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Clinical use of amyloid-positron emission tomography neuroimaging: Practical and bioethical considerations

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Abstract Until recently, estimation of β-amyloid plaque density as a key element for identifying Alzheimer's disease (AD) pathology as the cause of cognitive impairment was only possible at autopsy. Now with amyloid-positron emission tomography (amyloid-PET) neuroimaging, this AD hallmark can be detected antemortem. Practitioners and patients need to better understand potential diagnostic benefits and limitations of amyloid-PET and the complex practical, ethical, and social implications surrounding this new technology. To complement the practical considerations, Eli Lilly and Company sponsored a Bioethics Advisory Board to discuss ethical issues that might arise from clinical use of amyloid-PET neuroimaging with patients being evaluated for causes of cognitive decline. To best address the multifaceted issues associated with amyloid-PET neuroimaging, we recommend this technology be used only by experienced imaging and treating physicians in appropriately selected patients and only in the context of a comprehensive clinical evaluation with adequate explanations before and after the scan.

Keywords: Alzheimer's disease; Mild cognitive impairment; Bioethics in neurology; Positron emission tomography; Diagnostic use; Dementia; Biomarkers; Amyloid-β

1. Introduction

Amyloid-β positron emission tomography (hereafter termed amyloid-PET) neuroimaging has been a useful tool in Alzheimer's disease (AD) research [1–3] and as a technique for subject enrichment in AD clinical trials to ensure that only those with underlying β-amyloid plaque pathology are enrolled [4]. The recent clinical availability of amyloid-PET now allows physicians to estimate the

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density of β-amyloid plaques during life, rather than postmortem, and to assess whether significant amyloid-β burden (moderate-to-frequent neuritic plaques needed to meet pathologic criteria for intermediate or high likelihood that AD pathology is the cause of dementia) is present. However, although amyloid-PET accurately detects the presence of β-amyloid plaques, the scan by itself captures only one core element of AD pathology (neuritic plaques but not neurofibrillary tangles). For example, patients with amyloid-β pathology often have other neuropathologies such as Lewy bodies or cerebrovascular disease, and interpretation may be further complicated by factors such as depression and cognitive impairment due to medications. As amyloid-PET enters into clinical use, it is important that practitioners and patients understand the potential diagnostic benefits and limitations of amyloid-PET. Furthermore, they need to recognize the complex practical, ethical, and social implications surrounding this new technology.

To complement the practical considerations, Eli Lilly and Company (Lilly) sponsored a multidisciplinary Bioethics Advisory Board to consider bioethical issues that might arise when using amyloid-PET as an adjunctive diagnostic tool to clinically evaluate patients with cognitive impairment. Our intent was not to propose evidence-based guidelines for clinical use of amyloid-PET because these were already being developed and subsequently published by the joint efforts of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the Alzheimer's Association (AA) [5,6]. Instead, we considered whether clinical use might have unexpected implications within and beyond interactions between doctors and patients and their families.

Academic experts in dementia, PET neuroimaging, bioethics, and a representative from a United States-based caregiver advocacy group discussed issues with Lilly and Avid Radiopharmaceuticals staff. Topics included ethical issues related to the diagnosis, management, and practical life concerns faced by patients, caregivers, and physicians/health care professionals. After the advisory board meeting, a subgroup of attendees collaborated to refine the concepts discussed and to write this report. In addition to a description of pertinent ethical issues, we will also present case study examples that illustrate application of bioethical principles for decision-making with individual patients and clinical situations. Finally, we provide practical recommendations for clinicians to consider when discussing the use of amyloid-PET with patients and their families.

2. Background

AD is the most common cause of gradually progressive cognitive and functional decline in older persons and accounts for 60%–80% of all dementias [7,8]. Clinical diagnosis of AD has been primarily made by assessing progressive decline in cognitive abilities and ruling out other common causes for cognitive impairment [9–11]. Thus, clinical information was used to infer the presence of AD pathology. Understandably, this inference was not always accurate and neuropathologic examination has remained the "gold standard." Recently, studies have assessed the accuracy of clinical diagnostic methods for possible or probable AD compared with neuropathology at autopsy. One study reported that the sensitivity of clinical AD diagnoses ranged from 70.9% to 87.3% and specificity ranged from 44.3% to 70.8% versus pathology, depending on the levels of certainty for either clinical or neuropathologic criteria [12]. Difficulty in achieving accurate clinical diagnoses of AD may arise because common dementing diseases, such as vascular dementia, dementia with Lewy bodies, frontotemporal dementia and others, share many symptoms with dementia due to AD and frequently coexist with AD pathology [13,14]. It is not surprising in these circumstances that postmortem studies find that the accuracy of clinical diagnosis of cognitive disorders can range widely depending on the population studied, the intensity of evaluation, and the skill of the clinician [12,14–16].

Furthermore, the National Institute on Aging (NIA)-Reagan neuropathologic criteria for AD classified findings as indicating low, intermediate, or high likelihood that the pathology caused the dementia, explicitly recognizing that

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