Original Research Article

Clinical Assessment of Amyloid Imaging in Alzheimer's Disease: A Systematic Review of the Literature

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Key Words

Alzheimer's disease · Amyloid imaging · Clinical assessment of Alzheimer's disease ·
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Abstract

Background/Aims: Healthcare systems face an increased prevalence of Alzheimer's disease and increasing costs. The use of molecular biomarkers and imaging could offer an effective solution for these issues. The objective of this study was to assess amyloid imaging regarding clinical utility and impact. **Methods:** A literature search was performed in several databases, searching articles between 2008 and January 2013 following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The results are reported according to the clinical correlates of amyloid imaging. **Results:** Thirty-three studies were included in the final analysis. Five studies evaluated amyloid imaging for diagnosis. Nine studies assessed the prognostic value. Twenty-two studies provided correlations to cognitive measures. Amyloid imaging provides a high reliability in diagnosis and prognosis, but cognitive measures only showed weak correlations. **Conclusion:** The evidence clearly indicated that amyloid imaging has not arrived yet in clinical practice. However, it can provide substantial benefits in special aspects of diagnostic accuracy and for a diagnosis up to 10 years before clinical diagnosis. This can be a base for early preventive treatment strategies such as anti-amyloid therapy. In this context, amyloid imaging is crucial to understand the early pathologic process in Alzheimer's disease.

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Introduction

Among all mental disorders, dementia had the highest costs per person in 2010 [1]. Cost-effective drugs like donepezil can preserve dementia patients' independence and thus reduce costs for informal care [2]. The use of molecular biomarkers in oncology for a better stratification of patients encourages hopes for the field of psychiatry. Genetic testing can be used to select dementia patients for donepezil treatment in a cost-effective manner [3]. Molecular imaging is one of the most promising technologies to visualize molecular physiologic actions in real time. The pharmaceutical industry is already regularly using these methods to determine the dose-effect relationship of new drugs and to identify patient subgroups [4]. As molecular diagnostics has the potential to speed up diagnosis and treatment, it can also reduce the length of hospital stay [5] and finally the costs of dementia.

The diagnosis of Alzheimer's disease (AD) is currently based on clinical symptoms and signs of cognitive decline in multiple domains. However, it is challenging to distinguish other kinds of dementia and the pathologic features of AD regarding the transitional state of mild cognitive impairment (MCI) before AD develops [6]. In terms of molecular imaging, the hypothesis that AD is caused by amyloid deposition at a very early stage is accepted by many researchers, but has yet to be definitely proven. The fundamental limitation of amyloid imaging is that amyloid is a required aspect for diagnosing AD, however it is not sufficient as a sole factor for diagnosis. One reason is the lack of specificity for AD, as it is found in a significant proportion of healthy older people as well as in other non-AD dementias [7]. Therefore, the U.S. National Institute on Aging – Alzheimer's Association (NIA-AA) workgroups on diagnostic guidelines recommend using amyloid imaging in asymptomatic individuals only for research purposes. It is not appropriate to perform amyloid imaging in the absence of objective evidence of cognitive impairment [8].

A systematic review is important given the recent approval of amyloid positron emission tomography (PET) by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for clinical use and the active debate about the clinical utility of this technology [9].

A review of the latest literature referring to amyloid imaging in dementia is expected to provide a comprehensive summary and overview of the available evidence relating to amyloid imaging with the most studied tracer, Pittsburgh Compound B ([C-11]PiB) [10]. The objective of this review was to assess the clinical benefit of amyloid imaging via [C-11]PiB-PET in MCI and AD patients. Clinical benefits were defined as cognitive correlates, contributions to diagnosis and prediction of conversion.

Methodology

Search Strategy and Study Selection

The objective and the search strategy were established using the Population, Intervention, Comparator, Outcome (PICO) scheme [11]. The following databases were searched: Medline, PubMed, Scopus, Cochrane Library, PsycINFO, psychiatry online journals and the individual journals *Lancet*, *Health Affairs*, *Personalized Medicine* and *Pharmacoeconomics*. The search was performed for articles published between January 2008 and January 2013 in English and German. Since the technical feasibility of amyloid imaging is improving rapidly, we only considered studies published within the last 5 years [12, 13]. PICO-specific search terms regarding the population ('Alzheimer's disease', 'Alzheimer dementia', 'mild cognitive impairment', 'MCI') were combined with keywords concerning the examined intervention ('Pittsburgh compound B', 'PiB', 'positron emission tomography', 'PET', 'amyloid imaging'). The search terms used were the result of testing different search strategies. Finally, after performing the search, citation snowballing was used to make sure that all relevant literature was found. The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

Fig. 1. Schematic representation of how the papers were selected.

