Biochemical signature predicts progression to Alzheimer's disease

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A study led by Research Professor Matej Orešič from VTT Technical Research Centre of Finland suggests that Alzheimer's disease is preceded by a molecular signature indicative of hypoxia and up-regulated pentose phosphate pathway. This indicator can be analysed as a simple biochemical assay from a serum sample months or even years before the first symptoms of the disease occur. In a healthcare setting, the application of such an assay could therefore complement the neurocognitive assessment by the medical doctor and could be applied to identify the at-risk patients in need of further comprehensive follow-up.

Alzheimer's disease (AD) is a growing challenge to the health care systems and economies of developed countries with millions of patients suffering from this disease and increasing numbers of new cases diagnosed annually with the increasing ageing of populations.

The progression of Alzheimer's disease (AD) is gradual, with the subclinical stage of illness believed to span several decades. The pre-dementia stage, also termed mild cognitive impairment (MCI), is characterised by subtle symptoms that may affect complex daily activities. MCI is considered as a transition phase between normal aging and AD. MCI confers an increased risk of developing AD, although the state is heterogeneous with several possible outcomes, including even improvement back to normal cognition.

What are the molecular changes and processes which define those MCI patients who are at high risk of developing AD? The teams led by Matej

Orešič from VTT and Hilkka Soininen from the University of Eastern Finland set out to address this question, and the results were published on 13th Dec. 2011 in *Translational Psychiatry*.

The team used metabolomics, a high-throughput method for detecting small metabolites, to produce profiles of the serum metabolites associated with progression to AD. Serum samples were collected at baseline when the patients were diagnosed with AD, MCI, or identified as healthy controls. 52 out of 143 MCI patients progressed to AD during the follow-up period of 27 months on average. A molecular signature comprising three metabolites measured at baseline was derived which was predictive of progression to AD. Furthermore, analysis of data in the context of metabolic pathways revealed that pentose phosphate pathway was associated with progression to AD, also implicating the role of hypoxia and oxidative stress as early disease processes.

The unique study setting allowed the researchers to identify the patients diagnosed with MCI at baseline who later progressed to AD and to derive the molecular signature which can identify such patients at baseline.

Though there is no current therapy to prevent AD, early disease detection is vital both for delaying the onset of the disease through pharmacological treatment and/or lifestyle changes and for assessing the efficacy of potential AD therapeutic agents. The elucidation of early metabolic pathways associated with progression to Alzheimer's disease may also help in identifying new therapeutic avenues.

More information: M. Orešič, T. Hyötyläinen, S.-K. Herukka, M. Sysi-Aho, I. Mattila, T. Seppänan-Laakso, V. Julkunen, P. V. Gopalacharyulu, M. Hallikainen, J. Koikkalainen, M. Kivipelto, S. Helisalmi, J. Lötjönen, H. Soininen, Metabolome in progression to Alzheimer's disease, *Translational Psychiatry*, 13th December 2011.

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