

Editorial

Circular Inference in Dementia Diagnostics

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Abstract. Referring to recent international articles stating that amyloid imaging or detection has a high additive value in making a diagnosis of Alzheimer's disease (AD) when previous investigations are inconclusive, the authors of this editorial argue that this statement is based on circular reasoning and, hence, misleading. Since autopsy findings and other potential indicators fit poorly with amyloid PET, they conclude that this examination has no role in the diagnosis of AD.

Keywords: Alzheimer's disease, amyloid PET, circular inference, dementia

Circular inferences are conclusions based on assumptions that follow, rather than precede, the conclusions. It is not a new phenomenon in neuroscience [1–3]. A recent example is a report in the *European Journal of Nuclear Medicine and Molecular Imaging* (EJNMMI), authored by Brendel and co-workers [4]. The report immediately was cited by *Health Imaging* under the headline “Amyloid PET shows good additive value when standard PET isn't conclusive on dementia” [5]. This statement is misleading and dangerous because its circular message may help cement the claim that amyloid- β (A β) deposition determined by PET is beneficial to the management of patients with Alzheimer's disease (AD), and as such, superior to FDG deposition alone, as detected by PET. The EJNMMI article reports on [¹⁸F]florbetaben (FBB) PET in 107 patients with suspected dementia that remained unclarified after FDG-PET. It states that in

83% of formerly unclear cases, a “final diagnosis was reached through FBB-PET, and the most likely prior diagnosis was changed in 28% of cases” [4].

The article [4] initially offers a reminder that appropriate use of amyloid imaging applies to patient groups with 1) early onset of progressive dementia; 2) atypical or mixed presentation of AD; and 3) persistent or progressive unexplained mild cognitive impairment (MCI), according to the joint recommendations by the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association in the USA. In this way, the authors imply that the presented results meet these requirements, although they do not. Group #1 was not a subject for the Brendel et al. article, and no study to date has been able to demonstrate that A β PET can distinguish between early and late onset AD. In groups #2 and #3, the article states that FBB imaging has additive value, which unfortunately was not demonstrated, as this requires a study design with an infallible reference that answers with certainty whether or not AD was present. Had such a method existed, the current study would have

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no justification, but to reason inversely, that in the absence of a gold standard, the current study and its results are justified, is equally incorrect.

In brief, the article argues as follows: Amyloid plaques are a hallmark of AD and amyloid PET tracers like FBB are sensitive to the presence of brain amyloid pathology *in vivo* as confirmed by autopsy studies; therefore, FBB-PET can verify the presence or absence of AD by demonstrating amyloid deposits. Thus, the patients with MCI in the Brendel et al. study [4] had initially their most likely diagnosis established according to ICD-10 and “common diagnostic criteria”, after undergoing cognitive testing, MRI, CSF sampling, and FDG-PET examinations. Patient diagnoses were discussed by an interdisciplinary dementia board, which recommended an additional amyloid-PET for 107 selected cases with remaining “uncertainty in the final diagnosis.”

Of these, 65 were visually classified as amyloid-positive and in 61 of these 65 patients (94%), a positive amyloid finding led to the “final diagnosis” for which no independent definitive reference was offered. The board could decide that the addition of an amyloid scan accomplished a stratification of patients that was helpful in 94% of cases, when in actual fact no one could tell whether that was right. Thus, the circle was closed: Amyloid means AD, FBB traces amyloid, and therefore amyloid positive FBB-PET findings are consistent with a correct final diagnosis, except in the few cases that remained equivocal even after FBB imaging [4].

This logic is faulty on several grounds: 1) The criteria for neuropathological diagnosis of AD (National Institutes of Aging-Alzheimer’s Association (NIA-AA)) from the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) has established an “ABC” score for AD entailing a complex regional localization of tau and A β neuro-aggregates rather than the mere presence of amyloid burden [6, 7]. 2) For this reason alone, current A β imaging technology is not suitable to establish the diagnosis of AD. If the presence of amyloid neuropathology in postmortem amyloid pathology cannot provide diagnosis of AD, how can ‘amyloid imaging’ be used to accurately diagnose AD? For this reason, the FDA approval of FFB PET has been limited to the detection of amyloid aggregates, on the assumption that this is accurate.

