EMIF Deliverable 3.14: Report joint study AD/Metabolic

Executive summary

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Background: Clinical studies suggest a pathophysiological connection between type 2 diabetes mellitus (DM), insulin resistance (IR) and Alzheimer's disease (AD). Hypothetically, cognitively normal individuals with IR might have cerebrospinal fluid (CSF) indicators of incipient AD pathology, differences in CSF peptides related to insulin signaling and glucose homeostasis, and abnormalities in other metabolites associated with a risk of AD. This EMIF AD/MET joined study gives an insight into relationship between IR and AD pathology.

Objectives: To assess in the CSF of cognitively normal men with and without IR (1) the concentrations of AD biomarkers, and (2) the concentrations of other CSF biomarkers of potential relevance to IR and AD, and (3) To assess concordance of CSF and plasma proteome.

Methods & Results: 58 cognitive normal men (MMSE ≥ 25), out of which 28 were insulin resistant and 30 non-resistant (Matsuda index cutoff of 7.0) were drawn from the METSIM (Metabolic Syndrome in Men) study in Kuopio, Finland. CSF AD biomarkers, i.e. amyloid-β (Aβ) peptide, total tau (T-tau) and phosphorylated tau (P-tau), as well as concentrations of CSF neurofilament light chain and microglial markers (YKL-40, MCP-1) were examined with respect to IR. Plasma and CSF SOMAscan was performed to identify single proteins and multivariate signatures that associate with IR, CSF levels of AD biomarkers, and with cognition. CSF AD biomarkers did not differ between the groups. 200 proteins in CSF and 487 proteins in blood were differentially expressed between insulin resistant and non-resistant subjects. In addition, significantly enriched pathways, many of which have been previously implicated in AD, were identified.

Next steps: This deliverable gives an overview of the study and describes the results obtained so far. A manuscript is under way and is expected to be submitted in the autumn 2016. The work described here is a result of a joint collaboration between UOXF, UGOT, and UEF.

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