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COMMENTARY

The Early Diagnosis of Alzheimer's Disease: A Patient-Centred Conversation with the Care Team

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder which accounts for 60–80% of dementia cases, affecting approximately 10 million people in Europe. Neuroimaging techniques and cerebrospinal fluid biomarkers used in combination with cognitive assessment tools open the door to early diagnosis of AD. However, these tools present some challenges that need to be overcome, such as low sensitivity or specificity, high cost, limited availability or invasiveness. Thus, low-cost and non-invasive alternatives, such as plasma biomarkers, have the potential to drive changes in AD screening and diagnosis. In addition to the technical aspects, organisational challenges as well as ethical concerns need to be addressed. In many countries, there is an insufficient number of specialists to recognise, evaluate and diagnose dementia and the waiting times to see a specialist are long. Given that there is currently no cure for AD, it is important to consider the potential psychological impact of an early diagnosis. In addition, counselling before biomarker sampling and during diagnosis disclosure is vital to guarantee that the patients have all the information necessary and their queries are addressed in a sensitive manner. Here, we illustrate (using a clinical vignette) current challenges of diagnosis and discuss some of the benefits and challenges of early diagnosis in AD including the value of biomarkers in combination with clinical evaluation. Lastly, some guidelines for disclosing early diagnosis of AD are provided based on our experiences.

Keywords: Alzheimer's disease; Biomarkers; Cerebrospinal fluid; Early diagnosis; Neuroimaging; Patient management; Psychological impact of biomarker testing

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Key Summary Points

Many subjects with early-stage Alzheimer's disease (AD) remain undiagnosed as mild cognitive impairment may remain undetected or misinterpreted.

Receiving a timely diagnosis of dementia allows access to information, resources, support and available therapies that may improve cognition.

Neuroimaging techniques and biomarkers used in combination with cognitive assessment tools open the door to early diagnosis of AD.

Low-cost and non-invasive procedures have the potential to drive changes in AD screening and diagnosis.

READER QUESTIONNAIRE

On the basis of the results from the assessments in their case study, the authors have created a poll for readers to complete. A link to this poll is available here: https://www.surveymonkey.co.uk/r/TG38X6D.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterised by progressive decline in cognitive domains such as memory, language, visuospatial and executive functions, as well as behavioural changes, affecting the ability to perform daily life activities. This results in patients struggling to live independently, feeling less confident, and lonely [1–3]. AD also affects the family caregivers of people suffering from dementia, who often suffer from emotional stress and depression [4].

AD accounts for approximately 60–80% of dementia cases [5], currently affecting an estimated 10 million people in Europe, and by 2050, the number of patients will likely almost double to 18 million people [6]. The costs associated with AD and other dementia aetiologies are projected to increase by approximately 43% between 2008 and 2030, with a forecasted total cost in excess of €250 billion [7]. Thus, AD presents a considerable challenge not only for individuals and families affected by this disease but for society as a whole. It has been highlighted that healthcare professionals should work as part of an integrated patient-centred care team to manage the growing and diverse population with AD starting with diagnosis [8]. In support of this the importance of establishing an early AD diagnosis, guidance and tools that may be used throughout the diagnostic journey has been covered in a recent comprehensive review [9].

The neuropathological hallmarks of AD include features such as the presence of abnormal amyloid-β and tau biomarkers and cerebral amyloid angiopathy, neurofibrillary tangles, and glial responses, as well as neuronal and synaptic loss [10–12]. Significant evidence has been collected that supports a key role for amyloid-β dyshomeostasis in initiating AD. Thus the amyloid (or Aβ) hypothesis has become the dominant model of AD pathogenesis and is informing approaches to and the development of potential treatments [13]. However, it has been proposed that progress in drug development is likely to improve if a probabilistic model of AD is adopted where the condition is driven by genetic factors of decreasing penetrance and stochastic factors whose weight is inversely related to penetrance [14]. On the basis of research, AD can be understood as a clinical continuum covering the preclinical and clinical phases [15]. Although these hallmarks were initially characterised in post-mortem studies, biomarkers allow investigation into some of these neuropathological changes in vivo, having reached a high level of validity.