We hope that regulatory and reimbursement authorities are not seduced by this kind of logic, to the detriment of patients and health expenditures. The logic begs the question when the authors argue

that “AD is present because what we see with amyloid imaging when adding this to other findings can only be described as AD”. Without proof, they create the impression that they obtained a clinically significant result when the addition of a positive amyloid scan resulted in a board-determined AD diagnosis in 61/65 (93%) of patients with an amyloid positive scan, whereas the addition of a negative amyloid scan could rule out AD only in 28/42 (67%) of cases with a negative scan. At the same time, the most likely prior diagnosis was changed in 14/65 (22%) of cases in the former group versus 16/42 (38%) in the latter [4]. We argue that this reasoning has no clinical value.

In their *Decision Memo for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease* of September 2013, the Centers for Medicare & Medicaid Services (CMS) state that they will cover only one PET A β scan per patient through coverage with evidence development (CED) in clinical studies that meet the criteria in each of two scenarios: “(1) to exclude Alzheimer’s disease (AD) in narrowly defined and clinically difficult differential diagnoses, such as AD versus frontotemporal dementia (FTD); and (2) to enrich clinical trials seeking better treatments or prevention strategies for AD, by allowing for selection of patients on the basis of biological as well as clinical and epidemiological factors.” To get coverage, clinical studies “must be approved by CMS, involve subjects from appropriate populations, and be comparative and longitudinal” [8]. These conditions were not met by many published studies trying to demonstrate the efficacy of amyloid imaging in the clinical setting, nor by the current report of Brendel et al.

The reference given by Brendel et al. for autopsy confirmation was a phase III clinical study of 216 patients demonstrating correlations between regional FBB SUVs and consensus panel histopathology scores for amyloid plaques in the middle frontal gyrus, occipital, anterior, and posterior cingulate cortex/precuneus but not in the hippocampus/parahippocampal gyrus of 74 deceased subjects [9]. However, ρ -values for significant correlations ranged between 0.40 and 0.70, indicating no relations tight enough to characterize the individual patient as seen also in Fig. 3 of their supplementary material [9]. The Brendel et al. report further states [4] that “importantly, the results of amyloid-PET imaging bring added value in clinical management of individual patients”, even when it adds that: “advanced age hampers the value of amyloid-PET, as positivity is present in more than 40% of cognitively healthy

subjects older than 90 years.” The latter qualification is correct, but Brendel et al. did not take full account of the article they cited. It is a meta-analysis of 2,914 participants with normal cognition, 697 with subjective cognitive impairment (SCI), and 3,972 with MCI aged 18 to 100 years. It demonstrated an increase in prevalence of ‘amyloid imaging’ positivity from 10% at age 50 to 44% at age 90 among participants with normal cognition; from 12% to 43% among patients with SCI; and from 27% to 71% among patients with MCI [10]. Interestingly, a meta-analysis made by the same group of 1,359 participants with clinically diagnosed AD showed a *decrease* in ‘amyloid imaging’ positivity from age 50 to 90 years in APOE ϵ 4 non-carriers from 86% to 68% and to a lesser degree in APOE ϵ 4 carriers [11]. Combined, the reasonable conclusion of these studies is that with such major overlaps between groups, amyloid imaging cannot characterize the individual patient, nor correctly confirm or reject the presence of AD.

The previously described high degrees of amyloid presence in the frontal lobe and white matter further questions the sensitivity and specificity of amyloid imaging agents in detecting AD [12, 13]. Together with neuropathological criteria for the AD diagnosis [6, 7], and a decrease in amyloid deposits with age in demented patients [11], it is increasingly evident that amyloid-PET has no place as a diagnostic tool for AD.

