Stroke

INVESTIGATING THE MISSING LINKS BETWEEN THYROID HORMONES AND ISCHEMIC STROKE RISK AND OUTCOMES USING MENDELIAN RANDOMIZATION

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Background. The global burden of ischemic stroke necessitates the search for new factors influencing its risk and outcomes. One of the emerging risk factors is thyroid dysfunction, while thyroid hormones may have neuroprotective properties.

Aims. To clarify the effects of hypothyroidism, triiodothyronine (fT3) level on ischemic stroke risk, outcomes and related biomarkers, we adopted a Mendelian randomization approach to evaluate their causal relationship.

Methods. We used 6 independent single nucleotide polymorphisms (SNPs), extracted from 2 GWAS-studies in Split and Dalmania cohort (Croatia) as instrumental variables, genetically predicting fT3 level. Summary-level data for ischemic stroke outcomes (mRs 0-2 vs. 3-6) was obtained from GISCOME-network. SNPs associated with hypothyroidism were extracted from the UKBiobank database. SNPs associated with 24 circulating proteins of the apoptosis system were extracted from the Genomic Atlas of the Plasma Proteome. Summary data for stroke risk was obtained from MEGASTROKE study.

Results. MR-analysis showed that genetically predicted 1-SD increase in fT3 level is associated with reduce in risk of unfavorable (mRs 3-6) stroke outcome (OR=0.76, 95%CI 0.6-0.96). There was a causative association between hypothyroidism and levels of BCL-2-associated cell death agonist (beta=3.7488, p= 0.03594), mitochondrial apoptosis-inducing factor-1 (beta=1.953, p=0.02993), lacunar stroke risk (p=0,0006). Also, causative association between deiodinase-2 expression and reduction of lacunar stoke risk was revealed (OR=0.89, 95% CI 0.82–0.97).

Conclusion. This study showed that higher fT3 levels could be causally associated with decreased risk of unfavorable ischemic stroke outcome. Underlying mechanisms may be attributed to apoptosis downregulation. Hypothyroidism is predominantly associated with risk of lacunar stroke.