Original Research Article

Dementia and Geriatric Cognitive Disorders

Impact of Beta-Amyloid-Specific Florbetaben PET Imaging on Confidence in Early Diagnosis of Alzheimer's Disease

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Abstract

Background: Early diagnosis of Alzheimer's disease (AD) may be corroborated by imaging of beta-amyloid plaques using positron emission tomography (PET). Here, we performed an add-on questionnaire study to evaluate the relevance of florbetaben imaging (BAY 94-9172) in diagnosis and consecutive management of probable AD patients. **Methods:** AD patients with a clinical diagnosis in accordance with the NINCDS-ADRDA criteria or controls were imaged using florbetaben. Referring physicians were asked on a voluntary basis about their confidence in initial diagnosis, significance of PET imaging results, and their anticipated consequences for future patient care. **Results:** 121 questionnaires for probable AD patients and 80 questionnaires for controls were evaluated. In 18% of patients who had initially received the diagnosis of probable AD, PET scans were rated negative, whereas in controls 18% of scans were positive. An increase in confidence in the initial diagnosis was frequently reported (80%). Imaging results had a significant impact on the intended patient care, as judged by the referring physicians; this was most prominent in those patients with a contradicting scan and/or a low confidence in the initial diagnosis. **Conclusion:** Florbetaben amyloid imaging increases the overall confidence in diagnosis of AD and may frequently influence clinical decisions and patient management.

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Introduction

Biomarkers that support early diagnosis of Alzheimer's disease (AD) are useful in the differential diagnosis and urgently needed in disease-modifying therapeutic strategies and longitudinal monitoring of disease progression. A pivotal problem in early diagnosis of AD is that clinical symptoms as assessed by neuropsychological tests become apparent only after massive neuronal cell loss has already taken place. Today, there is general agreement that diagnosis of AD should be based on the results of various neuropsychological tests [1], brain imaging [2–4], cerebrospinal fluid (CSF) and blood studies [5–7],

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the patient's own and family history, and a physical examination. Recently, revised guidelines for the clinical diagnosis of AD have been proposed by the National Institute on Aging and the Alzheimer's Association [8]. These guidelines add altered biomarkers as a criterion to enhance the likelihood of underlying AD pathology in the diagnosis of probable AD. Additionally, since a number of disease-modifying therapies like vaccination and immune-modulating strategies are under investigation [9], better diagnostic tools within the biomarker field will be valued.

An ideal biomarker reliably reflects important processes of the underlying disease pathology. In AD, certain biomarkers become abnormal, presumably in a temporally ordered manner. According to a recently published model, at the earliest stage of AD, changes in CSF beta-amyloid appear first, reaching a plateau by the time clinical symptoms emerge [10]. Consecutively, an increase in biomarkers reflecting neuronal injury such as total- and phospho-Tau protein may be followed by first clinical symptoms. To date, beta-amyloid and Tau protein can be determined in the CSF using different techniques [11], but results may be sometimes difficult to interpret. CSF biomarker levels may be weighted by sources of error: Amyloid-beta 1-42 and total-Tau protein levels vary up to 3-fold in different studies [12, 13]. In addition, concentrations may differ depending on the modalities of lumbar puncture, such as time of day and amount of CSF taken [14].

Recently, compounds which can be used in positron emission tomography (PET) to directly visualize beta-amyloid plaques within the human brain have come into focus as a tool to improve diagnosis of AD. The Pittsburgh compound B (PIB), an analog of thioflavin T, represents the most widely used tracer for investigational PET imaging of beta-amyloid plaques in the brain. Retention of the 11C-labeled PiB ([C-11]PiB) has been shown to be approximately 2-fold greater in cortical areas of AD subjects relative to healthy controls, and the patterns of retention reflect the patterns of beta-amyloid deposition known from postmortem studies [15]. Florbetaben, an 18F-labeled tracer utilizing a radioisotope with a longer half-life than PIB [16, 17] is currently being tested in a phase III clinical trial program.

Here, we report on a study to address the question how in a clinical setting the information of results from amyloid-PET imaging in patients with possible or probable AD would influence diagnostic reevaluations of physicians, their choice of treatment options and their intended general patient management.

