The need for reliable biomarkers for monitoring potential treatments in Alzheimer's disease

Goran Šimić

The search for predictive biomarkers for Alzheimer's disease (AD) is a high priority in neurodegenerative disease research underlined by the lack of significant progress in identifying new treatments for the past 12 years. Despite major efforts and considerable investments the only treatments approved for AD are only palliative. They include the cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) that act on the cholinergic deficit, and the NMDA receptor antagonist, memantine, which has neuroprotective effects. These agents are generally considered to have marginal efficacy. As it can be logically assumed that a late therapeutic intervention would be less efficient than an early one, development of biomarkers for AD both to diagnose the disease early and to follow-up its progression, remains a major challenge. Currently, it is comprised of 6 main approaches: 1) behavioral assessment, including measurement of cognitive status using various neuropsychological scales (MMSE, ADAS-Cog, etc.) ; 2) changes in brain structure (mainly volume of the cerebral cortex, particularly entorhinal cortex and hippocampus) ; 3) alterations in brain metabolism (most notably within the default mode network) by using FDG-PET and fMRI ; 4) measurement of β-amyloid load within the brain by PIB-PET ; 5) cerebrospinal fluid (CSF) biomarker profiles (the three main CSF biomarkers of AD being β-amyloid, total tau, and phosphorylated forms of tau proteins) ; and 6) post-mortem confirmation of characteristic AD histopathology. In my talk I will attempt to describe new developments within each of these biomarker approaches by analyzing their pathological specificity, early diagnostic sensitivity, and correlation with AD progression. Finally, I will argue that, despite numerous publications and recommendation criteria, the predictive usefulness of these various biomarker approaches, individually or collectively, has yet to be established.