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Title: The use of biomarkers in Alzheimer's disease: a case report

Abstract: Uncertainties remain around the use of biomarkers in clinical practice to diagnose Alzheimer's disease (AD). There are several implications for both the patient and the clinician including the ethical and practical dilemmas of identifying a disease process early in its course when there are no disease modifying treatments available.

Key words: case report; Alzheimer's disease; dementia; PET amyloid scan; biomarkers;

Introduction: A person with AD typically presents with a gradual onset and progressive decline in episodic memory i.e. the ability to learn and retain new information, occurring usually for a period of at least 6 months. Later in the illness other higher cortical functions (for example language, visuospatial, and executive function) become affected and behavioural and psychiatric disturbances may be seen. There is also an associated decline in the patient's usual level of functioning.[1] The diagnosis of dementia is reached after careful history taking including information from a knowledgeable informant and impairment on formal cognitive testing (usually 2 standard deviations (SD) below that expected on the basis of age and education)[1]. Yet the clinical detection and diagnosis of AD is not always clear, particularly in the early stages. Patients may present with more subtle patterns of cognitive impairment which fall short of the standard definitions of dementia but which may represent a 'prodromal' or transitional dementia state. These include the terms Subjective Cognitive Impairment (SCI) and Mild Cognitive Impairment (MCI). The term SCI is not so much a diagnosis but rather a description of those who are experiencing cognitive complaints but formal testing fails to reveal any objective evidence of a cognitive decline. The syndrome of MCI has been defined as an isolated cognitive impairment (or impairments) identified as abnormal by a statistical rule (usually 1 to 1.5 SD below that expected on the basis of age and education) and representing a decline from previous level of functioning, but not so severe as to affect activities of daily living. [2] This is an arbitrary distinction based on clinical judgement and is subject to both clinician biases and patient or caregiver reporting errors. [3]

The National Institute on Ageing-Alzheimer's Association (NIA-AA), [1] and the International Working Group (IWG)[4] revised the clinical diagnostic criteria for AD to apply the use of biomarkers in conjunction with clinical assessment. Biomarkers, in this instance, provide objective evidence of the pathogenic process of the disease.[1, 4] In AD the different types of biomarkers relate to either amyloid deposition or neuronal degeneration.[1] Amyloid deposition occurs early, in some cases up to twenty years before symptoms occur,[5] and includes a positive amyloid positron emission tomography (PET) scan and reduced amyloid beta 42 in cerebrospinal fluid (CSF) analysis. Biomarkers for neuronal degeneration include hippocampal atrophy on structural MRI, hypometabolism on the 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET), and raised tau in CSF examination. These become abnormal later in the disease and are directly related to the cognitive symptoms of AD.[6]

According to the authors of the NIA-AA,[7] AD can be viewed as a continuum with a number of stages. The first phase in AD is a preclinical phase where the disease begins with a long asymptomatic period during which detrimental changes are progressing in the brain. During this stage patients may have subtle cognitive changes (SCI). If they are found to have an amyloid

biomarker (e.g. positive amyloid scan), they are considered to be at the starting point of the disease process and are at risk of progressing to Mild Cognitive Impairment (MCI), [2] and then to AD. The next phase is prodromal AD and includes MCI in AD. These patients have AD both neuropathologically and clinically but do not meet the criteria for dementia. Diagnostic confidence may be suggested by a positive amyloid beta marker, and a positive degeneration biomarker. Lastly patients with dementia due to AD meet the criteria for AD, and the presence of biomarkers enhances confidence in clinical diagnosis.

Similar to the NIA-AA criteria, the IWG [4] recognises that the onset of AD starts prior to dementia, and that there is a preclinical, prodromal and clinical (dementia) phase of AD. The IWG [4] criteria help to differentiate “Alzheimer’s disease” from “Alzheimer’s pathology”. The latter refers to the underlying neurobiological changes regardless of the presence of symptoms, whereas AD is the clinical disorder i.e. symptomatic stage which encompasses both the prodromal and dementia phases. An important difference between the two criteria is the IWG eliminates the ambiguous distinction between MCI and dementia. The IWG refer to a single clinico-biological approach that includes all symptomatic phases of AD and uses the same diagnostic framework at each stage of the disease [3]. If there are no symptoms present, then this is not a diseased state. Instead, individuals can be diagnosed as being “at risk for AD” where there is evidence of brain amyloidosis, even during the prodromal phase of the disease before it interferes with daily functioning.

