Diagnostic tests for Alzheimer disease

FDG-PET imaging is a player in search of a role

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Imaging with [^{18}F]fluorodeoxyglucose-positron emission tomography (FDG-PET) offers excellent insights into regional brain dysfunction but fails to deliver tangible benefits in most clinical settings in persons with suspected cognitive impairment. The radiation exposure from a single FDG-PET brain scan is 1.3 rem, equivalent to about 3 chest X-rays or 4 months of background radiation; therefore, while unnecessary exposure to radiation is to be avoided, my view is not driven by risks of PET scanning. It is the realities of clinical diagnostics and the lack of potent interventions for specific dementing illnesses that limit the value of FDG-PET.

Diagnoses of mild cognitive impairment (MCI) or dementia are entirely based on information obtained from the history and cognitive examination. Distinguishing abnormal cognition from normal cognition can sometimes be very challenging. As clinicians, we are often confronted with patients who report cognitive complaints that seem discordant with their level of daily functioning. Because there is a wide range of what is considered normal based on education, occupation, and cultural background, and because mood or motivation issues sometimes cloud performance, the distinction between normal and impaired can be very difficult. An FDG-PET scan will not solve this problem. The availability of FDG-PET offers a seductive but flawed logic that goes something like this: "Even though I don't know clinically whether the person has cognitive impairment or not, an abnormal FDG-PET would confirm that the cognitive complaints are real." One cannot and should not use a metabolic scan pattern to determine whether a person's function is abnormal or not. The problem is specificity. I acknowledge that the specificity of FDG-PET for Alzheimer disease (AD) might be as high as 90%[1] vs normal controls, yet in one well-studied cohort, the Alzheimer's Disease Neuroimaging Initiative, it was only 70%.[2] Thus, application of FDG-PET where the pretest probability is low will result in more false positives than true positives. "Abnormal" FDG-PET scans might occur in cognitively normal persons who are at risk for future cognitive decline, but there are many factors that modify risk, including age, comorbidity, and cognitive reserve. Until further research clarifies the time-dependent risks associated with age, comorbidity, and

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baseline intellect, it would be easy to falsely label a cognitively normal subject as abnormal by FDG-PET. Using FDG-PET in a situation where the diagnosis of cognitive status was uncertain is asking for trouble. Even in persons with early symptomatic cognitive decline, the lack of therapeutic options nullifies the value of FDG-PET.

The etiologic diagnosis of cognitive impairment can be made on clinical grounds in most patients to a reasonable degree of accuracy, and imaging biomarkers beyond routine structural MRI do not add much value. The clinical diagnosis of AD dementia has been extensively studied. The sensitivities and specificities are in the 80% and 70% range.[3] The clinical diagnosis is based on a set of criteria, recently updated, that have a track record of success. The clinical diagnoses of dementia with Lewy bodies (DLB) and the frontotemporal lobar degenerations (FTLD) also have good fidelity for pathologic diagnoses. To be sure, diagnostic accuracy in the degenerative dementias is not high, but it is "above average." It is of note that the majority of missed diagnoses involve multiple pathologies.

FDG-PET has a sensitivity of 87% vs other dementias.[1] There are distinctive patterns of hypometabolism for AD, FTLD, and DLB, but by the same token, there are also distinctive clinical syndromes that occur with these pathologies. I acknowledge there are instances of patients with complex histories and equivocal examinations when I would appreciate the anatomic information supplied by FDG-PET. One carefully designed study showed that FDG-PET offered additional diagnostic accuracy for distinguishing AD from FTLD.[4] The distinction between AD and FTLD-related disorders is probably the most justifiable one for the use of FDG-PET.[4,5] In fact, it is the one indication that the Center for Medicare and Medicaid Services endorses. Rather than waffling on the distinction between AD and FTLD, the images from an FDG-PET scan might offer family members a more satisfying sense of closure. While I cannot dispute the emotional importance of a sense of certainty, in practical terms, that comfort probably changes management very little or not at all, at least in 2012.

The distinction between AD and DLB can also be a difficult one. Unfortunately, there is extensive neuropathologic overlap of AD and DLB pathology, compromising the diagnostic distinction between AD and DLB by FDG-PET alone without using yet other imaging modalities. A diagnosis of DLB based on the presence of typical symptoms has value because it leads to therapeutic interventions for problems of parkinsonism, cognitive decline, and sleep disorders. An FDG-PET diagnosis of the metabolic pattern of DLB will not change therapy if the typical DLB symptoms are not present.

Cerebrovascular disease (CVD) invariably is in the differential diagnosis in later life cognitive disorders. CVD has extensive overlap with AD neuropathologically. Thus, it is possible that a patient with both CVD and AD could have an FDG-PET that shows an AD signature despite extensive vascular pathology. Because there is no FDG-PET signature of cerebrovascular cognitive impairment, FDG-PET imaging will not distinguish "pure" AD from AD combined with CVD. Structural MRI is still best at detecting CVD lesions.

The absence of interventional opportunities for the neurodegenerative dementias imposes a conceptual limit on the utility of FDG-PET, and no amount of meta-analysis of existing data can trump that fact. Still, patients and family members might not like to hear that there is uncertainty in the etiology of the disorder. I, too, am uncomfortable with that uncertainty. That uncertainty undermines confidence in the other aspects of the diagnostic process that, in

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turn, increases anxiety, stress, and frustration. However, with or without an etiologic label, I will treat the symptoms that the patient exhibits as best I can. I will discuss the future with family members (and the patient, if appropriate) with the uncertainty. In the future, I hope that I will be able to use FDG-PET, or some other biomarker, to identify persons who would benefit from potent disease-modifying therapies that we will have in our armamentarium.

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