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GUEST EDITORIAL

Dealing with uncertainty: biomarkers for the early detection of Alzheimer's disease

In neuropsychiatric tradition, Alzheimer's disease (AD) is a clinical diagnosis that requires demonstration of a progressive memory-predominant type of dementia and exclusion of alternative causes. This simple set of criteria is neither sensitive for early clinical stages of AD since amnestic dementia only arises when the underlying neurodegeneration is fairly advanced, nor is it specific because it also occurs in other brain disorders involving the medial temporal lobe and cannot be easily distinguished from AD on clinical grounds. Efforts to identify AD before full-blown amnestic dementia develops, i.e. at a prodromal or even asymptomatic stage, and to treat the driving components of the pathology rather than its end products, are fueling the search for diagnostic indicators that unveil the neurodegeneration independently of its typical clinical manifestation. Such indicators are termed *biomarkers* in current technical parlance.

Why diagnose AD early?

In a chronic medical condition, early diagnosis becomes an issue when treatment is available that can alter its course. Regarding AD, there is hope that novel pharmacological strategies such as secretase inhibitors, anti-amyloid immunization, or tau aggregation inhibitors will have the capacity of slowing down the neurodegeneration and the associated clinical decline. This optimistic prospect is often coupled with the expectation that such treatments may provide greatest benefit to patients at the stage of absent or minor cognitive impairment since higher levels of functioning, independence, and quality of life will be maintained (Foster *et al.*, 2009). However, all clinical trials conducted thus far suggest that the novel treatment approaches can achieve some effects on certain aspects of the pathophysiology of AD but have little or no impact on patient-relevant clinical outcomes. Furthermore, these interventions can be implemented in the routine management of AD only after long-term tolerability, safety, and cost-effectiveness have been established. Hence, upcoming availability of disease-delaying drugs presently is a far-fetched argument in favor of the early detection of AD. In contrast, providing evidence that AD is the reason for cognitive decline and behavioral change could be a valid reason for an early diagnosis since it may end uncertainty and reduce the likelihood of misunderstanding and conflict within affected families. Moreover, early diagnosis allows patients to make choices for their future lives while their decision-making capacity is still intact (Hamann *et al.*, 2011; Holt, 2011). Apparently, however, there is no great demand for this opportunity, since only few patients who receive an early diagnosis initiate advance care planning (Garand *et al.*, 2011). While offering limited benefits for patients and families, the early detection of AD can be associated with significant disadvantages and risks. Since effective treatment is currently lacking, people who receive an early diagnosis are faced with the prospect of gradually losing intellectual capacity and independence. The ambiguity of prognosis (see below) may bear significant psychological consequences including depression, despair, and in rare cases even suicide (Erlangsen *et al.*, 2008). Moreover, the diagnosis of progressive cognitive decline that will end in dementia may have negative repercussions on social relationships and employment.

How well do biomarkers perform in the early detection of AD?

Currently available diagnostic indicators can be divided into two groups. The first category provides information on the type of pathology that is present. It includes cerebrospinal fluid (CSF) concentrations of amyloid β $(A\beta)_{1-42}$ protein, total τ and phosphorylated τ $(p\tau)_{181}$ protein, and the amount of $A\beta$ deposition shown by certain positron emission tomography (PET) tracers. The second category comprises structural magnetic resonance imaging (MRI) and regional glucose metabolism as measured by ^{18}F-fluoro-2-deoxy-glucose (^{18}F-FDG) PET. Both methods display the topography of changes (Dubois *et al.*, 2010). A large number of cross-sectional and prospective studies have shown that sensitivity and specificity of these techniques for distinguishing prodromal AD from physiological aging (Bloudek *et al.*, 2011) and for predicting progression to dementia in individuals with minor degrees of cognitive impairment (Mattsson *et al.*,

2009) are remarkable but far from perfect. This implies that the probability of AD being present in someone who has a positive biomarker finding is less than 80% even in specialist settings where patients are highly selected, the prevalence of the disease is high, and comorbid conditions are rare.

How could biomarkers for AD be improved?

A principal problem with current biomarkers for AD is that they are insufficiently sensitive for early pathophysiological events. When using the presently available biomarkers, abnormal findings such as elevated τ and decreased $A\beta_{1-42}$ in CSF, and hippocampal atrophy or reduced glucose metabolic activity indicate an advanced stage of the disease, which has resulted in irreversible functional and structural brain damage. Early recognition of AD requires the identification of specific features of the pathological process that precede these end stages. One possible approach could be the measurement of activities of proteolytic enzymes within the amyloid cascade (Hardy and Higgins, 1992) that are responsible for the generation of pathogenic protein aggregates. Genetic markers may also be an option; however, all genes that have been associated with sporadic AD so far have a very small impact on disease risk and the strongest known genetic risk factor, apolipoprotein E (*APEO*), is not useful to determine individual AD risk (Hollingworth *et al.*, 2011).

Another issue with available biomarkers is that they either require invasive procedures such as lumbar puncture or involve radiation or costly equipment such as PET; therefore, the biomarker-assisted early diagnosis of AD can only be offered at specialized centers in most instances, and a provision of such services to the wider population is impossible. If the need for population-wide early recognition of AD arises, less invasive and affordable methods are required. Blood-based biomarkers could live up to the expectations and further research is urgently needed.

A third difficulty arises from the fact that many biomarkers are focused on a very narrow segment of AD pathogenesis. Factors related to the amyloid cascade may certainly offer important diagnostic information; however, the abnormal processing of $A\beta$ is probably only one, albeit central, aspect of a complex disease. One possible solution is to apply hypothesis-generating approaches instead of hypothesis-driven methods to biomarker discovery. Blood and CSF-based proteomic techniques offer a basis for this approach (Jahn *et al.*, 2011) but the success of this strategy remains to be seen.

How to deal with biomarker information?

In future, we will hopefully be in a position to reliably identify the AD pathophysiological process before it causes irreversible cerebral damage. We expect that by the same time, treatment options will be available which slow down the neurodegenerative process. In the meantime, we need to live with the imperfections of available biomarkers. To start with, they can only be used as an aid to the clinical diagnosis in individuals showing cognitive symptoms, not in cognitively normal subjects. Even in specialized centers, the biomarker-assisted early diagnosis of AD is still far from being perfectly accurate; therefore, a diagnosis of AD should never be solely based on laboratory or imaging findings. In case of a positive biomarker, the clinical course of the disease should be carefully monitored in order to initiate treatment with antidementia drugs if symptoms progress to dementia. Even if the biomarker results are negative, some follow up of the clinical course should be performed since AD could still be the cause of the symptoms. Importantly, if prodromal AD is diagnosed on the basis of biomarkers findings, affected individuals must not be left alone with their worries and fears. So far, no appropriate programs exist for these individuals. There is also limited knowledge about the psychosocial reactions to biomarker information and about the individual benefits that accompany the use of biological indicators of AD pathology. Research on these ethical considerations has to be conducted in addition to studies aiming to develop improved biomarkers in order to provide patient-oriented and individualized diagnostic services.

Conflict of interest

None

Robert Perneczky and Alexander Kurz
Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany
Email: robert.perneczky@lrz.tum.de

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