Studies have shown that alterations in both Aβ fluid and neuroimaging biomarkers, which link to the Aβ hypothesis for AD pathogenesis, precede clinical symptoms [16]. The preclinical phase refers to the stage at which AD pathology is present but cognitive performance (measured

with standardised cognitive tests) still lies within the normal range [17]. During the clinical phase, mild cognitive impairment is characterised by the onset of the earliest cognitive symptoms, while in the final phase of dementia the cognitive impairments are severe enough to produce loss of function [17].

Adequate early diagnosis of AD before symptom onset is of pertinent importance, as it would enable the development of secondary preventive and disease-modifying therapies [18]. However, early diagnosis of AD is not always straightforward. This was discussed in a satellite symposium—'The early diagnosis of Alzheimer's disease: a patient-centred conversation with the care team' presented at 7th EAN in 2021—the content of which forms the basis of this manuscript. By using a clinical vignette, we set out to illustrate some of the challenges that currently exist with early diagnosis and how neuroimaging and cerebrospinal fluid (CSF) biomarkers can help to correctly identify AD in its early stages.

CLINICAL VIGNETTE

An otherwise healthy man, aged 62 years, who was still fully employed in a managerial position sought a consultation as he had experienced cognitive difficulties at work, including memory lapses. For example, these took the form of confusion and some instances of absent-mindedness. Most of these episodes had occurred in the working environment, away from the home. He had otherwise a stable personality without anxiety or depressive episodes in the past, and was in good physical health except for minor hypertension and hypercholesterolaemia. His current medications included aspirin, atorvastatin, and losartan, and there was no family history of dementia.

The initial neurological examination performed by a dementia specialist was unremarkable. The cognitive assessment indicated a change in the Montreal Cognitive Assessment (MoCA, score 20/30) and California Verbal Learning Test, but normal findings in Geometric Figures Copy, Digit Ordering Task, and Word Fluency. The Trailmaking Test was not completed.

Psychiatric assessment showed high levels of anxiety according to the Hospital Anxiety and Depression Scale (HADS) and the State-Trait Anxiety Inventory (STAI).

The magnetic resonance imaging (MRI) report read 'MRI is within the normal range apart from very discrete white matter signal abnormalities at the supratentorial level of ischaemic origin'. This consultation suggested that acute anxiety and reduced self-confidence had resulted in cognitive impairment. Nevertheless, as this patient exhibited cognitive impairments further tests were carried out in order to reach a comprehensive diagnosis.

An ^{18}F-fluorodeoxyglucose (FDG) positron emission topography (PET) scan showed a hypometabolism in the parietal lobes and the retrosplenial cortex; the CSF analysis showed elevated tau, phosphotau (p-tau) and reduced 42 amino acid form of Aβ (Aβ42); the amyloid PET scan showed signal in the cerebral cortex, mainly on frontal and temporal regions; the tau PET scan showed abnormal uptake, mainly on the temporal and parietal cortices, corresponding to a Braak stage V–VI. Thus, the additional biomarker analysis indicated that the mild cognitive impairment (MCI) was actually due to AD in this patient. It is important to stress that there are aspects in this clinical vignette that highlight the appropriate use of biomarkers. For example, the use of amyloid PET is based on the requirement to have objectively confirmed cognitive impairments with progressive dementia at an atypically early age of onset (usually defined as age 65 years or less). The use of biomarkers should also result in an increase in diagnostic certainty and potentially alter management. The use of biomarkers in the current case facilitated the accurate diagnosis which otherwise may have resulted in an assumed psychiatric syndrome and associated treatment based on the reported increase in anxiety. The final diagnosis of MCI due to AD made sense to the family of the patient and although they were saddened by the diagnosis, they expressed relief in knowing the full picture. In summary, this clinical vignette illustrates the value of combining clinical

assessment tools in combination with biomarker analysis to help with an accurate diagnosis.

