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Fluorodeoxyglucose positron emission tomography: emerging roles in the evaluation of putative Alzheimer's disease-modifying treatments

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Abstract

Alzheimer's disease (AD) is associated with characteristic and progressive reductions in flourodeoxyglucose positron emission tomography (FDG PET) measurements of the regional cerebral metabolic rate for glucose. These reductions begin years before the onset of symptoms, are correlated with clinical severity, and may help predict an affected patient's clinical course and neuropathological diagnosis. Like several other AD biomarkers, FDG PET has the potential to accelerate the evaluation of AD-modifying treatments, particularly in the earliest clinical and preclinical stages. This article considers FDG PET's role in the detection and tracking of AD, its emerging roles in the evaluation of disease-slowing treatments, some of the issues involved in the acquisition, analysis, and interpretation of FDG PET data, and the evidence needed to help qualify FDG PET and other biomarkers for use in the accelerated approval of AD-slowing treatments. It recommends scientific strategies and public policies to further establish the role of FDG PET and other AD biomarkers in therapeutic trials and find demonstrably effective disease-modifying and presymptomatic AD treatments as quickly as possible.

Keywords: Alzheimer's disease; Brain imaging; Biomarkers; Clinical trials; Positron emission tomography; Magnetic resonance imaging; Cerebrospinal fluid; Dementia; Mild cognitive impairment; Preclinical; Presymptomatic; Treatment; Prevention

1. Introduction

As noted in the other Alzheimer's Disease (AD) Biomarkers Working Group articles, there is an urgent need to find demonstrably effective treatments to slow the progression of AD and a growing number of promising but unproven AD-modifying treatments that need to be evaluated. Right now, it takes too many research participants, too much money, and too much time to evaluate investigational AD-modifying treatments using clinical endpoints, particularly in the earliest clinical and preclinical stages of AD, when some of these treatments are likely to have their most profound benefit. The field urgently needs both the means and accelerated regulatory approval pathway to evaluate these treatments in the most rapid, cost-effective, and sufficiently rigorous way. Among other things, biomarker measurements of AD pathology and progression have the potential to reduce the number of research participants in randomized clinical trials (RCTs) and reduce the duration of these trials, particularly in the earliest clinical and preclinical stages of AD. The most promising biomarkers for the evaluation of putative AD-slowing treatments include volumetric magnetic resonance imaging (MRI) measurements of brain shrinkage, fluorodeoxyglucose positron emission tomography (FDG PET) measurements of regional reductions in the cerebral metabolic rate for glucose (CMRgl), PET measurements of fibrillar amyloid-β (Aβ) burden, and cerebrospinal fluid (CSF) measurements of low Aβ_{42} concentrations, high total tau and phospho-tau concentrations, and high total- or phospho-tau-to-Aβ_{42} ratios. These measurements have increasingly important, complementary, and converging roles in the evaluation of AD-slowing treatments.

In this review, we briefly consider FDG PET's established role in the detection and tracking of AD, its emerging

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roles in the evaluation of AD-slowing treatments in each of these stages, and some of the issues and uncertainties that need to be considered in the acquisition, analysis, and interpretation of FDG PET data for these purposes. We also consider the evidence needed to qualify FDG PET measurements for use as a surrogate endpoint, i.e., a biomarker considered reasonably likely to predict a clinical outcome—in the accelerated approval of AD-slowing treatments. Finally, we offer scientific and public policy recommendations to further establish the role of FDG PET and other AD biomarkers in the evaluation of AD-modifying treatments, galvanize the evaluation of investigational treatments in not only the clinical but preclinical stages of AD, and find demonstrably effective clinical and preclinical AD treatments as quickly as possible. For a more detailed discussion of these issues, please see Reiman and Langbaum (2009), and Reiman et al. (2010).

2. An established biomarker for the early detection and tracking of AD

FDG PET is the best established functional brain imaging technique for the detection and tracking of AD. AD is associated with preferential CMRgl reductions in precuneus and posterior cingulate, parietal and temporal cortex, beginning before the onset of symptoms, and extending into frontal cortex and whole brain in the later symptomatic stages of the disorder (Alexander et al., 2002). (A smaller number of studies have reported preferential CMRgl reductions in entorhinal cortex, hippocampal and medial temporal regions of interest [ROIs].) The CMRgl reductions are thought to reflect reductions in the activity or density of terminal neuronal fields or perisynaptic glials cells, mitochondrial or other metabolic dysfunctions, or a combination of these factors. (They are not solely attributable to the combined effects of brain atrophy and partial volume averaging.) Thus, FDG PET measurements are thought to provide information about AD-related synaptic dysfunction or loss, a downstream event in the pathogenesis of AD thought to be most closely related to cognitive impairment, thus complementing the information provided by other downstream biomarker measurements (e.g., MRI measurements of brain shrinkage and increases in CSF total tau and phospho-tau), and information about fibrillar Aβ burden, which may be an earlier event that is less well correlated quantitatively with cognitive decline, at least in the symptomatic stages of AD.

