Institutionen för medicinsk epidemiologi och biostatistik

The genetic and molecular markers of ischemic stroke: risk, prognosis, and treatment

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Petrénsalen, Nobels väg 12B

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ABSTRACT

Stroke is a major cause of mortality and morbidity worldwide, with ischemic stroke (IS) being the predominant type. With the current ageing population, IS burden will inevitably escalate leading to increasing demand for more effective prevention, diagnosis, and treatment strategies. The overall aim of this thesis was to elucidate various factors affecting IS in different stages, from risk to prognosis and subsequently treatment, by exploring potential genetic and/or molecular markers of IS in the hope to better understand this complex multi-factorial vascular disease.

In Study I, we estimated the familial risk of IS in a very large, nation-wide population-based study by exploring the effects of sibling kinship, sex, and age in the heritability of IS. We found a 60% increased risk for IS in individuals having a sibling with prior stroke, and the risk was stronger for full siblings compared to half siblings. Having a sibling with early IS doubled the risk of early IS. No sex differences were found in the familial inheritance of IS.

In Study II, we assessed the common familial risk between IS and MI in a large, population-wide matched cohort study where we observed a 44% increased risk for MI in individuals having a sibling with prior IS and a 41% increased risk for IS in individuals having a sibling with prior MI, indicating shared familial aggregation between these two conditions.

In Study III, we explored the utility of sub-acute C-reactive protein (CRP) measurement in the prediction of outcomes after IS in a large prospective cohort of Singaporean acute IS patients, and whether CRP addition improved a conventional prognostic model. Only CRP at high levels was significantly associated with outcomes independent of other risk factors. In addition, comparison of conventional prognostic models with and without CRP showed significantly better fit in predictor model improvement upon CRP addition.

In Study IV, we examined whether the efficacy of B-vitamin in reducing total homocysteine (tHcy) was modified by ethnicity in a Singaporean IS population. The magnitude of reduction in tHcy with B-vitamin therapy did not differ between ethnic groups despite differences in dietary intake and genetic makeup.

In conclusion, data from the Swedish registers showed that full siblings exposed to IS have a higher risk of IS compared to those unexposed, and that early exposure to IS doubled the risk of IS compared to those unexposed. Similar increased risks for MI and IS when exposed to IS and MI respectively suggested shared familial aggregation between these two conditions. Data from the Singapore IS patients cohorts suggested the potential added value of CRP measurement towards prediction of future outcomes, and that the effect of B-vitamins in lowering tHcy may be generalizable across Asian IS populations.

Keywords: ischemic stroke, family history, heritability, siblings, sex, onset age, myocardial infarction, c-reactive protein, prognosis, homocysteine, ethnicity, risk factors

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