BENEFITS OF TIMELY DIAGNOSIS: INCREASED OPTIONS FOR PATIENTS, FAMILIES AND CAREGIVERS

Given the challenges of early diagnosis of AD, it is worth pointing out the benefits that a timely diagnosis can provide. The "Imaging Dementia—Evidence for Amyloid Scanning (IDEAS)" study, with 11,409 participants from 343 imaging centres, highlighted the importance of timely diagnoses [19]. Following an amyloid PET scan, there was a change in clinical management for approximately 60% of patients within 90 days, which consisted of one or more of AD drug therapy, other drug therapy or counselling about safety and future planning.

Receiving a timely diagnosis of dementia allows access to information, resources, support and available therapies that may improve cognition. An early diagnosis can help patients to plan for the future, making adjustments for safety and quality of life, as well as seeking financial guidance or legal support [8, 9]. It also gives access to research, giving the option to patients to participate in clinical studies and registries [9]. Psychological support can also be very beneficial for families receiving a diagnosis of AD [20].

Finally, an early diagnosis can empower patients to make healthy lifestyle changes that can help to delay the onset of symptoms. A number of studies showed that an active lifestyle can help to build cognitive and brain reserve, which can confer resistance and resilience against neurodegeneration [21, 22]. Mounting evidence suggests that physical activity, diet, tobacco and alcohol use, hypertension and diabetes may influence the risk of cognitive impairment and AD [23–25]; however, the supporting evidence is limited by regional bias and lack of long-term controlled studies [26]. A large recent study concluded that the risk of cognitive impairment can be reduced by intensive blood pressure control (systolic blood pressure < 120 mmHg) in individuals with hypertension, but not by standard blood pressure control, suggesting that the protective effect of lifestyle changes may depend on the baseline condition and on the specific therapeutic target [24]. Together, these findings provide support and information to patients on the lifestyle changes that may help lower the risk of dementia.

CLINICAL ASSESSMENT TOOLS TO EVALUATE A MEMORY COMPLAINT

There are a number of clinical assessments tools that can be used to evaluate cognitive deficits. Here, we will focus on the main brief detection measures that are often used in primary care. Some of the most common scales are the Mini-Cog [27, 28], the Mini-Mental State Examination (MMSE) [28] and the MoCA [28, 29], with different degrees of sensitivity [30] (Table 1).

Other more extensive scales are often used in clinical trials as endpoints. They include Clinical Dementia Rating-Sum of Boxes (CDR-SB) [31] and Alzheimer's Disease Cooperative Study Scale for Activities of Daily Living Inventory (Mild Cognitive Impairment Version) (ADCS-ADL-MCI) [32], both of which represent composite measures assessing cognitive symptoms

Table 1 Cognitive scales used in the clinical practice to detect AD

Cognitive scale	Duration	Sensitivity for MCI [30]	Stage use
Mini-Cog [27, 28]	2–3 min	Low	Moderate dementia
MMSE [28]	5–10 min	Low	MCI or moderate dementia
MoCA [28, 29]	10 min	High	MCI

MCI mild cognitive impairment, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment

alongside functional impact of disease. CDR-SB dementia severity domains are linked to validated diagnostic criteria and CDR-SB is considered to be more reliable than other tools [28, 31]. Other scales that focus on symptoms alone include Alzheimer's Disease Assessment Scale–Cognitive 13-item subscale (ADAS-Cog) [33], MMSE [34] and Neuropsychiatric Inventory-10 item version (NPI-10) [35]. Together, these validated scales cover a large range of clinical symptom and disease measures with a minimal overlap between scales. Most are used alongside self-reports by patients, allowing one to capture subjective measures of disease and providing important support to physicians in diagnosis and development of management plans [35]. However, the administration time may take up to 1 h, making their use impractical for screening purposes in memory clinics or by first-line general/family practitioners.

From the brief scales mentioned above, the MoCA was specifically developed as a screening tool for MCI. It covers multiple cognitive domains, including executive functions. The initially proposed cut-off (25/26 points) showed good sensitivity for MCI ($\geq$ 83%) but poor specificity ($\leq$ 66%). Thus, new cut-offs have been proposed to enhance diagnostic accuracy [36].