Table 1. Correlation between the degree of confidence in the initial diagnosis and the level of impact on management of probable AD patients

Degree of confidence in preexisting diagnosis	Level of impact on patient management		
	strong + some	minor + none	total
Very high			
Probable AD patients	25	33	58
Confirming scan	24	30	54
Contradicting scan	1	3	4
Moderate + low			
Probable AD patients	50	13	63
Confirming scan	33	12	45
Contradicting scan	17	1	18
Sum			
Probable AD patients	75	46	121
Confirming scan	57	42	99
Contradicting scan	18	4	22

Fisher exact test (d.f. = 1). Probable AD patients: χ^2 15.35; p value 0.00009; odds ratio 0.20, CI_{95} 0.09–0.44. Confirming scans: χ^2 7.25; p value 0.007; odds ratio 0.29, CI_{95} 0.12–0.68. Contradicting scans: χ^2 6.45; p value 0.011; odds ratio 0.02, CI_{95} 0.00–0.41.

Methods

Participants

Between February 2010 and March 2011, a questionnaire study was conducted as an add-on to the multicenter beta-amyloid-specific florbetaben PET phase IIb trial with a total of 272 patients (demographic data in online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000339367). Study participants were either patients diagnosed with probable AD or healthy volunteers that were directly recruited as unimpaired controls from the community. The lack of cognitive impairment in healthy volunteers was based on an MMSE result ≥28 and a CDR of 0. Patients with probable AD had to fulfill both the DSM-IV criteria for dementia of AD and the NINCDS-ADRDA criteria for AD. The MMSE score had to be between 18 and 26 and the CDR 0.5, 1.0 or 2.0. Duration and history of the disease varied between probable AD patients. CSF biomarker values were only available for a small subset of patients, were not part of the study protocol, and were not further evaluated. For both groups, the diagnosis had been affirmed by magnetic resonance brain imaging before admission to PET scan.

The questionnaire was given to referring physicians in Australia, Germany, Japan, Switzerland, and USA whose patients received florbetaben PET imaging in the context of the phase IIb trial. Fourteen out of a total of 20 centers participated on a voluntary basis. A total of 201 questionnaires were completed and sent back to the authors (supplementary table 2).

Table 2. Analysis of homogeneity amongst the 14 participating centers

Questionnaire item and group	Value of the test statistic	p value
Confidence in diagnosis before PET scan		
AD, all results	8.5693	*0.0034*
AD, negative scan result	0.6341	0.4259
AD, positive scan result	10.5393	*0.0012*
UC, all results	3.5680	0.0589
UC, negative scan result	12.3381	*0.0004*
UC, positive scan result	2.3257	0.1273
Change of confidence in diagnosis after PET scan		
AD, all results	8.0577	*0.0028*
AD, negative scan result	n.v.	n.v.
AD, positive scan result	8.2022	*0.0042*
UC, all results	0.2456	0.6202
UC, negative scan result	2.5937	0.1073
UC, positive scan result	10.5670	*0.0012*
Impact on patient management after PET scan		
AD, all results	0.0248	0.8748
AD, negative scan result	1.9050	0.1675
AD, positive scan result	0.0237	0.8776
UC, all results	0.1591	0.6899
UC, negative scan result	9.2785	*0.0023*
UC, positive scan result	7.3014	*0.0069*

Cochran-Mantel-Haenszel test; p < 0.05, indicative of heterogeneity; p > 0.05, not indicative of heterogeneity; AD = probable AD patients; UC = unimpaired controls; n.v. = no variability.

Procedure

A face-validated, 'fit-for-purpose' clinician questionnaire was designed, consisting of six items evaluating (1) the level of confidence in the initial clinical diagnosis before PET imaging results were known, (2) the objective results of the florbetaben PET scan, (3) the congruency of the PET imaging and the initial diagnosis, (4) the potential change of confidence in the overall diagnosis on the basis of the PET scan results, (5) the importance, and (6) the characteristics of the potential impact on patient management. For the original questionnaire, please refer to the supplementary material.