Inclusion/Exclusion Criteria

Eligible studies were required to assess at least diagnostic accuracy. Diagnostic accuracy is defined by clinical measures which ‘attempt to measure performance of the imaging for the purpose of making diagnoses’ [15]. Clinical studies with less than 10 MCI or AD patients or studies comparing amyloid imaging to other biomarkers were excluded. Studies had to be published as peer-reviewed journal articles. The title and abstract of all retrieved articles were reviewed by the first author (P.W.). The full texts of articles that met the inclusion criteria were reviewed more closely in conjunction with a medical expert (P.L.K.R.) who has a clinical background in neurology and psychiatry. The quality of research papers was evaluated according to adequacy of description of the theoretical framework, background and methodology. We used a modified version of the QUADAS items [16].

Data Extraction

A data extraction form was tested using a sample of studies before initiating full data extraction. Data collected from individual papers included author, year of publication, reference test, study population and main results regarding amyloid imaging.

Reporting of Results and Synthesis

Results of amyloid imaging studies were reported by sorting the information into different groups of clinical applications. The results are reported according to the clinical correlates of amyloid imaging.

Results

Search Results

Within the search, 3,226 papers were retrieved and 2,535 were excluded for not being focused on amyloid imaging, including duplicates. 691 papers were retrieved and 634 were excluded for not being original research on amyloid imaging in AD. Again the selection was refined accordingly. From this cohort, papers were selected for the literature synthesis. The reasons for exclusions are outlined in figure 1. We also included 3 studies with elderly subjects who were assessed with normal cognition, but with a follow-up to diagnosis of AD [17–19]. In 2 cases, 2 different publications described the same patient population and were counted as 1 study [7/22 and 20/21]. Finally, 33 studies were included in the synthesis [17–50].

Table 1. Evaluation parameters for amyloid imaging in selected studies

Reference (first author)	Year of publication	Reference test	Study population	Follow-up	Amyloid imaging interpretation
Forsberg [40]	2008	diagnosis AD/MCI, CSF Aβ1–42, FDG-PET, EM (Rey Auditory Verbal Learning and Retention as well as Rey Osterrieth retention), MMSE	6 HC, 21 MCI, 27 AD	none	quantitative, continuous and dichotomous
Fripp [44]	2008	MMSE, EM	18 HC, 15 MCI, 15 AD	none	quantitative, continuous and dichotomous
Jack [27]	2008	MRI, CDR-SB, MMSE, memory performance with the WMS-R visual reproduction II, WMS-R logical memory II, AVLT delayed recall and AVLT sum of learning trials 1–5	20 HC, 17 aMCI, 8 AD	none	quantitative, continuous and dichotomous
Li [36]	2008	diagnostic efficiency, FDG-PET, MMSE	7 HC, 13 MCI, 17 AD	none	quantitative, dichotomous
Grimmer [42]	2009	CDR-SB	32 AD	none	quantitative, continuous
Jack [29]	2009	MMSE, CDR, ApoE4	21 HC, 32 MCI, 8 AD	1 year	quantitative, continuous and dichotomous
Mormino [30]	2009	EM (RAVLT), structural MRI	37 HC, 52 MCI, 35 AD	none	quantitative, continuous
Morris [18]	2009	CDR, diagnosis to AD	159 HC, 9 diagnosed with AD during follow-up	0.8–5.5 years	quantitative, continuous
Okello [47]	2009	conversion rate to AD	31 MCI	3 years	quantitative, dichotomous
Tolboom [50]	2009	cognitive function (MMSE, Digit Span backward, Digit Span forward, RAVLT immediate recall, RAVLT delayed recall, VAT, VAT picture naming, TMT A and B, Stroop 1–3, category fluency, Rey Figure Copy Test)	12 AD, 13 MCI, 15 HC	none	quantitative, continuous
Tolboom [38]	2009	structural MRI, MMSE, RAVLT	14 AD, 11 MCI, 13 HC	none	quantitative, continuous
Wolk [25]	2009	standard psychometric battery of attention, memory, language, visuospatial construction, and executive functions (MMSE), structural MRI, diagnosis to AD	26 MCI	21.2 months (16 SD)	quantitative, dichotomous
Forsberg [20, 21]	2010/2012	diagnosis AD/MCI, CSF Aβ1–42, FDG-PET, EM (RAVLT total learning, RAVLT retention)	6 HC, 21 MCI, 37 AD	none	quantitative, dichotomous
Jack [28]	2010	diagnosis of MCI to AD	218 MCI	2 years	quantitative, dichotomous
Resnick [49]	2010	MMSE, CVLT immediate recall, CVLT delayed recall, Trails B	51 HC, 6 MCI	mean follow-up 10.8 years	quantitative, dichotomous
Pike [7]/Rowe [22]	2011/2010	ApoE status, CDR, MMSE and other cognitive tests	177 HC, 57 MCI, 53 AD	none	quantitative, dichotomous

