Department of Clinical Neuroscience
Molecular and Clinical Markers in Ischaemic Cerebrovascular Disease

AKADEMISK AVHANDLING
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Ischaemic stroke and TIA, together labelled as Ischaemic Cerebrovascular Disease (ICVD), is a heterogeneous, complex disorder with great impact on morbidity and mortality worldwide. Genetic predisposition and environmental factors interact and confer susceptibility to different pathologies that are associated with increased ICVD risk. The most common aetiological mechanisms include large vessel atherosclerosis, sources of cardioembolism and small vessel disease. Distinct pathologies underlying ICVD may occur alone or co-exist in various combinations where their causal relation to the actual ischaemic event is difficult to determine. The TOAST system has been the most widely accepted classification approach that assigns patients in one of the three main aetiological subtypes, if evidence for a causal relation exists, or to unknown if the investigation has been inconclusive. The ASCO system has recently suggested a different approach by which all the three pathologies are evaluated and graded for the likelihood to have a causative association with the ischaemic event. Related comorbidities, risk factor profile, treatment choices and prognosis differ in each aetiological subtype of ICVD, yet with several overlapping features. One common aspect, though with diverse pathways, involves inflammatory mechanisms that contribute to the initiation and progress of pathologies mediating ICVD, and have an ambiguous role in brain tissue damage during cerebral ischaemia. Moreover, factors of coagulation and metabolism have been suggested to correlate with aetiological subtypes of ICVD and to serve as predictors of long-term disability. The purpose of this project was to investigate the role of genetic and blood-based biomarkers in ICVD susceptibility, aetiology and prognosis.

Ischaemic stroke and TIA patients admitted over different periods in the stroke-unit of Karolinska University Hospital in Huddinge, as well as healthy individuals comprised the population of our studies. In the first, case-control study on delta32 mutation that abolishes CCR5 from cell surface, we found that the presence of the mutated allele was less common in patients with cardioembolic ICVD compared to those with other aetiological subtypes. Hence, we assumed that CCR5 might play a role in predisposition to cardiac conditions that confer increased embolic risk. In the subsequent studies we investigated the association of blood-borne markers with aetiological subtypes and long-term survival in ICVD. Our results imply that increased levels of glucose, white blood cell count and fibrinogen, as well as low levels of cholesterol on admission, may be associated with poorer long-term survival after stroke and TIA. Investigation of aetiological phenotypes according to TOAST and ASCO showed very good agreement between the two classification systems in all subgroups except for large vessel stroke where the matching was good. Long-term survival was higher in patients with small vessel stroke and poorer in patients with incomplete work-up followed by cardioembolic and cryptogenic aetiology.

Overall, our findings indicate that molecules involved in inflammation and metabolism may play a role in the pathology and prognosis of ICVD. We also addressed the issue of aetiological classification in stroke, and how different approaches may improve research accomplishments. Our studies are not designed to serve as sources of conclusions on causal mechanisms associated with disease occurrence and outcome. Future studies on larger, well-described populations are needed in order to clarify the processes involved in different aetiopathogenesis of stroke.

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