CSF BIOMARKERS IN NEURODEGENERATION: PRELIMINARY FINDINGS AND CUT-OFFS RECOMMENDATIONS OF THE CROATIAN PROJECT ON EARLY DETECTION OF ALZHEIMER'S DISEASE

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The National Science Foundation project "Detection and tracking of biological markers for early therapeutic intervention in sporadic Alzheimer's disease" is a large-scale 3-year project (2012-2014) designed to determine the diagnostic accuracy of potentially useful biological markers for discrimination among subjects with Alzheimer's disease (AD), mild cognitive impairment (MCI), non-demented healthy controls (HC), and patients with other primary causes of dementia. To identify those patients most likely to benefit from therapeutic intervention, our ultimate long-term objective is to develop reliable diagnostic criteria for detection of preclinical stages of AD. Preliminary findings obtained on 126 patients, of which 54 were patients with probable AD, 30 with MCI, 9 with vascular dementia (VaD), 4 with Lewy body disease (LBD), 11 with frontotemporal dementias (FTD) and 18 healthy controls will be presented. Cut-off levels for the CSF concentrations of amyloid β1-42 (Aβ42) and total tau protein (t-tau) were derived from receiver operating characteristic (ROC) curve analysis, when the sum of specificity and sensitivity was maximized. Both CSF t-tau and Aβ42 have recently been added to the clinical diagnostic criteria for MCI and AD (McKhann et al., Alzheimers Dement., 2011). Our preliminary results showed that 23.3% of MCI subjects had Aβ42 and t-tau levels as patients with probable AD, while 53,3% of them had either Aβ42 lower or t-tau higher than cut-off levels. As a follow-up period of at least 5-10 years is needed to assess reliably MCI patients who will develop AD (the annual conversion rate from MCI to AD in specialist clinical settings is approximately 9.6%, Mitchell and Shiri-Feshki, Acta Psychiatr. Scand., 2009), only then will we be able to conclude if defined cut-off levels indeed distinguish MCI patients that will progress to AD from those who will not. Additionally, phosphorylated tau (p-tau231) measured in 36 subjects was shown to distinguishing AD from healthy controls with sensitivity of 76.5% and specificity of 80% (for details, see the poster presentation of Babić et al.). In view of the fact that the use of clinical diagnosis instead of neuropathological diagnosis lead to a 14-17% underestimation of the biomarker accuracy (Toledo et al., Acta Neuropathol., 2012), these results emphasize the critical importance of CSF biomarker standardization to increase the accuracy for the early diagnosis of neurodegenerative diseases. This work is supported by the Croatian Science Foundation grant no. 09/16.

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