Table 1 (continued)

Reference (first author)	Year of publication	Reference test	Study population	Follow-up	Amyloid imaging interpretation
Tolboom [39]	2010	diagnosis (specificity, sensitivity, accuracy)	20 HC, 21 AD	none	visual ratings, dichotomous and quantitative
Chételat [26]	2011	EM composite score (RCFT, CVLT), MMSE, structural MRI	93 HC, 43 MCI, 34 AD	none	quantitative, continuous
Koivunen [45]	2011	MMSE scores, structural MRI, progression to AD	13 HC, 29 MCI	2 years	quantitative, dichotomous
Lee [46]	2011	MMSE, CDR, CDR-SB, GDS, PEPs, attention, language, visuospatial functions, memory, executive functions	10 HC, 45 subcortical vascular dementia, 14 AD	none	quantitative, dichotomous
Marshall [33]	2011	IADL	19 HC, 36 MCI	none	quantitative, continuous
Meyer [37]	2011	MMSE	4 MCI, 15 AD, 3 frontotemporal lobar degeneration	none	quantitative, continuous
Rabinovici [48]	2011	specificity, sensitivity of diagnosis, CDR, CDR-SB, MMSE, ApoE	25 HC, 62 AD, 45 frontotemporal lobar degeneration	none	quantitative, visual rating and dichotomous
Villemagne [24]	2011	EM composite score (RCFT, CVLT), non-memory cognition score, MMSE, CDR, diagnosis to AD	106 HC, 65 MCI, 35 AD	20 months to 3 years	quantitative, continuous and dichotomous
Ewers [17]	2012	ADAS-cog, RAVLT EM, predicting conversion from MCI to AD	124 HC, 229 aMCI, 112 probable AD	2 years	quantitative, dichotomous
Furst [41]	2012	MMSE and CDR-SB	39 AD	none	quantitative, continuous and dichotomous
Grimmer [31]	2012	ApoE4, CDR, diagnosis (AD, other dementia)	28 MCI	2 years	quantitative, dichotomous
Kadir [43]	2012	FSIQ, WAIS-R composites for semantic memory, visuospatial ability, short-term memory, EM, attention with TMT A and B, ApoE, FDG-PET	5 MCI, 9 AD	3 years for MCI, 2 and 5 years for AD	quantitative, continuous
Knopman [19]	2012	ApoE4, MMSE, cognitive z scores, FDG-PET, structural MRI, diagnosis	296 HC	1 year	quantitative, dichotomous
Koivunen [32]	2012	MMSE, psychometric test scores, conversion rate	16 aMCI	2 years	quantitative, dichotomous
Nordberg [34]	2012	MMSE, verbal and non-verbal memory, visuoconstruction, verbal fluency, ApoE, conversion rate	51 HC, 72 MCI, 97 AD	28-month follow-up data of 64 MCI patients	quantitative, continuous and dichotomous
Ossenkoppele [35]	2012	MMSE, FDG-PET	11 HC, 12 MCI, 8 AD	2.5 (2–4) years	quantitative, continuous
Ossenkoppele [23]	2013	diagnosis, FDG-PET	154 dementia patients (different diagnosis)	2 years for 39 patients	visual rating, dichotomous