In patients with Alzheimer's dementia, the CMRgl reductions are correlated with clinical severity, predict subsequent clinical decline, and the neuropathological diagnosis of AD with about 84%–93% sensitivity and about 73% specificity (Jagust et al., 2007; Silverman et al., 2001), and continue to decline over time. In patients with mild cognitive impairment (MCI), the CMRgl reductions, alone or in conjunction with other information (such as apolipoprotein E [APOE] ε4 carrier status or smaller hippocampal volumes) have shown the potential to predict subsequent rates of progression to Alzheimer's dementia. Characteristic and progressive CMRgl reductions have also been reported in cognitively normal late-middle-aged carriers of the APOE ε4 allele, the major genetic risk factor for late-onset AD; baseline reductions and 2-year declines were correlated with APOE ε4 gene dose (reflecting 3 levels of genetic risk for AD), were apparent before evidence of hippocampal shrinkage, and were found at roughly the same ages in which PET and CSF evidence of Aβ pathology have been reported in other studies. While some of the CMRgl reductions have been reported in young adult APOE ε4 carriers almost 5 decades before the estimated average age at clinical onset, may even be developmental, and may not progress further until middle age, these reductions predict some of the brain regions associated with the earliest progressive CMRgl decline and fibrillar Aβ burden at older ages. CMRgl declines in cognitively normal carriers of certain early-onset AD-causing mutations and in cognitively normal older people who subsequently show cognitive decline, even after controlling for their APOE genotype. Analyses from a small single-center study and the larger multicenter AD Neuroimaging Initiative (ADNI) support the possibility that FDG PET could be used as an endpoint to evaluate the efficacy of putative AD-modifying treatments in a fraction of the Alzheimer's dementia patients, MCI patients, and cognitively normal subjects at genetic risk for AD who would be needed to evaluate the treatment using clinical endpoints. Indeed, one could argue that FDG PET and other biomarkers are critically needed to provide a sufficiently rapid and cost-effective way to evaluate these treatments in the preclinical stages of AD.

3. Emerging roles in therapeutic trials

3.1. Use as a therapeutic trial endpoint

Like several of the other AD biomarkers described in our Working Group articles, FDG PET could be used as an endpoint to reduce the number of Alzheimer's dementia, MCI, and cognitively normal at-risk subjects in trials and the time to evaluate putative AD-slowing treatment effects. For instance, we used longitudinal natural history data from ADNI to estimate a need for about 70 Alzheimer's dementia patient completers per group to detect a 25% treatment effect (in this case, a slowing of CMRgl decline in an empirically predetermined statistical region of interest) with 80% power and 2-tailed $p = 0.05$ in a 12-month, multicenter, parallel-group, placebo-controlled RCT (Chen et al., 2010). This number (70) is roughly comparable to the number of completers needed using the best MRI-based measurements of regional or whole brain shrinkage, and it is a fraction of the approximately 600 completers per group estimated to detect a 25% treatment effect using the com-

monly used AD Assessment Scale—Cognitive (ADAS-Cog). We used ADNI longitudinal data to estimate a need for about 220 MCI patient completers per group to detect a 25% treatment effect with 80% power and 2-tailed $p = 0.05$ in a 12-month, multicenter, parallel-group, placebo-controlled RCT, again roughly comparable to the number of patients needed using the best MRI-based measurements of regional or whole brain shrinkage, and a fraction of the approximately 4400 completers estimated to detect a 25% treatment effect using the AD Assessment Scale—Cognitive (Chen et al., 2010). We used longitudinal data from a study of initially late-middle-aged cognitively normal APOE $\varepsilon 4$ homozygotes, heterozygotes, and noncarriers to estimate the need for fewer than 200 cognitively normal APOE $\varepsilon 4$ homozygote or heterozygote completers per group to detect a 25% treatment effect with 80% power and 2-tailed $p = 0.05$ in a 24-month parallel-group, placebo-controlled RCT (Reiman et al., 2001; Reiman et al., unpublished data), thus providing the potential to evaluate a range of putative AD-modifying treatments in the clinical stages of AD without having to study many thousands of research subjects or wait many years to detect a clinical benefit.