In addition, the MoCA Memory Index Score (MIS) was devised to predict conversion from MCI to AD. The MoCA-MIS is calculated by adding the number of words remembered in free delayed recall, category-cued recall, and multiple choice-cued recall multiplied by 3, 2 and 1, respectively, with a score ranging from 0 to 15. Individuals with MCI with a low MoCA-TS (total score less than 20/30) and a low MoCA-MIS (Memory Index Score less than 7/15) are at greater risk of short-term conversion to AD [37].

Although cognitive assessment tools can accurately predict future development of AD in patients with MCI, combining them with biomarkers is recommended to provide greater accuracy [38, 39]. In addition, biomarkers may be useful to diagnose patients that present borderline clinical manifestations of disease.

CONFIRMING ALZHEIMER'S DISEASE PATHOLOGY USING IMAGING AND FLUID BIOMARKERS

AD was initially defined as a clinical-pathologic entity, which was diagnosed definitely at autopsy [40]. In the 1980s, amyloid-β peptide plaques assumed a cornerstone position in the diagnostic framework; later, they also gave the name to the so-called amyloid hypothesis that suggested the accumulation of Aβ peptides into senile plaque as the main cause of neurotoxicity, neuronal cell death and subsequent neurodegeneration [41, 42]. The hypothesis is supported by the genetic evidence in familial cases of AD, e.g. mutations in amyloid precursor protein (APP) or presenilin-1/2, a component of γ-secretase involved in Aβ production [41]. However, the term AD is often used to also describe prototypical clinical syndromes without neuropathologic verification [43]. It is estimated that between 10% and 30% of individuals with a clinical diagnosis of AD do not display neuropathological features of AD at autopsy [43].

The amyloid hypothesis has been challenged with recent advances in imaging that showed that amyloid deposits in the brain can reflect ageing in general, and are not always associated with dementia [41]. Accumulating evidence suggests that the pathophysiological disease progression in the brain may be only in part mediated by amyloid burden; numerous other genetic and environmental factors may impact cellular response and resilience and the lag between plaque accumulation and development of clinical symptoms [26].

In 2018, the National Institute on Aging and Alzheimer's Association (NIA-AA) proposed a purely biological definition of Alzheimer's disease given that amnestic multidomain dementia is neither sensitive nor specific for AD [43]. The NIA-AA suggested a research framework, grouping biomarkers in living persons into those of Aβ deposition, pathologic tau, and neurodegeneration [43].

Although the authors emphasised that this research framework should not be used in general medical practice, it generated debate and

challenges in everyday clinical practice. One of the concerns raised was that cognitively unimpaired individuals can have biomarker evidence of both Aβ and tau pathology without developing clinical manifestations in their lifetime. Recently, the International Working Group (IWG) proposed that confirmation of AD diagnosis requires biomarker evidence of AD pathology together with specific AD clinical phenotypes [18]. According to the IWG, cognitively unimpaired individuals with a biomarker-positive result should be considered only at-risk for progression to Alzheimer's disease. In addition, the IWG does not recommend biomarker testing for cognitively unimpaired individuals.

Taking these guidelines into consideration, different biomarkers can be used to assess the risk of developing AD in individuals exhibiting cognitive impairments.

Neuroimaging Biomarkers

A variety of neuroimaging techniques can be used as biomarkers in AD, offering complementary information, overall with a high level of analytical and clinical validity [44–46]. MRI allows the identification of atrophy when this is marked enough, with medial temporal atrophy being a possible sign of AD. However, atrophy patterns overlap with other diseases and unusual forms of AD can present atypical patterns of atrophy [47].

PET is another neuroimaging technique used for AD diagnosis that offers different possibilities depending on the tracer used. The most common PET tracer for AD in clinical practice is FDG, which measures the cerebral metabolic rates of glucose, a proxy for neuronal activity, although the use of Aβ and tau tracers is growing rapidly [47, 48]. Studies have shown a FDG-PET endophenotype for AD characterised by hypometabolism in regions of the default-mode network, with metabolism deficits gradually worsening as the disease progresses [47]. However, hypometabolism is less severe or consistent in the early stages of AD [47].