aMCI = Amnesic MCI; AVLT = Auditory Verbal Learning Test; CVLT = California Verbal Learning Test; FDG-PET = fluorodeoxyglucose (¹⁸F) positron emission tomography; FSIQ = Full Scale IQ; GDS = Global Deterioration Scale; HC = healthy controls; PEPs = peripheral ethanalamine plasmalogens; RCFT = Rey Complex Figure Test; TMT = Trail Making Test; VAT = Visual Association Test; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WMS-R = Wechsler Memory Scale-Revised.

Table 2. Cognitive parameters

Cognitive test	Population	Correlations/regression to amyloid deposition	Follow-up changes
MMSE	HC, MCI, AD		$r = -0.27, p < 0.001$ [24]
	HC, MCI, AD		
	HC, MCI, AD	not significant [27], $r = -0.25, p = 0.09$	
	HC, MCI, AD	$\beta = -0.66, R^2 = 0.52, p < 0.01$ [50]	
	AD	$r = -0.75, p < 0.001$ [38]	
	MCI, AD	no correlation [41]	
	AD	no correlation [37]	
	HC, MCI, AD		$r = -0.38, p = 0.04$ [24]
	HC, MCI, AD		$r_s = -0.42 (p < 0.05)$ [35]
	HC, MCI, AD		not significant, $r = -0.22, p = 0.09$ [29]
EM	HC, MCI, AD	$r = 0.67$ [44]	
	HC, MCI		
	HC, MCI, AD	$r = -0.45, p < 0.001$ [34]	annual decline of 0.13 (linear mixed model), $p < 0.05$ [49]
	HC, MCI	$R^2 = 0.17, p = 0.049$ [30] (to RAVLT)	
	HC, MCI	$r = -0.59, p < 0.001$ [24]	
	MCI	$r = -0.57, p < 0.0001$ [24]	
	MCI	$r = -0.45, p < 0.043$ [40]	
	HC, MCI	$R^2 = 0.378, p < 0.001$ [26]	
	MCI, AD	$r = -0.42, p = 0.004$ [20] (to RAVLT)	
	HC, MCI, AD	$\beta = -0.76, R^2 = 0.57, p < 0.01$ [50] (to RAVLT)	
CDR	HC, MCI, AD	$r = -0.63, p < 0.0001$ [38] (to RAVLT)	
	HC, MCI, AD	$r = 0.71$ [44]	
	MCI		difference between amyloid-positive and -negative subjects: $\beta = -0.44, p = 0.01$ [17] (to RAVLT)
ADAS-cog	HC, MCI, AD		no significant correlation [18]
	AD	$R^2 = 0.106-0.219, p < 0.05$ [42]	
	AD	no correlation [41]	
	HC, MCI, AD	$r_s = 0.54, p < 0.001$ [27]	no correlation [29]
IADL	HC, MCI	$\beta = 5.8, R^2 = 0.40, p < 0.001$ [33]	
	MCI	$\beta = 6.1, R^2 = 0.28, p = 0.003$ [33]	
HC = Healthy controls.			

Table 1 summarizes the findings for different clinically relevant endpoints for AD. The interpretation of amyloid imaging was mostly performed in a quantitative, continuous manner. Amyloid imaging was assessed using the following clinically relevant cognitive measures: Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR) and Clinical Dementia Rating Sum Boxes (CDR-SB), Instrumental Activities of Daily Living (IADL), Alzheimer Disease Assessment Scale – Cognitive Subscale (ADAS-cog), Episodic Memory (EM) measured by means of the Rey Auditory Verbal Learning Test (RAVLT) and others as well as diagnosis (healthy and MCI to AD) and prognosis (healthy and MCI to AD).

Cognitive Parameters

A summary of the correlations of amyloid load to cognitive parameters is shown in table 2. Correlations between [C-11]PiB imaging and CDR-SB were assessed by 5 studies [18, 27, 29, 41, 42], but only 2 detected significant correlations. One study only found a very weak correlation for patients with AD ($r = 0.106$ – 0.219) whereas another stated an intermediate correlation of 54% ($p < 0.001$) [29].

