NEUROPSYCHOLOGY VS. BIOMARKERS IN PRE-CLINICAL AND EARLY AD: PRO BIOMARKERS

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Alzheimer's disease (AD) is a slowly progressive neurodegenerative disorder with a duration of several decades. During the first third of its course, AD is preclinical and asymptomatic. In the second third, cognitive performance starts to decline but normal daily activities are still largely intact; in the current nomenclature, this stage is termed "mild cognitive impairment" (MCI). Only the last third of the disease course is characterised by the typical memory-dominant dementia syndrome, in which cognitive impairment becomes severe enough to significantly impair everyday activities and patient autonomy. In neuropsychiatric tradition, AD could only be diagnosed in a clinical setting if dementia was present, but recent years have seen a paradigm shift towards a more biologically defined AD diagnosis. For example, the new National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines conceptualise AD as a progressive disorder including all possible stages from pre-symptomatic to severely demented. This way of thinking implies that tissue changes precede the onset of clinical signs by many years, and neuropathological lesions can be found in elderly individuals who presently do not have, and may not live long enough to ever suffer from, cognitive impairment and associated disability.

During the past 30 years, a large body of evidence has accumulated indicating that a cascade of events related to the faulty production, degradation and clearance of beta amyloid protein (Aβ) lie at the heart of AD pathogenesis. Upstream events within this cascade include the overproduction of the amyloid precursor protein (APP) caused by rare mutations in the *APP*, *PSEN1* or *PSEN2* genes, malfunctioning of Aβ-degrading proteases and impaired clearance as a result of ineffective active or passive transport mechanisms. The imbalance between production and clearance results in excess amounts of Aβ, which are believed to trigger a sequence of subsequent, i.e. downstream, pathological changes such as loss of synapses and neurons, impaired glucose utilisation, oxididative damage, brain metabolic reduction, tau hyperphosphorylation and associated neurofibrillary tangle formation, Aβ deposition in plaques and eventually neurotransmitter changes and widespread neurodegeneration. This complex cascade of pathological events continues throughout the course of AD, leading to an accumulation of structural and functional cerebral damage causing the typical clinical picture.

The hope for disease modification as well as technological advances in biomarker discovery fuel the search for biological indicators of the AD pathophysiological process, which can be used to identify neurodegeneration independently of its clinical manifestations. Ideally, such a biomarker, alone or in combination with other markers, would distinguish between individuals with and without AD pathology independently of the clinical symptomatology. Individuals with asymptomatic early AD would probably benefit most from interventions aiming to prevent further neural damage to maintain their independence, ability to work and fulfilment of social roles. Furthermore, pathophysiological markers may also offer the added benefit of directly assessing response to treatment options that target core processes of AD pathogenesis. The application of novel therapeutics with potentially significant side effects could thereby be restricted to patients with biological evidence of treatment response in line with the notion of personalised medicine. However, biomarker evidence of treatment efficacy should not replace clinical evidence of patient benefit.

Currently available AD biomarkers can generally be grouped into two categories. The first category comprises markers that indicate the type of pathology present, including cerebrospinal fluid (CSF) levels of $A\beta_{1-42}$, total tau (tTau) and phosphorylated tau $(pTau)_{181}$ [9] and positron emission tomography (PET) tracers of fibrillar amyloid such as flutemetamol, florbetapir, florbetaben and Pittsburgh Compound B. The second category consists of markers that provide information on the topography of pathological changes, such as magnetic resonance imaging (MRI) and fluorodeoxyglucose PET. Published evidence consistently shows that these biomarkers, alone or in combination with psychometric test results, offer an added value for the diagnosis of the early clinical stages of AD.