

Inflammation-related protein biomarkers in ischemic stroke

Akademisk avhandling

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av Annelie Angerfors

Fakultetsopponent:

Professor Jemma Hopewell

Oxfords Universitet, Storbritannien

Avhandlingen baseras på följande delarbeten:

- I. Stanne TM, Angerfors A, Andersson B, Brännmark C, Holmegaard L, Jern C. Longitudinal study reveals long-term proinflammatory proteomic signature after ischemic stroke across subtypes. *Stroke*. 2022;53:2847-2858.
- II. Angerfors A, Brännmark C, Lagging C, Tai K, Svedberg RM, Andersson B, Jern C**, Stanne TM**. Proteomic profiling identifies novel inflammation-related plasma proteins associated with ischemic stroke outcome. *Journal of Neuroinflammation*. 2023;20(1):224.
- III. Angerfors A*, Granelli B*, Klasson S, Nguyen H, Brännmark C, Andersson B, Stanne TM**, Jern C**. Elevated acute-phase plasma levels of S100A12 [EN-RAGE] are associated with increased risk of vascular recurrence after ischemic stroke. *Submitted manuscript*.
- IV. Angerfors A, Andersson B, Klasson S, Chong M, Jern C**, Stanne TM**. Genetically determined levels of inflammation-related proteins and functional outcome after ischemic stroke: A Mendelian Randomization study. *Submitted manuscript*.

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**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN**



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Abstract

Ischemic stroke is a leading cause of death and disability worldwide. Inflammation plays a role in both ischemic stroke pathophysiology and response to cerebral injury. However, the mechanisms remain inadequately understood and few inflammation-related proteins have been analyzed in clinical cohorts. This thesis aims to investigate a broad range of inflammation-related proteins in ischemic stroke and its subtypes, their associations with functional outcome and vascular recurrence, and their potential causal relationships with functional outcome. The studies rely on two hospital-based cohorts: the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS) and its continuation (SAHLSIS 2). Plasma levels of inflammation-related proteins were measured by a proximity extension assay.

Paper I studied 65 plasma proteins in ischemic stroke patients compared to controls in a longitudinal study. It identified over 30 proteins that were elevated in cases across all timepoints, even in the long-term, which could reflect underlying pathophysiological processes. Subtype-specific patterns were also observed for some proteins. Paper II investigated the relationships between acute-phase levels of the 65 proteins and functional outcome 3 months post-stroke. It revealed 20 proteins that were associated with outcome, several with experimental evidence indicating a role in injury or recovery after stroke. Paper III identified S100A12 as a novel biomarker for vascular recurrence, showing that elevated levels increased the risk. Paper IV employed a two-sample Mendelian randomization design to investigate potential causal relationships between the 20 proteins identified in Paper II and functional outcome. This study provided evidence for causal associations between genetically determined levels of four proteins, including S100A12, and functional outcome.

In conclusion, this thesis demonstrates that inflammation-related plasma proteins have diverse patterns after ischemic stroke and identifies several potential biomarkers for prediction of functional outcome and vascular recurrence. These results advance our understanding of the role of inflammation in ischemic stroke and may guide the development of novel therapeutic strategies for improved stroke care.

Keywords: Stroke, Inflammation, Biomarkers, Prognosis