Amyloid PET predicts presence of fibrillary aggregates of Aβ, offering higher specificity for AD than MRI or FDG-PET [47]. It can help in the differential diagnosis of AD and frontotemporal lobar degeneration [49]. However, a positive result does not definitively diagnose AD and amyloid imaging may not be sensitive enough in the early stage of some patients.

While amyloid PET has been used for over a decade, tau PET ligands have only become available recently, showing robust differences between healthy controls and patients with MCI [50]. Tau PET holds particular promise as a biomarker for AD, as studies suggest that tau deposits mediate the association between Aβ and cognitive impairment [51]. Tau PET has been found to be more sensitive than Aβ PET, being associated with worse performance on a variety of neuropsychological tests in both prodromal AD and advanced stages of the disease [52]. Despite being approved by the US Food and Drug Administration (FDA) [53], tau PET is still not reimbursed, limiting access.

Cerebrospinal Fluid Biomarkers

Given the direct contact of the CSF with the extracellular space of the brain, biochemical changes in the CSF can offer valuable information. Thus, CSF has been the focus of much research on diagnostic biomarkers for AD. Three biomarkers, total tau (t-tau), p-tau, and Aβ42, have been evaluated in numerous studies, showing a high ability to differentiate AD from normal aging, depression and Parkinson's disease, but lower specificity against vascular dementia and Lewy body dementia [54]. It is hypothesised that decreases in soluble $A\beta_{1–42}$ in CSF signal its aggregation into plaques. A recent review highlighted the usefulness of using $A\beta_{1–42}/A\beta_{1–40}$ in CSF for the diagnosis of AD in people with dementia, and its potential utility in identifying early signs of AD [55]. Indeed, the FDA recently approved the first $A\beta_{1–42}/A\beta_{1–40}$ CSF test for the early detection of amyloid plaques associated with AD [56]. In addition, ratios of p-tau/$A\beta_{1–42}$, $A\beta_{1–42}/A\beta_{1–40}$ and t-tau/$A\beta_{1–42}$ in CSF have demonstrated good concordance with amyloid PET [57]; furthermore, these biomarker assays are associated with lower costs than PET [18]. Consequently, CSF investigations for Aβ and tau are included in the IWG

recommendations for clinical diagnosis of Alzheimer's disease, with PET investigations providing an alternative in cases where lumbar puncture is contraindicated [18].

In order to improve the predictive value of CSF biomarkers and allow for risk stratification, the Erlangen Score Algorithm [58] and other scales [59] that combine measures of Aβ42, t-tau, and p-tau have been developed. For the Erlangen Score Algorithm, the CSF results of a patient are determined depending on the pattern of Aβ42, t-tau, and p-tau alterations. Scores range from 0, where there is no evidence of AD, to 4, where AD is probable.

Current Challenges and Future of Biomarkers

Despite the clinical utility of both neuroimaging and CSF biomarkers, there are still some obstacles to overcome. Firstly, availability of different techniques varies significantly between centres, with tau PET being available only in research contexts. In addition, the high costs of PET scanning and the lack of reimbursement for these examinations in some countries hinder accessibility. On the other hand, the invasiveness of CSF testing often elicits reluctance towards lumbar puncture among clinicians and patients, despite the overall risk of complications being relatively low [60].

Thus, low-cost and non-invasive alternatives such as plasma biomarkers have the potential to drive changes in AD screening and diagnosis. This demand has motivated the development of ultra-sensitive assays, able to measure very low levels of AD-related biomarkers in blood samples. However, validation in multiple independent cohorts and across platforms as well as comparison with existing validated biomarkers is still lacking [61, 62].

Other promising non-invasive biomarkers for AD are neurophysiological markers such as cortical excitability measured with transcranial magnetic stimulation (TMS) [63] as well as retinal changes, including structural, vascular and electrophysiological biomarkers [64]. Digital biomarkers using mobile and wearable device-derived data may also aid early detection of AD [65]. Lastly, combining biomarkers with genotyping can provide greater accuracy in the early diagnosis of AD.

