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Featured Article

Safety of disclosing amyloid status in cognitively normal older adults

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Abstract

Introduction: Disclosing amyloid status to cognitively normal individuals remains controversial given our lack of understanding the test's clinical significance and unknown psychological risk.

Methods: We assessed the effect of amyloid status disclosure on anxiety and depression before disclosure, at disclosure, and 6 weeks and 6 months postdisclosure and test-related distress after disclosure.

Results: Clinicians disclosed amyloid status to 97 cognitively normal older adults (27 had elevated cerebral amyloid). There was no difference in depressive symptoms across groups over time. There was a significant group by time interaction in anxiety, although post hoc analyses revealed no group differences at any time point, suggesting a minimal nonsustained increase in anxiety symptoms immediately postdisclosure in the elevated group. Slight but measureable increases in test-related distress were present after disclosure and were related to greater baseline levels of anxiety and depression.

Discussion: Disclosing amyloid imaging results to cognitively normal adults in the clinical research setting with pre- and postdisclosure counseling has a low risk of psychological harm.

Keywords: Amyloid PET imaging; Depression; Anxiety; Truth disclosure; Diagnostic imaging; Preclinical Alzheimer's disease; Biomedical ethics; Safety

1. Introduction

Molecular imaging techniques allow the in vivo detection of amyloid plaques in the brain, a hallmark neuropathological feature of Alzheimer's disease (AD) [1]. This technique has stimulated a new era of prevention studies focused on the 20%–40% of cognitively normal adults who have evidence of cerebral amyloid deposition at levels similar to those observed in people with AD [2–5].

The clinical relevance of the presence of amyloid plaques in the absence of cognitive symptoms remains imprecisely defined at the individual level. Early studies are mixed [6] but suggest cerebral amyloid is associated with greater mean rates of cognitive decline [3,7,8] and brain atrophy [9,10] at a group level. Additionally, the odds of developing AD over time are higher for those with an elevated amyloid level compared with those with nonelevated cerebral amyloid [11]. Not all individuals with cerebral amyloid, however, progress to dementia. Currently, precise estimates of the magnitude and timeframe for future risk of dementia are not available although imaging and pathological studies suggest plaques may accumulate up to 10 to 15 years before the onset of clinically recognized dementia [12].

Prevention trials are increasingly leveraging this potential window of opportunity using amyloid imaging to enrich a clinical trial sample with individuals at higher risk of developing AD. Based on trial design, these studies necessitate disclosing amyloid positron-emission tomography (PET) results to the individuals enrolled, raising ethical and safety issues. The psychological and behavioral impact of amyloid PET disclosure is currently not well described [13]. One

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small study [14] of only four participants found no evidence of deleterious psychological effects. Other survey-based studies of individuals who had not been scanned suggested some may use the information to plan ending their life [15,16]. Thus, understanding the psychological impact of disclosing amyloid imaging results to cognitively normal adults remains important.

We examined the safety and tolerability of disclosure in an ongoing study testing the effects of exercise on cognitively normal individuals with elevated cerebral amyloid (the University of Kansas Alzheimer's Prevention through Exercise [APEX] Trial). We assessed measures of anxiety, depression, and distress at baseline, day of disclosure, and at 6 weeks and 6 months postdisclosure.

2. Methods

The APEX study is a randomized trial examining the effects of aerobic exercise on AD biomarkers (amyloid burden and magnetic resonance imaging volumetrics) and cognitive decline in cognitively normal older adults 65 years and older (NCT02000583) conducted at the University of Kansas Alzheimer's Disease Center. Participants are screened with amyloid PET imaging, and those with elevated cerebral amyloid are randomized to 52 weeks of aerobic exercise versus a stretching/toning control intervention (2:1 ratio) conducted under supervision at community-based exercise facilities. For this study, we used data collected on the first $n = 101$ participants who were screened with amyloid PET imaging and completed.

Participants complete a standard in-person clinical and cognitive evaluation through the University of Kansas Alzheimer's Disease Center to exclude dementia or mild cognitive impairment. A trained clinician completes a Clinical Dementia Rating (CDR) [17,18] and a psychometrician performs a neuropsychological test battery. Clinical and cognitive data are reviewed at a consensus diagnostic conference, and cognitively normal participants are defined as having a CDR 0 and no clinically significant deficits on neuropsychological testing. Participants are also required to be sedentary or underactive based on the Telephone Assessment of Physical Activity [19] (score of $\leq$4) and willing to participate in a 52-week exercise intervention. Family history of dementia was ascertained by participant self-report of late-life cognitive impairment or behavior change in a first-degree relative (National Alzheimer's Coordinating Center Uniform Data Set, versions 2 and 3) [20]. Exclusion criteria included clinically significant depression or anxiety per clinician impression or as indicated by exceeding cut points on the Geriatric Depression Scale [21] (GDS $\geq$ 5) or Beck Anxiety Index (BAI $>$ 16) [22]. Participants meeting these criteria proceed to florbetapir PET scanning to screen for those with elevated amyloid who are eligible for enrollment into the 1-year exercise trial. All participants provide institutionally approved informed consent before participating.

2.1. Disclosure process

Florbetapir PET scanning and disclosure involve three in-person visits (prescan counseling visit, amyloid PET scanning visit, and disclosure visit) and 6-week and 6-month follow-up surveys by e-mail or phone.

2.1.1. Prescan counseling

Participants are provided a detailed Participant Guide (see Supplementary Material) for review at home before their prescan counseling session. The guide provides information on AD, amyloid, amyloid imaging, and the possible results of amyloid imaging. An in-person counseling visit is conducted to discuss the amyloid PET scan, possible results (elevated versus nonelevated), limitations of the scan (it is not a diagnostic test), and to ensure the participant remains interested in obtaining the scan and learning the result. A clinician meets with the participant, reviews the Participant Guide, and answers questions. We developed general talking points (see Supplementary Material) that provide the clinician with an outline for guiding the discussion. First, the clinician discusses known AD risk factors of age, family history, and modifiable AD-related risk factors (i.e., cardiovascular-related risk factors) and introduces the concept of amyloid PET scanning as a risk factor for developing AD. Next, amyloid is explained as something present in those with AD and about one-third of those age 65 and older without evidence of cognitive decline. The two possible results (elevated vs. nonelevated) are next explained. An elevated result is explained to mean an individual is at higher risk of developing AD, stressing that this does not mean an individual will develop AD or has AD currently. A result of nonelevated indicates a lower risk, but not without risk, of developing AD. Additionally, we stress this is a new technique and that false positives and false negatives are possible. Scan results are not shared with the participant's physicians or entered into the medical record.

2.1.2. Amyloid imaging and scan interpretation

PET images are obtained on a GE Discovery ST-16 PET/CT scanner after administration of intravenous florbetapir F-18 (370 MBq). Two PET brain frames of five minutes in duration were acquired continuously, approximately 50 minutes postinjection of the florbetapir. Frames were then summed and attenuation corrected before interpretation. MIMneuro software (MiM Software, Inc., Cleveland, OH) quantitatively normalized the amyloid-β PET image to the entire cerebellum to calculate the standard uptake value ratio (SUVR) for six regions of interest (ROIs): anterior cingulate, posterior cingulate, precuneus, inferior medial frontal, lateral temporal, and superior parietal cortex. Three trained raters reviewed the visual images, the quantitative SUVR ROI data, and MIMneuro-generated cortical projections of amyloid burden (z-scores comparing the SUVRs with an SUVR map of 74 individuals [48 males and 26 females] between the ages of 18 and 50) to assess the scans as