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Editorial

Is Amyloid Imaging Really Helpful in Diagnosing AD?

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Editorial

Alzheimer's disease (AD) is a slowly progressive neurodegenerative disorder with disease 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 characterized 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 conceptualize 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.

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 fulfillment 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 personalized 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 Aβ1-42, total tau (tTau) and phosphorylated tau (pTau)181 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.

Contrary to hypothetical models proposed, the scientific literature supports that certain cognitive domains (e.g., episodic memory, executive function) decline well before the diagnosis of MCI. Specifically, the rate of cognitive decline increases and is detectable 4-to-6 years before the diagnosis. In addition, there is supporting evidence from the Alzheimer's disease Neuroimaging Initiative database that baseline measures of cognition were more robust predictors of conversion from MCI to AD than biomarkers. Overall, there are many challenges when conducting studies in preclinical and early AD, but at present the scientific evidence supports that measures of cognition move many years before the diagnosis of MCI and are predictors of conversion [1].

In vivo visualization of amyloid plaques using PiB PET has been possible for more than a decade. The practical use of PiB, however, was hampered by its short shelf-life. Now that fluoride-based compounds have become available and florbetapir has been approved by the FDA for in vivo imaging of amyloid, are we ready to use this method for the pre-mortem diagnosis of AD? Are the questions on sensitivity, specificity and cut-off values sufficiently answered?

Recently two relevant decisions for this most pertinent question in clinical psychogeriatrics were published by US agencies. The United States Preventive Services Task Force (USPSTF) decreed that routine screening of all older individuals for cognitive impairment is not supported by the available evidence. After reviewing 55 studies examining the accuracy of screening instruments, and more than 130 studies of interventions aimed at slowing or stopping cognitive decline in patients who tested positive for cognitive impairment or relieving caregiver burdens, the USPSTF resolved that a clear benefit for screening has not been recognized, relative to the potential for harm. Thus, notwithstanding many new studies of cognitive screening and interventions since 2003, when the USPSTF last examined the issue, the overall conclusion remained the same. The task force emphasized that the review covered only routine, universal screening for older patients without clear signs or symptoms of cognitive impairment. Nearly at the same time the US Food and Drug Administration (FDA) has approved a third agent for imaging β-amyloid, florbetaben F18 injection (*Neuraceq*, Piramal Imaging). Florbetaben is indicated for positron emission tomography (PET) of the brain to estimate β-amyloid neuritic plaque density in adults with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline. It was lately also approved in Europe. As with other imaging agents, a positive florbetaben scan does not establish a diagnosis of AD or any other cognitive disorder, but a negative scan indicating sparse to no amyloid plaques "is inconsistent with a neuropathological diagnosis of AD at the time of

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image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD," the company notes.

In the last year the impact of measuring fibrillar amyloid-beta load and glucose metabolism on the diagnostic process in a memory clinic population was assessed. One hundred fifty-four patients underwent paired dynamic and static scans soon after the administration of a standard dementia screening. Two-year clinical follow-up data were available for 39 patients. Clinical diagnosis and confidence in said diagnosis before and after disclosing imaging results were defined as the outcome measures. PIB scans were positive in 40 of 66 (61%) patients with a clinical diagnosis of AD and in 3 of 10 (30%) patients with other dementias. FDG uptake patterns matched the clinical diagnosis in 38 of 66 (58%) of AD patients. PET results led to a change in diagnosis in 35 (23%) patients. Diagnostic confidence increased from 71% before to 87% after PET ($p<0.001$). The authors concluded that in the setting of a memory clinic combining PIB and FDG PET are of additional value on top of the standard diagnostic work-up, especially when prior diagnostic confidence is low [2]. I would suggest that this may be an optimistic reading of the results. While diagnostic certainty increased by employing imaging studies this can more easily and with better clinical outcome can be achieved by practice and education of personnel.

Nearly at the same time an investigation of AD and other dementia diagnoses in three national registers in Finland was undertaken. The Hospital Discharge Register (HDR), the Drug Reimbursement Register, and the Causes of Death Register (CDR) were examined. The researchers had the benefit of basing their baseline "gold" standard on the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study where in participants were first evaluated in 1972 to 1987, and were reexamined in 1998 and in 2005 to 2008. Sensitivity of the HDR was for AD diagnosis was55.6%.

The positive predictive value was 100% for AD. Sensitivity and PPV of the HDR were greater after 1998. For AD in the Drug Reimbursement Register alone, sensitivity was 63.5% and PPV was 97.1%. The authors conclude that diagnoses in registers have very good accuracy [3].

The accuracy of clinical diagnoses in registers is notoriously low. The fact that this is not upheld in the diagnosis of AD emphasizes the fact that practice, clinical acumen and dedication are the infrastructure of AD diagnosis.

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