OPTIMISING MANAGEMENT FOR PATIENTS WITH ALZHEIMER'S DISEASE

Major System Constraints

In order to achieve early diagnosis in AD, it is important to also consider whether countries are prepared to incorporate innovation. The "Dementia Innovation Readiness Index 2017" investigated this in the G7 countries and found that, in most cases, there was an insufficient number of specialists to recognise, evaluate and diagnose dementia [66]. In addition, in some European countries such as France and the UK, the waiting times to see a specialist is more than 12 months [67].

Psychological Impact of Early Diagnosis

With the currently limited availability of disease-modifying treatment for AD, it is important to consider the psychological impact of early diagnosis. Studies have begun assessing the psychological effects of disclosing both AD-related genetic and biomarker information to cognitively unimpaired adults. In one study, participants who learned they had elevated amyloid levels did not experience short-term negative psychological sequelae [68].

A recent literature review [69] suggests that the potential benefits of disclosure, such as increased autonomy, outweigh the low risk of psychological distress or self-harm in cognitively unimpaired research participants. However, other factors such as potential discrimination in the workplace or insurance need to be considered.

It is also important to point out that pre- and post-biomarker counselling varies across centres [70], which calls for better biomarker counselling and better training to improve communication skills. In this regard, Huntington's

disease, for which genetic testing has been available for longer than any other adult-onset genetic disorder, can serve as an example, as genetic testing is offered as part of comprehensive specialist counselling [71].

Considerations to Disclose an Early Diagnosis

As disclosing early diagnosis is a sensitive topic, we suggest some points to consider across the diagnosis process.

Firstly, during pre-biomarker sampling counselling, it is important to provide basic information and establish that the patient understands the diagnostic process and the information that will be disclosed. The four components of clinical competency need to be considered: understanding, appreciation, reasoning, and expression of choice. It is also important to discuss the purpose, limitations and any possible benefits and disadvantages [72]. In addition to providing information, it is also vital to ask whether there are any questions before continuing with next steps.

During the diagnosis disclosure, it is advisable that the patient is accompanied by a caregiver to offer support and to be 'an extra pair of ears'. Communication should be adjusted to the individual patient and information should preferably also be provided in writing for future reference. Patient wishes in terms of level of information should be respected.

The physician should be open about the uncertainty in biomarker interpretation and avoid a deterministic interpretation, adopting a probabilistic interpretation. If the diagnosis is uncertain, a discussion of further diagnostic evaluation or offering the option of a second opinion evaluation may be relevant.

The patient should always be given information about follow-up and post-diagnostic care. Lastly, advice on brain-healthy behaviour and attention to modifiable risk factors can help to empower the patient to do something themselves to influence the disease course.

CONCLUSIONS

Current diagnosis of AD usually relies on clinical signs of cognitive impairment. Cognitive screening using the MoCA can help detect MCI and stratify risk of conversion to AD dementia. In addition, biomarkers, used in combination with clinical assessment in people with specific AD phenotypes, allow for early and more accurate diagnosis in AD [18]. However, use of biomarkers also presents some challenges, such as limited availability and high cost in the case of PET, and invasiveness in the case of CSF. Biomarkers are also critical to the evaluation of disease-modifying therapies in clinical studies in AD through the identification of suitable participants, proof of target concept, determining disease progression and monitoring safety outcomes [73].

Future biomarkers such as plasma and neurophysiological measures could be an attractive advance both in terms of low cost and non-invasiveness. In addition, specific work should address comparability between biomarkers to develop adequate diagnostic algorithms combining them. However, technical advances in biomarkers need to happen together with a change in national health systems to overcome any constraints or barriers. This is of paramount importance, given the increasing prevalence of AD and the burden of this disease on individuals, families and society as a whole.

Biomarker assessment is generally viewed favourably by patients, as the information provided can help individuals to plan and make informed decisions. However, debate continues over how and when to return biomarker information to the patients. Pre-test counselling and diagnostic disclosure whilst respecting the wishes of the patient is as important as correct and accurate diagnostic evaluation.

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