The questionnaire was validated in advance for clarity and appropriateness by clinical physicians. The questionnaires were completed by the clinical centers that were referring patients to the respective nuclear medicine departments. The returned questionnaires had been fully anonymized.

Statistical Analysis

For statistical analysis, SAS version 9.1 was used. Results are expressed as number (%) or means ± SD unless indicated otherwise. Frequency distributions for categorical variables (see fig. 4) were compared using the Fisher exact test (table 1).
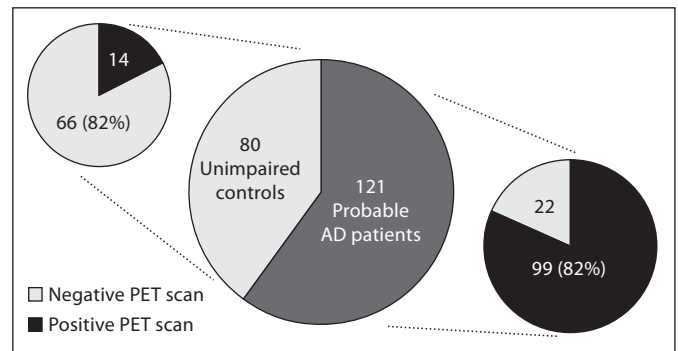
Fig. 1. Frequency of positive and negative florbetaben PET scan results. Numbers are given for patients with the clinical diagnosis of probable AD and for unimpaired controls.

Homogeneity of the participating centers (table 2) was analyzed using the Cochran-Mantel-Haenszel test stratifying for centers. The variables collected were dichotomized as follows: the item 'confidence in diagnosis before PET scan' into 'high confidence' and 'moderate + weak + very weak confidence'; the item 'change of confidence in diagnosis after PET scan' into 'increased + decreased confidence' and 'unchanged confidence'; the item 'impact on patient management after PET scan' into 'strong + some impact' and 'minor + no impact'.

Results

Fourteen out of the 20 centers participating in the florbetaben phase IIb clinical trial returned 201 questionnaires (74% response rate): 121 referred to probable AD patients and 80 to unimpaired controls. Among the 121 probable AD patients, 22 (18%) patients showed no significant beta-amyloid plaque load as examined using the onsite beta-amyloid plaque load visual assessment score [17]. On the other hand, 18% (n = 14 out of 80) of the controls presented with a significant plaque load as assessed by the onsite nuclear physician (fig. 1).

After Knowledge of PET Outcome, Change of Confidence in Diagnosis Is Common

Focusing on AD patients, we were interested to learn whether the results of the beta-amyloid-specific PET scan lead to a change of diagnostic confidence. The overall change of confidence in the initial diagnosis after receiving the PET scan results was common: in 83% of all probable AD cases, a change of confidence, either an increase or a decrease, in the original diagnosis was reported (n = 22 + 77 + 2 = 101 of 121; black and light
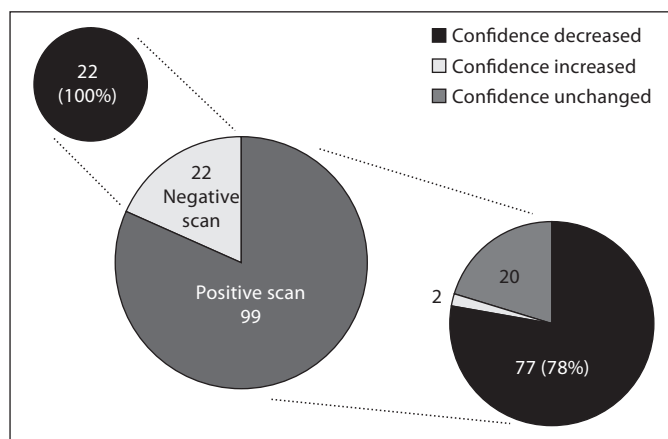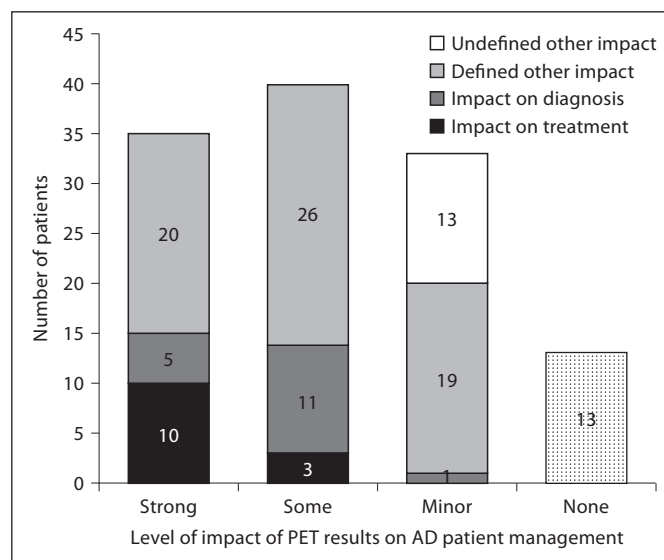
Fig. 2. Frequency and direction of change of confidence in the initial diagnosis on receiving the result of the florbetaben PET scan. Numbers are given for the 121 probable AD patients.

