords
Intracerebral hemorrhage, hemorrhagic stroke, factor XII, D-dimer, von Willebrand factor, ABO blood groups, phosphatidylethanol, alcohol, risk markers, biomarkers

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