Another cognitive parameter is the EM composite score [17, 20, 24, 26, 30, 40, 44, 50]. The correlations range from -0.42 [20] up to -0.71 [44] for different patient groups. A linear regression model of amyloid imaging as a predictor, including age, gender and years of education as covariates, could predict the EM scores for healthy and MCI subjects with 37.8% ($p < 0.001$) [26]. The independent variable of frontal PiB load was a good predictor, with 57% for RAVLT delayed recall adjusted for age and sex ($\beta = -0.76$, $R^2 = 0.57$, $p < 0.01$) [50]. However, no significant correlations of amyloid load to cognition in episodic memory and other parameters for MCI and AD patients were found in a study with a 3- to 5-year follow-up [43]. Another follow-up study of MCI patients converting to AD and higher baseline [C-11]PiB uptake detected a decline in word list saving memory ($r = 0.73$, $p < 0.05$) and a decline in the Stroop interference score ($r = -1.00$, $p < 0.01$) [32].

The most extensively examined cognitive parameter was MMSE in 12 studies [24, 27, 29, 34, 35, 37, 38, 41, 44, 46, 49, 50]. Correlations for MMSE ranged from -0.45 up to -0.75 based on mixed populations of healthy, MCI and AD subjects. The author who stated the strongest correlation of 0.75 ($p < 0.001$) [38] reported in a different study a prediction of 52% between MMSE and [C-11]PiB load ($\beta = -0.66$, $R^2 = 0.52$, $p < 0.01$) in a linear regression model adjusted for age and sex [50]. The MMSE was found to be lower in amyloid-positive patients (18.6 in amyloid-positive vs. 22.6 in amyloid-negative patients, $p < 0.001$) [46].

During follow-up, changes in amyloid retention could predict changes in MMSE with correlations from -0.27 up to -0.42 [24, 29, 35]. One study suggested an annual decline of 0.13 ($p = 0.05$) by high amyloid burden adjusted for age and education [49]. Other research groups found a negative correlation between [C-11]PiB and MMSE [37, 41].

Amyloid load also correlated with IADL in a linear multiple regression model with the predictors global PiB retention, age, IQ, MMSE and RAVLT delayed recall. The predictive value was 40% ($\beta = 5.8$, $R^2 = 0.40$, $p < 0.001$) for healthy and MCI subjects and still 28% ($\beta = 6.1$, $R^2 = 0.28$, $p = 0.003$) for MCI patients excluding the predictors MMSE and RAVLT [33]. Regarding the ADAS-cog, the difference between amyloid-positive and -negative MCI patients was 1.42 ADAS-cog/year calculated by 2-year follow-up ($p < 0.001$) [17].

Diagnosis

Amyloid imaging was also used for the diagnosis of AD within the 5 studies shown in table 3 [22, 23, 36, 39, 48]. The sensitivity and specificity of amyloid imaging ranged between 62 and 100%, depending on the examined population and on how data interpretation was undertaken. Accuracy ranged from 70 to 97%. [C-11]PiB-PET also contributed to the diagnostic certainty in terms of different types of dementia (23–28%) [23].

Prediction of Conversion

Nine studies assessed amyloid imaging regarding the predictive value for conversion shown in table 4. Four studies assessed the risk of conversion during a 2-year follow-up for amyloid-negative MCI patients. This risk ranged from 0 to 19% [28, 31]. During a 20-month follow-up study, there was a 98% chance to stay cognitively stable for amyloid-negative patients. The risk of conversion to MCI or AD was 16% for amyloid-positive healthy patients.