Fig. 3. Level and type of impact on patient management in probable AD patients. For the 121 probable AD patients, the frequency of strong, some, minor, and no impact reported by the physicians is depicted in the four columns. The various shades of the columns indicate the type of impact. Note that although all these patients had been diagnosed with probable AD before receiving a PET scan for beta-amyloid, there is a remarkable number of patients with a significant impact reported.

grey areas, fig. 2). In all probable AD cases with a negative PET scan (n = 22), physicians reported a decrease in confidence in their original diagnosis (fig. 2). In probable AD cases with an expected positive PET scan result, the physicians indicate in 78% of the cases an increase (n = 77), in 2% a decrease (n = 2; reportedly due to lower signal intensities in the PET scans than expected by the physicians), and in 20% no change of confidence in their initial diagnosis (n = 20).

Even in the group of controls, a change of confidence in the initial clinical evaluation was reported in 43% of all the cases (n = 34 out of 80; data not shown). Within the group of controls with an unexpected positive scan, 10 out of 14 cases (71%) reported a decrease in confidence in the original diagnosis; within the group of controls with an expected negative scan, 24 out of 66 cases (36%) reported an increase in confidence.

Physicians Anticipate Impact on Patient Management
In a second step, we aimed to determine whether the results of the PET scan could have an influence on patient management. Overall, physicians reported an anticipated impact on their patient management of probable AD patients in 89% of the cases (n = 108 out of 121) and in 35% of the controls (n = 28 out of 80). Regarding the impact level (strong, some, minor, no impact), we detected a wide range (n = 35 vs. 40 vs. 33 vs. 13 cases, respectively; fig. 3), and in about 2 out of 3 probable AD patients either a strong or some impact. In controls, this distribution was more pronounced (n = 1 vs. 17 vs. 10 vs.

52 cases, respectively; not shown). The actual measures and changes in patient management at a later time point were not evaluated within this study.

When further dissecting the characteristics of the impact in cases of probable AD, we frequently found for 'strong impact' and 'some impact' a relevance regarding the intended treatment or alternative diagnostic options (fig. 3, black and dark grey areas). The term 'defined other impact' in strong, some and minor impact categories includes 'reassurance to continue the preexisting treatment', 'recommendations for a modified lifestyle', 'change in communication with the patient', and occasionally 'validation for inclusion into a vaccination trial' (fig. 3, light grey areas). A minor impact with no further specification was reported in 13 patients (fig. 3, white area in the column 'minor').