A core element in the foundation of A β imaging is the “Amyloid Hypothesis”, i.e., the claim that amyloid deposition disrupts communication among neurons and eventually leaves them without synapses, and the additional claim that FBB and similar PET tracers actually mark pathologically important species of amyloid and not other tissue targets. Against these claims speaks the fact that neuropathological determinations unquestionably show that A β plaques may be present in the brain of some normal controls, but rarely in ‘widespread, dense AD-type neocortical lesions in cases lacking documented *ante mortem* cognitive decline’ [14]. If so, why would approximately 30% of cognitively normal control subjects, based on amyloid PET, have been reported to have an A β load comparable with that found in AD patients [15]? An additional element against the validity of the concept is the large number of failures that anti-amyloid therapies have suffered during the last decade, see for example reference [16], a fate that recently also befell the antibody treatment of tau deposits that emerged in recent years as an alternative cause of AD [17].

Instead, it previously was said that amyloid deposits would be like open airbags in car accidents, just by-products of neuronal degeneration and not the reverse, such that removal of amyloid plaques not necessarily would bring back neurons that already are highly dysfunctional or dead [18]. Rather than providing added value for the diagnosis of AD, amyloid imaging brings further confusion and little expectation that it would be of value in monitoring effects of upcoming new AD medicines. The high sensitivity of PET and the possibility of quantifying disease extent and severity do not benefit amyloid scanning, as long as the correct association between amyloid deposits and AD is questionable. At this moment, there is little doubt that FDG-PET imaging in AD is the approach that corresponds best with meaningful functional brain activity in patients with suspected dementia [12, 13], and has significant value in its diagnosis, as recognized by CMS approval for reimbursement [19].

The German group, which Brendel et al. belong to, reported earlier this year in another study authored by Daerr et al. about the use of early-phase dynamic FBB uptake as a surrogate marker of cerebral flow [20] as this may be a better way to establish the diagnosis of AD or rather discriminate between various forms of dementia as has recently been shown with ^{11}C -PIB [21]. However, this is an entirely different ball game more in keeping with FDG PET imaging than with late-phase FBB PET.

It is indeed thought-provoking that the reported presence of cerebral amyloid deposits 20–30 years before symptoms develop [10] was not translated into common use of amyloid imaging to detect very early AD. FBB has been reported to increase the confidence of diagnosticians [22], but this does not mean that FBB imaging serves to make a diagnosis of AD, as claimed in the report by Brendel et al. The question of whether A β -PET can discriminate early onset from late onset AD has been addressed several times and the short answer is that it cannot [23, 24]. A recent study aimed to evaluate the cost-effectiveness of the use of [^{18}F]florbetapir (FBP) as an adjunct to standard diagnostic assessment for the diagnosis of AD in France and found that A β -PET used as an adjunct to standard diagnostic assessment increased quality adjusted life years (QALYs) by 0.021 years and 10 year costs by €470 per patient [25]. The authors, several of whom are employed by the company that produces FBP, concluded that A β -PET is likely to affordably increase QALYs. From an independent standpoint, we would conclude the opposite, namely

that the use of A β -PET with FBP is not worth the effort or the cost.

The many reports on A β imaging live their own self-reinforcing life based on the pervasive assumption that presence or absence of amyloid is determinant in the management of AD. An example of this is a brand new letter in *Nature* about the detection of A β biomarkers in blood, using PIB-PET as an assertive reference, which is the focus of circular reasoning [26]. As evidence of this inference, the authors indicate that when there is ‘diagnostic uncertainty about a clinical diagnosis of AD, A β -PET is considered to have a major clinical effect’, and that ‘the plasma biomarker could be helpful for the differential diagnosis of AD and aid in determining therapeutic strategies, by providing additional information on the brain A β deposition status of individuals’ [26].

Common to the failure of these claims, including the current report in EJNMMI, is the state-of-the-art that no infallible reference renders the conclusions unequivocal. Therefore, we ask why there is still faith in amyloid-PET as a diagnostic tool. From scientific and health-economic points of view, the diagnostic use of A β -PET has no justification. The load of insufficient or contradictory information including suboptimal sensitivity and specificity, mismatches among the location of pronounced pathological changes and typical amyloid deposits, insufficient distinction between early and late onset AD, decreasing prevalence of amyloid plaques with age in demented persons, and minimal or non-existent cost-effectiveness, all make for the conclusion that A β PET has no place in the routine work-up of suspected AD.

DISCLOSURE STATEMENT

Authors’ disclosures available online (<https://www.j-alz.com/manuscript-disclosures/18-0050r1>).

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