The conversion of amyloid-positive MCI patients ranged from 38% [25] to 86% [23] within a 2-year follow-up. MCI patients who converted to AD had significantly higher PiB

Table 3. Diagnostic value of amyloid imaging

Diagnostic parameter	Population	Value
Sensitivity	HC, AD	98% [22]
	HC, AD, frontotemporal lobar degeneration	89–90% [48]
	HC, AD	100% [39]
	HC, AD	94% [36]
	HC, MCI	62% [36]
	MCI, AD	94% [36]
Specificity	HC, AD	66% [22]
	HC, AD, frontotemporal lobar degeneration	82–84% [48]
	HC, AD	85% [39]
	HC, AD	100% [36]
	HC, MCI	100% [36]
	MCI, AD	62% [36]
Accuracy	HC, AD	73% [22]
	HC, AD, frontotemporal lobar degeneration	97% [48]
	HC, AD	93% [39]
	HC, AD	96% [36]
	HC, MCI	75% [36]
	MCI, AD	70% [36]
Positive predictive value	HC, AD, frontotemporal lobar degeneration	89% [48]
Negative predicted value	HC, AD, frontotemporal lobar degeneration	84% [48]
Positive likelihood ratio	HC, AD	6.7 [39]
	HC, AD, frontotemporal lobar degeneration	5.3 [48]
Negative likelihood ratio	HC, AD	0 [39]
	HC, AD, frontotemporal lobar degeneration	0.1 [48]
Contribution to diagnostic certainty	AD	23% [23]
	MCI	27% [23]
	different kinds of dementia	28% [23]
HC = Healthy controls.		

uptake in various areas compared to stable MCI patients ($p < 0.005$) within a period of 2 years [32, 45]. An extensive study with 218 MCI patients showed that amyloid-positive patients were more likely to convert to AD (50 vs. 19% of amyloid-negative patients) during 2 years. Besides, amyloid load could predict the time to progression within all patients. However, magnetic resonance imaging (MRI) was more successful in predicting the time to progression for amyloid-positive patients [28]. One study calculated a hazard ratio of 4.82 ($p < 0.05$) for conversion of healthy subjects to AD with follow-up times between 0.8 and 5.5 years [18]. A large multi-center study provided 28-month follow-up of 64 MCI patients. None of the amyloid-negative patients converted to AD, whereas a conversion rate of 25% per annum was calculated for amyloid-positive patients [34]. Another study validated these results: 80.7% of the amyloid-positive subjects converted from MCI to AD within 2 years, but only 16.6% of the amyloid-negative subjects [17]. The application of the new NIA-AA preclinical AD criteria concluded that amyloid-positive status alone was associated with 17% progression within the three preclinical stages during 1 year [19].

Table 4. Predictive value of amyloid imaging

Predictive value	Popu- lation	Follow-up	Value
Risk of conversion for amyloid-negative patients	MCI	2 years	19% [28]
		2 years	16.6% [17]
		2 years	0% [23]
		2 years	0% [31]
Risk of conversion for amyloid-positive patients	HC	1 year	17% progression within preclinical stages [19]
		20 months	16% (to MCI, AD) [24]
		3 years	25% (to MCI, AD) [24]
	MCI	2 years	80.7% [17]
		2 years	86% [23]
		2 years	53% [31]
		20 months	67% [24]
		2 years	50% [28]
		28 months	67.4% (calculated per annum: 25%) [34]
		3 years	82%, $p < 0.01$ [47]
		21 months	38%, $p = 0.046$ [25]
Accuracy for follow-up diagnosis	MCI	2 years	70% [31]

HC = Healthy controls.

Fig. 2. Potential benefit of preclinical diagnosis of AD by amyloid imaging.

Discussion

An extensive literature search was conducted to compile a state-of-the-art overview of amyloid imaging via [C-11]PiB-PET. The evidence shows a potential benefit of amyloid imaging in terms of predictive information and diagnosis (fig. 2).

Correlations to Cognitive Criteria

Several studies found correlations between amyloid status and cognitive measures. These correlations depended on the study population (AD, MCI, MCI + AD, MCI + AD + healthy). The most extensively studied cognitive measures were MMSE and EM. As the results of this review suggest, amyloid imaging is not a good predictor for cognitive performance [24, 42]. However, the link between cognition and amyloid status was stronger for MCI patients. Overall, the predictive value of amyloid imaging for cognitive performance was weak [24, 29, 35, 41, 49] and even non-existent regarding CDR [18, 29]. This result was confirmed in healthy older persons post mortem [51]. A possible explanation is that amyloid deposition may occur before cognitive symptoms are seen [26]. Alternatively, amyloid-independent factors can contribute according to the second pathway hypothesis. This could be a hint to cognitive decline across AD and MCI patients as well as healthy subjects [35]. Structural brain measures such as MRI and fluorodeoxyglucose PET (FDG-PET) are more accurate than amyloid imaging to detect cognitive performance as the time frame of the pathologic process suggests [43]. Amyloid burden affects hippocampal atrophy and structural decline affects cognition. Therefore, the link between amyloid load and cognition is indirectly bridged by structural decline.