Level of Impact Correlates with Degree of Confidence in NINCDS-ADRDA-Based Diagnosis
To understand what renders results of amyloid-specific PET scans having a potentially high or a low clinical impact, we tested for a possible correlation between the degree of impact and the level of confidence in the origi-

	Level of impact of PET results on patient management		
Degree of confidence in prior diagnosis		Strong + some	Minor + none
	Very high	25	33	58
	Moderate + low	50	13	63
		75	46	121

Fig. 4. Confidence in the initial diagnosis versus impact on patient management in the 121 probable AD patients. The numerics in the contingency table represent the numbers of the combined groups. The numbers in italics represent the sums across the respective rows and columns. Refer to table 1 for statistical analysis.

nal diagnosis of all probable AD cases. In this analysis, we dichotomized the categories impact and confidence and merged the answers 'strong impact/some impact', 'minor impact/no impact', and 'moderate confidence/low confidence'. The frequencies of cases in the resulting three categories and the fourth category 'very high confidence' were compiled in a 2 × 2 contingency table as shown in figure 4. Considering the subgroups of confirming and contradicting PET scan results, we found a significant correlation using the Fisher exact test (table 1). The level of the anticipated impact is profoundly influenced by the degree of confidence in the preexisting diagnosis. This correlation is strongest in the group of preexisting AD diagnosis with a contradicting, negative, PET scan result (odds ratio 0.02; p value 0.011). Moreover, this effect can also be observed in probable AD cases where the initial diagnosis was confirmed by the PET scan result (odds ratio 0.29; p value 0.007).

Analysis of Consistency in Reporting

To test whether the participating physicians show center-specific variability in their judgments, we performed a statistical analysis of the homogeneity of their reporting to the questions about (1) the degree of confidence in original diagnosis, (2) the change of confidence in original diagnosis, and (3) the impact on patient management after PET scan results have been communicated (table 2). For reasons of simplicity, we combined the two categories 'decrease in confidence/increase in confidence' into a single category 'change of confidence'.

The 14 participating centers were only in partial agreement with regard to the diagnostic and therapeutic

potential of amyloid imaging. Most physicians reported a change of confidence in their initial diagnosis when receiving a contradicting, negative, PET scan result. The physicians, however, varied with respect to their inclination to report a change of confidence in their original diagnosis when receiving positive PET results, both for probable AD patients and for controls. No significant variability amongst the centers was found for the estimated impact on patient management, irrespective of whether the PET scan results were substantiating or contradicting the initial diagnosis.

Discussion

Within the past decade, amyloid imaging was more or less restricted to highly specialized research centers because the only available tracer, the Pittsburg compound (PIB), contains the short-lived 11-carbon nuclide which has to be produced with a cyclotron onsite. With the advent of 18-fluorine-based tracers with longer half-lives amyloid-imaging will become more broadly available within the next years, and will potentially constitute an essential part of routine diagnostic procedures in AD.

Therefore, we here evaluated the impact and usefulness of beta-amyloid-specific PET imaging using the 18F-labelled tracer florbetaben [16]. Physicians were asked about their confidence in clinical diagnosis before and after the PET results were known. Our analysis focuses on the evaluation of probable AD cases, since the use of beta-amyloid PET imaging in controls presently does not reflect clinical routine.

Florbetaben PET Contributes to the Overall Confidence in Clinical Diagnosis

The added value of beta-amyloid-specific PET scans within the clinical routine of physicians has not been assessed so far. Not surprisingly, negative PET scans showing no amyloid burden in demented patients classified in advance as probable AD by DSM-IV and NINCDS-ADRDA criteria, resulted in a decreased confidence in the original diagnosis in all cases. However, in as many as 80% of probable AD cases when diagnosis was confirmed by a positive PET scan, results were also judged to change the confidence in the initial diagnosis. This high percentage appears unexpected, especially if one takes into account that the evaluation was conducted in specialized centers well familiar with the clinical diagnosis of AD. This finding might reflect the uncertainty of non-biomarker NINCDS-ADRDA criteria-based AD diagno-

sis and indicate the added value of the amyloid-specific PET scan as a method to directly visualize a patient's amyloid burden in vivo.

Anticipated Treatment Regime Changes with Confidence in the Diagnosis

One might argue that a change, i.e. a decrease or increase, of confidence in the original diagnosis has no added value for clinical physicians per se and will especially not have further implications in terms of treatment options. Our data, however, indicate that the intended treatment regime apparently changes for probable AD patients. Possible changes that were described included continuation of antidementive treatment, recommendation of lifestyle changes (i.e. increase in physical and social activity, etc.), and altered communication with the patient, all most likely reflecting a stronger confidence of the physicians in their actions. This might in turn contribute to a higher acceptance of and adherence to the recommended treatment amongst patients and their relatives.

