Abstract

Alzheimer´s disease (AD) is a neurodegenerative disorder where genetic, biochemical and environmental factors are involved. AD mainly affects individuals over 60 years of age, but an early form of AD which is both more progressive and more serious also exists. The loss of cognitive function is typical for AD, on histological level senile plaques and neurofibrillary tangles are typically present. Diagnostics of AD is very problematic and accurate diagnosis is only possible *post mortem*. The only known gene that is associated with the risk of AD is *Apolipoprotein E*, respectively its allele ε4. Genome-wide association studies revealed more candidate genes for AD that have a connection with the disease. Except genetics background, there are some changes in biochemical markers including steroid hormones that can contribute to AD development.

This thesis has two parts – a genetic and a biochemical one. The genetic part focuses on selected polymorphisms in candidate genes for AD and on its eventual connection with disorders of glucose metabolism. In total there were 2172 persons (550 women with gestational diabetes, 391 patients with type 2 diabetes mellitus, 116 persons with impaired glucose tolerance and 1115 appropriate healthy controls) examined. Using Real-Time PCR, polymorphisms in *BIN1, CLU*, *CR1* and *PICALM* genes were detected. Our results show that variant rs3851179 in *PICALM* gene is associated with higher risk of gestational diabetes and that it has a connection with impaired glucose tolerance. This part of thesis also focuses on searching for new variants in some exones in selected candidate genes for AD. In total there were 173 persons (97 patients with AD and 76 healthy senior controls) examined. Thanks to massive parallel sequencing selected exones in *APOE*, *BIN1*, *CLU* and *CR1* genes were examined. All variants found in our study have already been discovered and described. No new variants which could be associated with AD were found.

The biochemical part of this thesis focuses on the spectrum of adipokines, cytokines, incretines and neurodegenerative parameters. In total there were 163 persons (87 patients with AD and 76 healthy seniors) examined. The analysis was performed by multiplex ELISA method. Our results show elevated levels of visfatin, resistin, GLP-1, sCD40L and enolase-2 in AD patients compared to senior controls. In AD patients we also detected manifold increased levels of chemokine RANTES compared to controls. Further, this part of thesis focuses on steroid hormone levels and its potential association of their

conjugated and unconjugated ratios with AD. The analysis was done using a gas chromatography-mass spectrometry method. The results show lower levels of C19 steroids in AD patients that show reduced enzyme activity in adrenal *zona reticularis*. Furthermore, patients with AD have higher levels of C21 steroids compared to controls that show increased enzyme activity in adrenal *zona fasciculata.* We found lower ratios between conjugated and unconjugated C19 steroids in AD patients. This result shows again a lower enzyme activity in adrenal *zona reticularis*, specifically an attenuated sulfonation of these steroids by enzyme *sulfotransferase family 2A member 1* (SULT2A1).

This Ph.D. thesis contributes to the elucidation of genetic and biochemical background of AD which is very complex. Together with other studies involved in AD problematics it could contribute to the creation of a model to improve the diagnostics of AD.