Diagnostic Value

It is important to separately assess the diagnostic value of amyloid imaging for different kinds of dementia [23, 46]. The likelihood of being amyloid-positive is increased in mild AD in comparison to prodromal AD [32]. In these cases, amyloid imaging contributes to a more exact diagnosis. The diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) as well as the Alzheimer's Disease and Related Disorders Association (ADRDA) provide a sensitivity of 81% and a specificity of 70% [52]. Amyloid imaging seems to improve diagnosis with a sensitivity of 98% [22] or 89–90% [48] and a specificity of 66% [22] or 82–84% [48]. These values satisfy the requirements of the National Institute on Aging Working Group on Molecular and Biochemical Markers of Alzheimer's Disease 'to detect a fundamental feature of neuropathology and be validated in neuro-pathologically-confirmed cases. According to the working group sensitivity of larger than 80% for detecting AD and a specificity of larger than 80% for distinguishing other dementias is required. In addition, the test should be reliable, reproducible, non-invasive, simple to perform and inexpensive' [53]. Still, the diagnosis of AD via PET needs to be coupled 'with a more comprehensive approach to the diagnostic process' [54]. The technical efficiency for a standard quantitative analysis, criteria and cut-off values of amyloid deposition and the significant brain regions are still in question. A critical point is that not all AD patients are amyloid-positive [41].

Predictive Value to Conversion

The detection of amyloid plaques before diagnosis is important in order to identify the preclinical stage of AD pathology. This was already claimed by post mortem studies in 1999 [55]. Amyloid imaging is a unique opportunity to identify preclinical AD patients without meeting clinical criteria for AD. Several studies confirmed that MCI patients with amyloid-positive status are at high risk of developing AD [17, 25, 28, 34, 47].

Context of Other Biomarkers

All clinical benefits of amyloid imaging are increased by combining it with other biomarkers. The highest correlation to cognitive performance was achieved by a combination of imaging biomarkers (hippocampal atrophy + perforant path atrophy + temporal PiB) [26]. The diagnostic uncertainty can be optimally decreased by combining the diagnostic contribution of PiB and FDG-PET scans with other biomarkers [23]. Biomarkers of neuronal injury are not specific for AD, but can provide information about progression of disease from the MCI to the AD state. In a hypothetical framework for structural and amyloid information, the likelihood for amyloid-positive patients without positive indicators of neuronal injury is only intermediate. Patients who had positive results for both biomarkers had the highest likelihood of progression from MCI to AD [56]. Genetic tests like the one for apolipoprotein E (ApoE) can help select patients for imaging. Several studies showed a higher amyloid burden and progression to AD in healthy subjects and MCI and AD patients with positive ApoE4 status [45, 47]. Data mining approaches can help understand amyloid imaging in the context of other biomarkers. At the moment, the evidence for combining different biomarkers is still fragmented. The complexity of neurodegenerative disease needs adequate multimodal approaches to identify patient subgroups with similar characteristics.

