

Ischemic Stroke Outcomes

Analyses of Protein and Genetic Biomarkers

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, fredagen den 10 maj 2019, klockan 9.00

av Annie Pedersen

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Avhandlingen baseras på följande delarbeten:

- I. Pedersen A, Redfors P, Lundberg L, Gils A, Declercq PJ, Nilsson S, Jood K, Jern C. Haemostatic biomarkers are associated with long-term recurrent vascular events after ischaemic stroke. *Thromb Haemost.* 2016;116: 537-543.
- II. Pedersen A, Stanne TM, Redfors P, Viken J, Samuelsson H, Nilsson S, Jood K, Jern C. Fibrinogen concentrations predict long-term cognitive outcome in young ischemic stroke patients. *Res Pract Thromb Haemost.* 2018;2:339-346.
- III. Pedersen A, Stanne TM, Nilsson S, Klasson S, Rosengren L, Holmegaard L, Jood K, Blennow K, Zetterberg H, Jern C. Circulating neurofilament light in ischemic stroke: Temporal profile and outcome prediction. *Submitted manuscript.*
- IV. Söderholm M*, Pedersen A*, Lorentzen E, Stanne TM, Bevan S, Olsson M, Cole JW, Fernandez-Cadenas I, Hankey GJ, Jimenez-Conde J, Jood K, Lee J-M, Lemmens R, Levi C, Mitchell BD, Norrving B, Rannikmäe K, Rost NS, Rosand J, Rothwell PM, Scott R, Strbian D, Sturm JW, Sudlow C, Traylor M, Thijs V, Tatlisumak T, Woo D, Worrall BB, Maguire JM**, Lindgren A**, Jern C**, on behalf of the International Stroke Genetics Consortium, the NINDS-SiGN Consortium, and the Genetics of Ischaemic Stroke Functional Outcome (GISCOME) network. Genome-wide association meta-analysis of functional outcome after ischemic stroke. *Neurology*, 2019;92:e1271-e1283. *These authors contributed equally to this work. **These authors jointly supervised this work.

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The overall aim of this thesis was to identify novel biomarkers for ischemic stroke outcomes. The specific aims were to test the hypotheses that circulating concentrations of hemostatic biomarkers predict the long-term post-stroke risk of recurrent vascular events/death (paper I) and/or cognitive impairment (paper II) and that circulating concentrations of a marker of neuronal damage (neurofilament light chain, NfL) predict post-stroke functional and neurological outcomes (paper III) as well as to identify genetic variants associated with post-stroke functional outcome through a genome wide association study (GWAS) approach (paper IV).

Papers I-III are based on the first 600 cases and 600 controls recruited to the Sahlgrenska Academy Study on Ischemic Stroke, which includes consecutive ischemic stroke cases aged 18-69 years and sex- and age-matched population-based controls. In cases, blood sampling was performed in the acute phase, after three months, and in a subset also 7 years post-stroke. Controls were sampled once. These blood samples were used to analyze the protein and genetic biomarkers investigated in this thesis. Vascular events and death up to 14 years after inclusion were identified. In cases, functional and neurological outcomes were assessed at 3 months by the modified Rankin scale (mRS) and the NIH Stroke Scale (NIHSS), respectively. At 2 years, the mRS was assessed again, and in a subsample, long-term (7-year) outcomes were assessed by mRS and NIHSS. The 7-year follow-up also included cognitive testing with the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) and Trailmaking Test. Paper IV was based on a GWAS approach, i.e. genetic variations spread throughout the entire genome were analyzed with respect to their association to 3-month post-stroke functional outcome in a hypothesis free manner. This study was performed within the Genetics of Ischemic Stroke Functional Outcome (GISCOME) network, and included 6,165 ischemic stroke cases from 12 studies in Europe, USA and Australia.

In paper I, we found that plasma levels of hemostatic protein biomarkers were associated with vascular death and coronary events, but not with recurrent stroke. In paper II, we found that, in cases <50 years at index stroke, higher concentrations of the hemostatic protein fibrinogen were independently associated with worse cognitive outcome. In paper III, we found that acute phase and 3-month serum levels of NfL were independently associated to NIHSS and mRS both in short- and long-term follow-up. In paper IV, we identified one genetic variant associated with functional outcome (mRS score 0-2 vs 3-6) at genome-wide significance. In addition, several genetic variants demonstrated suggestive associations, and some of these are located within or near genes with experimental evidence of influence on ischemic stroke volume and/or brain recovery.

In conclusion, the results from this thesis demonstrate associations between circulating protein levels as well as genetic markers and ischemic stroke outcomes. These results add knowledge on potential mechanisms influencing outcomes after ischemic stroke and may in the long run contribute to a more personalized post-stroke management.

Keywords: Stroke, Prognosis, Biomarkers, Genetics, Genome-Wide Association Study