It is important to note several caveats and lingering questions, almost all of which could be addressed as FDG PET and the other promising biomarkers are embedded into clinical trials. First, the sample-size estimates noted above were based on data from a limited number of subjects and have a large confidence interval. Second, the estimates are at least partly based on the specific image analysis technique used, and researchers continue to develop, test, and compare numerous image analysis techniques in terms of their statistical power and freedom from the type I error associated with multiple regional comparisons. Third, with the increasing use of FDG PET in clinical trials, it will be possible to determine the extent to which different treatments can slow the decline in FDG PET and other biomarker measurements (some of which may be harder to budge than others) and the extent to which the treatment's biomarker effects are reasonably likely to predict a clinical outcome—the evidence needed for regulatory agencies to qualify FDG PET for use (as an unvalidated but reasonably likely surrogate endpoint) in the accelerated approval of AD treatments. Fourth, it is important to anticipate and prepare for the possibility that a treatment might have a confounding effect on FDG PET or other biomarkers of interest unrelated to disease slowing (e.g., an effect on synaptic activity, metabolism, or density unrelated to synaptic loss in the case of FDG PET or an effect on brain swelling unrelated to brain atrophy in the case of volumetric MRI). To help address this issue, we have proposed the acquisition of additional FDG or MRI images shortly after a treatment is started or discontinued to help address treatment effects unrelated to disease-slowing as well as the use of complementary biomarkers to help overcome any modality-specific confounding effect.

3.2. Use in subject selection and subgroup analyses

In addition to using information from sequential scans as an endpoint in therapeutic trials, FDG PET could also be used to help select research participants for enrollment or subgroup analyses in clinical trials of putative AD-modifying treatments. For instance, FDG PET measurements could be used alone or in combination with other information to select those MCI patients at highest risk for clinical progression to Alzheimer's dementia, further reducing the sample size and treatment duration needed to detect treatment effect (Chen et al., 2011; Landau et al., 2010). It may also have a role in identifying those patients most likely to benefit from an AD-slowing treatment, reducing attrition in the drug product's development. Consider, for instance, the evaluation of an Aβ-modifying therapeutic agent in cognitively normal people with PET or CSF evidence of Aβ pathology: one could make a plausible case that those individuals who also show FDG evidence of significant synaptic pathology may show a preferential response to treatment during the trial due to a higher risk of subsequent clinical decline or, conversely, a preferential resistance to the treatment due to the extent to which the downstream events have already ravaged the brain.

4. Methodological issues

In order to maximize statistical power, the ability to compare findings from different studies, and freedom from potentially confounding effects (like a sensory or task-dependent increase in local neuronal activity), ADNI researchers developed standard operating procedures for the acquisition of FDG PET scans, some of which have been further developed for use in clinical trials. For instance, they have proposed the acquisition of images in the resting state (eyes open and directed forward in a dark room with minimal sensory stimulation) to minimize potentially confounding effects of sensory and motor activity of regional CMRgl, use of phantom data to qualify PET systems for use in clinical trials, standardized radiotracer uptake and dynamic scanning periods, manufacturer-dependent image reconstruction and attenuation-correction algorithms, real time quality assessment and quality control, the centralized standardization of PET images to a common spatial resolution, and strategies to minimize the likelihood of scanner changes during the study. Researchers continue to develop, test, and compare different image analysis techniques in terms of their ability to predict clinical progression, track CMRgl decline, and evaluate AD-modifying treatments with the best statistical power and freedom from the type I error associated with multiple comparisons. As previously noted, we recommend the use of additional scans and complementary biomarker endpoints to help address the potentially confounding effects of treatment on different biomarker measurements.

5. Scientific and public policy recommendations

Despite the expense, we recommend the use of multiple brain imaging and CSF biomarker endpoints in clinical trials for these reasons: (1) to provide converging evidence in support of a treatment's AD-modifying effects; (2) to help overcome the possibility of modality-specific confounding effects on any individual biomarker measurement (e.g., it might have been useful in characterizing the AD-modifying effects of the investigational Aβ immunization therapy AN1792 in the face of its possibly confounding effects on volumetric MRI measurements of brain shrinkage); (3) to help address different questions and anticipate the possibility that a combination of biomarker effects (e.g., Aβ-modifying plus 1 or more downstream biomarker effects) may be needed to predict a treatment's clinical benefit; and (4) to provide additional evidence to qualify 1 or more of these biomarker measurements for use in therapeutic trials, including those trials initiated before symptoms, when the use of clinical endpoints is not practical and when some of the treatments now in development may be likely to have their most profound clinical benefit. Because FDG PET has been shown to characterize AD-related CMRgl declines in the preclinical stages of AD, its inclusion in clinical trials would not only advance the evaluation of the particular investigational treatment but also help provide the evidence needed to suggest its use for the accelerated approval of preclinical AD treatments.

We recommend testing potentially disease-modifying treatments in the earliest clinical stage or even the preclinical stage of the disorder, not only to be able to observe a benefit but also to provide evidence that a treatment's biomarker effects are reasonably likely to predict a clinical benefit. The field urgently needs both the means and the accelerated regulatory approval pathway to find demonstrably effective clinical and preclinical AD treatments as quickly as possible.

Conflict of interest statement

The author discloses no conflicts of interest.

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