Treatment Options

The impact of amyloid imaging will increase if an anti-amyloid therapy becomes available, which makes continuous monitoring of the amyloid load necessary. Several clinical trials are assessing potential candidates for anti-amyloid therapy. One study [57] highlights the use of amyloid imaging to assess the success of a new anti-amyloid antibody therapy. The [C-11]PiB retention rate decreased by 0.09 ($p = 0.014$) for AD patients and increased by 0.15 ($p = 0.022$) for the control group, but without significant impact on cognitive decline. These results and the latest failure of two phase 3 studies on bapineuzumab need to be considered regarding the missing treatment benefit on cognition and functional parameters [58]. In contrast, a meta-analysis of two studies about another amyloid monoclonal antibody (solanezumab) showed a significant cognitive benefit on each measure with solanezumab versus placebo for patients with mild AD, and also 18% less functional decline ($p = 0.045$) [59]. Another phase 3 study of solanezumab in patients with mild AD is planned. Additionally, several secondary prevention trials with amyloid-positive patients in the preclinical stage are currently ongoing: the Alzheimer's Prevention Initiative (API), the Dominantly Inherited Alzheimer Network (DIAN) and the Amyloid Treatment of Asymptomatic Alzheimer's Disease (A4) trial [60]. As in cancer, Sperling et al. [8] suggest to treat AD as early as possible, 'before significant cognitive impairment in the preclinical stage of AD'. Furthermore, AD should be defined as 'encompassing the underlying pathophysiological disease process'. Patients can mostly benefit from early therapeutic interventions before irreversible cognitive loss. The Australian Imaging, Biomarkers and Lifestyle (AIBL) study confirmed that amyloid deposition increased with the age of the subjects. The uptake changed from 18% in the group of people aged 60–69 years to 83% in the group aged over 85 years, which shows a time lag of 15 years between amyloid-positive status and AD prevalence [22].

Cost-Effectiveness

There have been no studies about the cost-effectiveness of amyloid imaging yet. A PET scan using a radiotracer causes costs of approximately USD 700 [61]. A recently published Markov simulation to assess MRI for screening of AD showed that screening is only cost-effective with a very high diagnostic accuracy and effective treatment options [62]. A face-name-based memory test adjusted to amyloid load could substitute imaging for screening in a broad population [63]. Selecting and stratifying patient subgroups is important for expen-

sive treatments. A model of the Levin group for the Alzheimer's Association shows that a hypothetical treatment that delayed the onset of clinical symptoms by 5 years could reduce the number of patients by 57%, with corresponding cost reductions. A diagnostic instrument like PET imaging with 90% sensitivity and specificity in combination with a treatment that reduces cognitive decline by 50% would reduce the lifetime risk of dementia of a 65-year-old person from 10.5 to 5.7% [64].

Ethical Considerations

There remain clinical and ethical questions on the value of amyloid imaging as long as there is no appropriate treatment. One can argue that patients can make plans for their remaining life when clinical symptoms occur [65]. On the other hand, a diagnosis can diminish the remaining quality of life when patients worry about being at risk. If risky treatments are available only for certain dementia subgroups, amyloid imaging can reduce the harm caused by side effects. Therefore, early biomarkers require a very high accuracy.

Limitations of the Study

Nearly all included studies were conducted in populations meeting standard clinical research criteria, with virtually no post mortem confirmation of the underlying pathology. A spectrum bias may exist because different MCI and dementia subtypes could affect the transferability of the diagnostic performance. Additionally, 3 years have proved too short a follow-up time to make final conclusions about the predictive value of amyloid imaging [22]. High-quality evidence like randomized controlled trials of PET diagnostic studies is still rare [66]. We only assessed [C-11]PiB for amyloid imaging. There are also important fluorine-18-labelled radiotracers for broad clinical application because the half-life of fluorine-18 is many times longer than that of [C-11]PiB. Still, [C-11]PiB is the option most widely used [10], and evidence suggests that its usefulness is transferable to other radiotracers such as fluorine-18 florbetapir [67].

Conclusion

This study highlights the current status of amyloid imaging in AD. Imaging is not used in clinical practice yet, although it can provide substantial benefits in special aspects of diagnostic accuracy, e.g. stratifying patient subgroups. In terms of preclinical diagnosis, it offers an opportunity for diagnosis in the time period of up to 10 years before clinical diagnosis. This is particularly interesting from an epidemiological viewpoint, regarding the increasing prevalence of amyloid deposition and later AD. Preclinical diagnosis can be a base for early, more effective treatment options. Approaches to combine different biomarkers can help increase the value of amyloid imaging. As the economic and societal burden of AD is increasing, research is required to develop and implement biomarkers for early screening, accurate diagnosis and monitoring of treatment. Improved diagnostics can improve patients' outcomes and reduce costs. In this context, amyloid imaging provides the key to understanding the early pathologic process in AD.

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Disclosure Statement

The authors report no competing interests.

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