In this respect, the benefit is rated highest for those cases where physicians have substantial doubts in their initial diagnosis. As this likely includes patients at early stages of their disease, one can hypothesize that they would benefit from an earlier start of drug treatment. Further, the increased confidence in diagnosis could also influence the communication and reassurance between specialist physician and primary care physician who cares for the patient in an outpatient/routine setting. Also, on the basis of the PET scan results, some patients of this study might have been included in ongoing clinical trials with beta-amyloid antibodies or other potentially disease-modifying drugs. This reflects another aspect and particular value, since a better diagnosis in terms of a quantifiable biomarker means a more meaningful evaluation of the treatment options [18]. CSF biomarker analysis was performed only in a subset of patients and was not part of the study protocol. The envisaged correlation of the PET scan and CSF biomarker results will further define the value of different diagnostic methods.

Negative PET Scans in Probable AD Prompting Further Investigation

Our study shows negative PET scans in 18% of the probable AD cases that had been identified by applying the DSM-IV and the NINCDS-ADRDA criteria. This could be interpreted as a limitation of the clinical assessment on the basis of which the AD patients have been identified and included in the phase IIb study [16]. Postmortem neuropathological examination which is now underway for florbetaben in a phase III trial may clarify whether this interpretation reflects reality. To date, the correspondence of the florbetaben PET signal to the beta-amyloid plaque burden in the brain has not been described. But, the correlation of amyloid beta aggregates in frontal cortical biopsy specimen to a higher uptake of the PET tracer [11C] PiB has clearly been demonstrated [19].

As to the 18% positive PET scans in the unimpaired controls, it is almost certain that these individuals while having already beta-amyloid deposits in their brain do not, or not yet, suffer from cognitive deficits, which is in line with the temporal cascade concept recently reviewed [10]. Furthermore, studies that compare postmortem histopathological analyses with results of PET scans performed with the beta-amyloid tracer PiB did not yield any false-positive results [20].
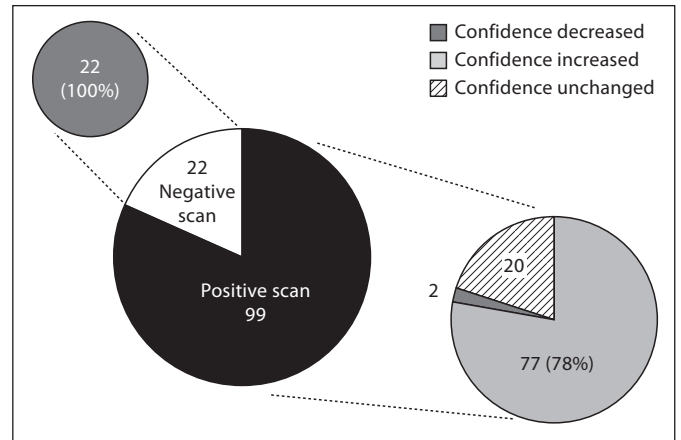
Taken together, this questionnaire study shows that AD diagnosis supported by florbetaben PET imaging may increase confidence of clinicians and may influence patient management. In the context of the recently revised guidelines for the clinical diagnosis of AD [8], which for the first time incorporate altered biomarkers of the underlying disease state as a supportive criterion for the diagnosis AD, the push for a stronger focus on biomarkers in the diagnosis of AD is evident.

Acknowledgements

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Figure 2 of the article 'Impact of Beta-Amyloid-Specific Florbetaben PET Imaging on Confidence in Early Diagnosis of Alzheimer's Disease' by Schipke et al. [Dement Geriatr Cogn Disord 2012; 33: 416–422 (DOI: 10.1159/000339367)] has been published with an error. Please see below the correct figure:

Fig. 2. Frequency and direction of change of confidence in the initial diagnosis on receiving the result of the florbetaben PET scan. Numbers are given for the 121 probable AD patients.