THE ROLE OF FUNCTIONAL NEUROIMAGING IN THE EVALUATION OF PATIENTS WITH COGNITIVE/BEHAVIORAL IMPAIRMENT OR DEMENTIA

Bradford C. Dickerson, MD
Alzheimer's Disease Research Center
Athinoula A. Martinos Center for Biomedical Imaging
Massachusetts General Hospital and Harvard Medical School
Boston, MA, USA

The evaluation of a patient with cognitive impairment or dementia is part of many neurologists' daily practice. Once it has been established that a patient has mild cognitive impairment (MCI) or dementia, our job is to determine the etiology and then consider prognosis and treatment. Although specific pharmacologic treatment options are still limited at present for most dementias, there are a growing number of clinical trials in which patients may participate. Furthermore, it is imperative for the neurologist to guide a comprehensive approach to the treatment of cognitive impairment and dementia including management of behavioral symptoms, programs and strategies to optimize functional independence, caregiver education and support, and assistance with prognostication, planning, and connection with specific resources to assist with these issues.

In 2011, new diagnostic criteria were published for Alzheimer's disease (AD)(McKhann et al., 2011), behavioral variant Frontotemporal Dementia (FTD)(Rascovsky et al., 2011), and Primary Progressive Aphasia(Gorno-Tempini et al., 2011), and a new consensus statement was published on Vascular Cognitive Impairment(Gorelick et al., 2011). New criteria are emerging for other dementias as well. All of these criteria emphasize the value of structural and functional/molecular neuroimaging (including not only amyloid and tau biomarkers but also fluorodeoxyglucose PET (FDG-PET)), as well as cerebrospinal fluid markers, in increasing diagnostic confidence or specificity. Although these criteria are in large part aimed at the clinical research communities studying these diseases, they also serve as guidance for practicing clinicians. These reports emphasize elements that can be summarized as the practitioner's two major goals: 1) start by establishing a diagnostic hypothesis based on a careful clinical evaluation emphasizing history and examination (including office-based cognitive testing that may be supplemented with formal neuropsychological testing); 2) perform diagnostic testing judiciously to test this hypothesis.

For most clinicians, the first diagnostic test in a patient with cognitive impairment is a brain MRI. In many patients with a presentation that is prototypical for a specific neurodegenerative disease, this test and a few other tests (e.g., vitamin B12, thyroid testing) may be all that is required to establish a confident diagnosis. For example, multiple studies have shown that the original 1984 diagnostic criteria for AD, which advocate essentially this approach, demonstrate a sensitivity and specificity of approximately 81% and 70%, respectively (Knopman et al., 2001).

Yet there are many patients in whom the diagnosis is still uncertain after this information has been obtained. In my opinion, the clinician faced with this situation should strongly consider using additional diagnostic testing to further evaluate the patient: molecular neuroimaging with FDG-PET and amyloid PET imaging or a spinal fluid examination for amyloid-β and tau proteins. For example, a patient presenting in her 50s or 60s with a syndrome of executive or language impairment and a relatively unrevealing MRI scan can be challenging to confidently diagnose. In such patients, I find FDG-PET to be an extremely valuable next step in the diagnostic evaluation, since it is minimally invasive and may provide a clear indication of whether the patient has a hypometabolic pattern consistent with atypical AD as opposed to a pattern supportive of FTD or another neurodegenerative disease.

In 2004, the U.S. Centers for Medicare and Medicaid Services approved reimbursement of FDG PET for the purposes of differential diagnosis of AD vs. FTD. Several studies have supported the value of this neuroimaging tool in dementia diagnosis (Hoffman et al., 2000; Silverman et al., 2001). In a clinicopathologic study, Jagust et al. (Jagust et al., 2007) demonstrated that FDG PET improved upon the sensitivity and specificity of clinical diagnostic evaluation in predicting a pathologic diagnosis of AD versus non-AD. Foster et al. have performed a series of studies evaluating the practical value of FDG PET in the diagnostic assessment of patients with dementia, with a particular emphasis on AD and FTD, and showed that FDG PET improved upon clinical assessment with particular value in situations in which clinical diagnostic confidence was not high (Foster et al., 2007); this concept has recently received further support from another group that performed a similar study in patients with MCI or dementia (Laforce et al., 2010). Thus, while the 2001 American Academy of Neurology practice parameter for the diagnostic evaluation of dementia did not recommend the use of FDG PET or related techniques, citing the need for "further prospective studies … to establish the value that it brings to diagnosis over and above a competent clinical diagnosis," (Knopman et al., 2001) a number of studies in the decade since then have begun to provide evidence of added value in certain situations (summarized in a recent review (Bohnen et al., 2012)).

Nevertheless, FDG PET faces several challenges in becoming more routinely used in the diagnosis of AD and related disorders. First, the clinician needs to be familiar with its utility and have access to a facility in which it is performed. Second, reimbursement for FDG PET in the diagnostic evaluation of dementia or cognitive impairment needs to improve in the private sector; it is often particularly difficult (and sometimes impossible) to obtain authorization from private insurers for FDG PET in patients younger than Medicare-eligible age, ironically the patients in whom it may be most useful. Finally, improved standardization of interpretation and quantification of FDG PET scans is an important goal; a number of research groups are working on comparisons of different quantitative techniques and on comparisons of visual interpretation vs. quantitative analysis, partly with the goal of incorporating FDG PET into clinical trials.

Further research in clinical practice settings will be necessary to determine the best place for FDG PET in relation to structural MRI, other forms of MRI, amyloid PET, and spinal fluid markers of diseases causing cognitive impairment and dementia (Dickerson, 2014; Bischof et al., 2016; Dronse et al., 2017). As these new tests become more widely available, practically-oriented studies will contribute importantly to dialogue among neurologists aiming to balance diagnostic rigor with cost effectiveness. These discussions will move to center stage if we are fortunate enough to move into an era in which we have effective disease-modifying therapies.

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