Increasingly clinicians have access to these biomarkers, however the application of the various diagnostic criteria for AD as outlined above is limited to research purposes. The implications of using biomarkers in a clinical setting to find out about having a progressive condition possibly up to two decades prior to symptoms emerging and with there being no disease modifying treatment currently available is an interesting topic which is discussed further following the case presentation below.

Initial presentation: A 52 year old gentleman was referred by his GP in April 2015 with a 4 month history of becoming increasingly forgetful with names, appointments and dates. He was seen for an initial assessment by the local Old age psychiatry service in July 2015. Here he spoke of his concerns relating to his memory problems and difficulties with carrying out tasks at work where he is employed as a mechanic. There were a couple of incidents where he had made some errors on repairs to cars. On one occasion he forgot to replace the dipstick in a car he had been working on, and on another he neglected to replace a clip which later caused a leak. He had also put in an application for leave without realising he had already done so. Other than these incidences at work there were no other changes in his functioning. He continued to drive without concerns. There was no word finding difficulties or changes in his use of language. He did not experience any abnormal motor symptoms. There were no significant changes in his mood or temperament, and neither he nor his wife felt he was particularly anxious. He was sleeping well at night and had a good appetite. There were no psychotic symptoms reported. The patient's wife also attended the appointment and she had no concerns regarding his memory or level of functioning.

In terms of his background history his father died of a myocardial infarction at the age of 62 and his mother at 79 of ovarian cancer. He is a twin and has three older siblings. There is no known family history of dementia or other psychiatric illness.

On mental state examination at the time of assessment he was a neatly casually dressed, middle aged man with an attentive and cooperative manner. He made good eye contact and rapport. There were no abnormal movements. His speech was quiet but fluent with normal variability and no repetitiveness or word finding difficulty. His affect was reactive and he was not evidently anxious or depressed. There were no abnormalities of thoughts or perceptions. On cognitive testing he scored 86/100 on the ACE-R with the following subsections: attention and orientation 18/18, memory (19/26), fluency (7/14), language 26/26 and visuospatial 16/16 His insight was good in that he did not seek to downplay or exaggerate his memory problems.

On physical examination his pulse was 68bpm, regular and of good volume. His blood pressure sitting was 163/93 and 160/89 on standing. Examination of all systems including the central nervous system was normal.

Investigations: Blood tests were normal other than raised cholesterol levels. A MRI brain scan in July 2015 showed a few white matter hyperintensities in the frontal lobes but otherwise no abnormality. He underwent formal neuropsychometric testing in February 2016. This consisted of the Wechsler Test of Adult Reading (WTAR) which assessed his pre-morbid predicted verbal IQ to be 99 which put him in the average range (47th percentile). . The Cambridge Cognitive Examination-Revised (CAMCOG-R) and Trail Making Tests A and B were used to assess a range of cognitive functions. Memory was assessed through a logical memory test which is taken from the Wechsler Memory Scale (WMS). The patient listens to two different stories read by the examiner and is then asked to recall each from memory both immediately and following a delay. The patient's ability to remember the stories and list of words both immediately and after a delay was impaired (<2nd percentile). The patient's working memory was assessed by new learning, for example asking him to remember a string of numbers and repeat them back in reverse order where he scored in the low average range (10th to 24th percentile). The CAMCOG-R testing also revealed deficits in attention (10th to 24th percentile), and aspects of executive function (<10th percentile)..

Differential diagnosis:

- Systemic cause such as a metabolic disease but unlikely given normal physical examination and investigations including bloods and structural brain imaging
- Psychiatric illness such as depression – although subjectively and objectively the patient did not appear depressed
- Degenerative illness such as AD - on memory testing he scored 2 SD below that expected of age and education. There were also deficits in attention and aspects of executive function relative to his peers.

Follow up and outcomes: In April 2016, following the results of the neuropsychological testing the patient was given a diagnosis of dementia in AD of young onset and recommended for a cholinesterase inhibitor. He was also given advice on making lifestyle changes including to his diet and physical exercise. The GP was advised of his hypertension and cholesterol levels which were subsequently treated. However he and his wife disputed the diagnosis and he was referred to colleagues for a second opinion.

In August 2016 he was reviewed by a separate clinical team in the trust comprising of Old age psychiatrists and psychologists and underwent further cognitive testing. The WTAR assessed his pre-morbid predicted verbal IQ to again be in the average range. However the CAMCOG-R and Trail Making Tests A and B revealed entirely normal scores other than an isolated deficit in verbal fluency (10th-24th percentile). In view of the discrepancy between his performance on neuropsychological testing it was felt, based on the current evidence that a diagnosis of AD could not be supported and he was given a diagnosis of subjective cognitive impairment (SCI).

