IL6 trans-signalling associates with atherothrombotic but not with cardioembolic stroke

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Funding Acknowledgement: Type of funding source: None

Background: Pro-inflammatory processes underlie ischemic stroke, albeit it is largely unknown if they selectively associate with the risk of atherothrombotic and cardioembolic ischemic stroke. Here we analyse whether the pro-inflammatory interleukin (IL) 6 trans-signalling, associates with the risk of ischemic stroke and underlying atrial fibrillation (AF).

Method: During a 20-year follow-up, 203 incident ischemic strokes were recorded from national registers in the cohort of 60-year-old men and women from Stockholm (n=4232).

For each study participant, we have estimated the activity of the IL6 trans-signalling through the calculation of the ratio between the circulating pro-inflammatory binary IL6:sIL6R complex and the circulating inactive ternary IL6:sIL6R:sgp130 complex, the so called B/T ratio. An excess of the binary complex, mirrored by a high B/T ratio, is associated with an increased risk of cardiovascular events. The B/T ratio has been dichotomized at the median. The risk of ischemic stroke associated with B/T ratio $>$ median was estimated by Cox regression and expressed as hazard ratio (HR) with a 95% confidence interval (CI) in the presence and absence of AF. Risk estimates were adjusted for cardiovascular risk factors and anticoagulant treatment. In a secondary analysis, the association of IL6 trans-signalling with the risk of incident AF (n=279) was analysed.

Results: B/T ratio $>$median was associated with the risk of ischemic stroke only in study participants without AF diagnosis (adjusted HR 1.49; 95% CI 1.08–2.06). No association was observed with ischemic stroke in study participants also diagnosed with AF. Moreover, the B/T ratio was not associated with the risk of AF (HR 0.96; 95% CI 0.75–1.24).

Conclusions: IL6 trans-signalling, estimated by the B/T ratio, is associated with atherothrombotic but not cardioembolic stroke. Consistently, the B/T ratio did not associate with the risk of incident AF. Our results support the relevance of IL6 trans-signalling in atherosclerosis related ischemic stroke.