The patient and his wife had been given contrasting diagnoses of YOAD and SCI. They were in "shock" and "disbelief" when told he may have dementia. With the diagnosis of SCI they felt relieved but conflicted. On one hand they were pleased and felt the term SCI was more in keeping with their views on his memory complaints, but at the same time questioned the possibility of repeated cognitive testing which may have accounted for his improved scores. There was uncertainty, as well as anger and despair by the patient and his wife on which diagnosis was the right one, and what was going to happen next.

The patient was retested by the original team in February 2017 where he showed improvements in various aspects of cognitive testing and there were no objective deficits. This was attributed to cognitive stimulating exercises, improvement in his diet, physical activity and treatment of underlying hypertension. There was also the possibility of improved test scores due to practice effects with repeated testing. In hope of clarifying this gentleman's diagnosis he was referred for a brain amyloid PET scan with (18)F-florbetapir which he had in May 2017. This revealed the presence of beta-amyloid in the cerebral cortex of both frontal, temporal, posterior parietal and occipital lobes. The scan confirmed the changes in the brain were consistent with the presence of a disease process such as AD. The patient was given feedback of the scan and disclosure of his diagnosis in July 2017. It was explained that whilst he reports some problems with his memory, retesting showed no impairment of his episodic memory, and he continues to function well including driving with no concerns. However as the amyloid PET scan of his brain showed amyloid pathology he was told the AD process had started, and he was given a disclosure of a diagnosis of prodromal AD in its early stages. He was subsequently started on a cholinesterase inhibitor, referred to the Alzheimer's society for possible cognitive stimulating activities to take part in, and advised to inform the Driving and Vehicle Licensing Agency (DVLA) and his employers of his diagnosis.

The patient was then followed up in the medication monitoring service and seen by a senior community nurse in October 2017. He was initially started on donepezil 10mg once daily (od) but he was unable to tolerate this and it was changed to the rivastigmine transdermal patch 9.5mg od. At the time of assessment he reported no changes in his memory or functioning, and on cognitive testing using the M-ACE he scored 29/30: attention 4/4, memory 7/7, fluency 7/7, visuospatial 5/5, memory recall 6/7. He then had 6 monthly follow ups. In April 2018 there was no change in his clinical assessment but on M-ACE he scored 27/30: attention 4/4, memory 7/7, fluency 6/7, visuospatial 5/5, memory recall 5/7. At his most recent review in November 2018 there was again no concerns with his memory reported, or any change in his functioning observed. He continues to work as a mechanic at his local garage, manages his activities of daily functioning independently, and drives without concern. He declined to take part in any cognitive testing on this occasion due to wanting to get to work.

Discussion: In summary the case highlights the challenges facing clinicians when presented with a relatively young patient complaining of cognitive difficulties and the use of biomarkers to aid the diagnosis of AD. Furthermore, the complexity of the terminology used to describe an individual's cognitive difficulties can be confusing.. To briefly recap, to make a diagnosis of AD the core clinical components must first be satisfied. Then the use of positive biomarkers in AD can be used to support such a diagnosis. In this case the criteria for dementia was not fulfilled and therefore, regardless of the presence of positive biomarkers, he does not have dementia in AD of young onset. The patient can be considered to be in the preclinical stages, and depending on which criteria for AD is used, the IWG would describe this patient as "asymptomatic at risk for AD", and the NIA-AA would refer to this patient being at stage 3 and at risk of progressing to the clinical stage (see Table 1).

Table 1. The use of the IWG and NIA-AA criterion for AD in this case

	Preclinical stages	
	Cognitive criteria	Biomarker criteria
IWG Asymptomatic at risk for AD	No impairment	Any pathophysiological biomarker
NIA-AA Stage 3 (at risk of progressing to MCI)	Subtle cognitive changes	Positive amyloid biomarker

There is no doubt that a pre-dementia stage of AD exists, however understanding the relationship between the clinical manifestations and the pathological changes are still evolving. A recent review of the biochemical and neuroimaging studies in individuals with SCI identified two research studies that used amyloid PET to confirm the presence of amyloid deposition [7]. One of these studies [8] found brain atrophy in 49 persons with SCI was strongly related to Pittsburgh Compound B (PiB) uptake, a ligand that attaches to amyloid in the cerebral tissue, compared with the 45 'cognitively healthy' individuals. The other study [9], compared the amyloid deposition in 48 individuals with SCI and their performance on episodic cognitive testing. They found those with high PiB uptake performed worst on episodic memory testing and had lower confidence regarding their memory than those with low PiB uptake. These two studies provide preliminary evidence of the relationship between beta amyloid deposition, atrophy and cognitive decline very early in the disease process. However, the concept of SCI is currently a matter of debate. In the view of the IWG [4], SCI is not a proxy for preclinical AD, as these individuals only present with a small increased risk when compared to non SCI patients. Also individuals with positive amyloid beta associated with SCI are only "at risk for AD" and should not be considered as having clinical AD.

The patient in this case is thought to be in a prodromal stage of AD, which has had a significant impact on him and his family. The decision to pursue biomarker testing in clinical practice therefore raises a number of issues and should not be taken lightly. At present there appears to be little evidence currently on the meaning and impact of a positive amyloid PET scan, and other AD biomarkers. From an individual's perspective being diagnosed with prodromal AD means for many years they are left with uncertainty of the duration of this phase of the disease.[3] This may have an adverse effect such as psychological distress including anxiety and depression.[10] Some patients may misinterpret a positive biomarker to mean they have AD and then make unwise decisions so as not to be a burden in the future to their families.[11, 12] From a clinician's perspective there is the risk of overuse, misuse and over reliance of biomarkers to diagnose AD and subsequent inappropriate use of resources.[13] On the other hand the finding of positive AD biomarkers may have a number of benefits to both patient and clinician. Such as increased confidence in the diagnosis of or exclusion of AD, and resulting management of care. For example, there may be earlier initiation of treatment such as cholinesterase inhibitors, although the current evidence base in the use of such drugs in an early AD patient is poor. Other potential benefits of positive AD biomarkers include lifestyle modifications by the individual including diet, exercise, smoking and alcohol intake; better management of co morbidities and vascular risk factors; and enable future planning for example advanced care directives regarding welfare and finances, and make environmental changes if needed.[13]

As with a clinical diagnosis, a degree of uncertainty remains with the use of AD biomarkers. Structural imaging scans (CT/MRI) in patients with AD are often normal.[14] The amyloid PET scan, in comparison, has greater sensitivity and specificity.[15] A negative amyloid scan provides strong evidence that an individual does not have AD and a positive amyloid scan is highly suggestive of AD pathology.[16] However it does not differentiate patients from having other concomitant neuropathologies such as Lewy bodies.[17] A further limitation of the amyloid PET scan is the high prevalence of amyloid pathology in normal older individuals.[17, 18] This may lead to the possibility of false positives, false negatives or intermediate results. There is also the dichotomous reporting i.e. positive/negative which does not reflect the intermediate or borderline changes sometimes seen in clinical practice.[13, 19]

During the disclosure of the results patients should receive an educational session about the meaning of the results and the possible implications of a diagnosis of prodromal AD.[20] These include issues around driving, employment, finances and those for life and health insurance coverage.[21] Individuals may also encounter stigma following the diagnosis,[22] for example discrimination in the workforce, [19] and being at risk of financial exploitation by others.[21] Conversely providing a label such as AD to the individual may lead to behaviour or characteristics perceived as belonging to this label.[10] Another concern is the limited data and legal protection for individuals with positive biomarkers for AD, and the need for these to be developed similar for those who undergo predictive genetic testing.[10, 18, 19] At disclosure, patients should also be screened for anxiety and depression, and suitable follow up arrangements made to monitor for such symptoms.[20]

To conclude, further research and validation of AD biomarkers is needed before clinicians can apply the latest revised diagnostic criteria for AD [1, 4] into clinical practice. Until then dementia remains a clinical diagnosis and should be made only after a comprehensive clinical evaluation by a dementia

expert. The use of biomarkers namely neuroimaging and CSF analysis should only be used in clinical practice where there is doubt or clinical uncertainty about the aetiology of cognitive impairment. These are likely to include cases of young onset, atypical presentations and/or persistent unexplained MCI.[6] Guidance for clinicians on gaining informed consent and disclosure of biomarker test results, as well as what this means in terms of clinical management is needed. There also needs to be provisions put in place to give advice on the ethical, social, practical and legal issues that may arise from positive biomarker testing.

Learning points:

- The clinical assessment of a patient with cognitive impairment should be the same regardless of age at presentation, but in view of the wider variety of diseases that can present in younger patients, a thorough approach is particularly important
- It is recommended that all patients with suspected YOAD should undergo structural neuroimaging and CSF examination. [23]
- Genetic testing should also be considered in cases of YOAD, particularly in a patient less than 50 years old
- Where a diagnosis of YOAD has been made it is important the patient is regularly followed up with repeat cognitive testing to observe cognitive decline consistent with AD
- Guidance is needed for clinicians on the use of biomarker investigations such as the amyloid PET scan and what this means in terms of clinical management.

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