Diagnosing Alzheimer's disease: are we any nearer to useful biomarker-based, non-invasive tests?

Abstract

Background: Alzheimer's disease (AD) accounts for 60–80% of cases of dementia and causes significant morbidity in patients and carers, and expense for health and social services. There is a need for a validated, non-invasive and cheap test to diagnose early AD, as diagnosis may enable prompt treatment and service planning.

Aim: To identify emerging biomarker-based tests for the early diagnosis of AD which could be available for use in primary or generalist care in the near future.

Design: Horizon scanning review.

Methods: We searched online sources to identify emerging non-invasive, biomarker-based tests. Tests were included if they used blood, saliva or urine; and there was evidence of use in trials in patients with AD. For tests licensed for use in clinical or research settings we requested information from the developer on the intended place of use and plans for availability in Europe.

Results: We identified 6 biomarker-based tests of which 5 are available for research or clinical use. The closest to market were AclarusDX™ (ExonHit Therapeutics) a gene signature test, and INNO-BIA plasma Aβ forms assay (Innogenetics N.V.) which may be CE marked for clinical use in 2015. We found no evidence of clinical utility or cost.

Conclusion: Although biomarker-based tests are nearing clinical availability and may have a future role to help target AD-specific treatment and guide prognosis, they are not yet ready for trials of clinical utility in primary care.

Keywords: Alzheimer's disease, diagnosis, biomarker, emerging health technology, primary health care, dementia

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Introduction

There are over 820,000 people estimated to have dementia in the United Kingdom (UK) with around one third being undiagnosed [1], [2]. Alzheimer's disease (AD) accounts for 60–80% of cases of dementia and has an estimated UK incidence of 4.9 per 1,000 person-years in those over 65 [3]. The high prevalence and debilitating nature of AD leads to a large economic and caring burden for health and social services, families and individuals. Many patients who develop dementia present initially to primary care with mild cognitive impairment (MCI), which is cognitive decline greater than that expected given an individual's age and educational level that does not interfere with activities of daily life [4]. A subset of these patients will be in the prodromal or early phases of AD and early identification could enable the early use of symptom modifying drugs, e.g. acetylcholinesterase inhibitors [3]. Early diagnosis also offers other benefits to patients and carers including the assessment and treatment of co-morbid conditions such as depression, and the opportunity to organise practical aspects of care, social support and financial decision-making in advance of significant functional decline [5]. Together these early interventions have the potential to improve and/or prolong a patient's function, independence and quality of life [6].

AD is thought to be the result of extracellular accumulation of longer forms of the beta-amyloid (Aβ) peptide which forms amyloid plaques and an intra-cellular accumulation of hyperphosphorylated tau (phospho-tau) which causes neurofibrillary tangles. Aβ40, a 40 amino acid peptide, is the most frequent form of Aβ but is not usually associated with plaques. Longer forms of Aβ, e.g. Aβ42, are more susceptible to plaque formation. As AD progresses cerebrospinal fluid (CSF) levels of Aβ42 are known to fall and phospho-tau levels to increase [7], [8], [9]. The onset and progression of AD is also affected by the normal ageing process, genetics, e.g. by Apolipoprotein E (APOE) genotype and the environment.

A definitive diagnosis of AD currently relies on clinical and pathological evidence only available at post-mortem. Current diagnostic options in the living include a combination of clinical history, the exclusion of other causes of cognitive impairment, and cognitive and mental state examination [10]. Structural imaging with computed tomography (CT), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used as an aid to diagnosis, and to help differentiate AD from other types of dementia, but is expensive [6]. Because of diagnostic uncertainty, particularly in early disease, there is an unmet need for a validated, sensitive, non-invasive, relatively cheap and easily applied test that could distinguish, or help to distinguish, between pathological and age-related cognitive decline, and perhaps between the different underlying causes of dementia [11].

Previous reviews of the development of biomarkers for AD have identified a range of CSF and plasma-based biomarkers including Aβ42, Aβ40, the Aβ42: Aβ40 ratio, lipoproteins, inflammatory markers, α1-antichymotrypsin and an 18 peptide microarray of plasma signalling proteins [12], [13], [14]. These reviews are, however, either out of date or were undertaken to identify tests available for monitoring the effect of drug treatments in clinical trials. There is a need to update the previous findings, search for new biomarkers of relevance to use in primary care and investigate each biomarker's progress towards clinical availability. In the work reported here, we aim to identify and characterise emerging biomarker-based tests for the diagnosis of early AD which may be suitable for use in primary or generalist care settings.

Methods

We undertook a search of online sources in January 2011 (see list at the end of the section) to identify candidate biomarker tests using a mix of keywords including Alzheimer's disease, mild cognitive impairment, biological markers, biomarker, diagnostic test and/or diagnosis. Medline was searched from 1996 to week 1 January 2011 using both MESH and text words separately and combined. Clinicaltrials.gov searching was limited to trials first received between January 2006 and January 2011. We limited searches of Google and Google Scholar to articles posted during 2010. Biomarker-based diagnostic tests were included if they utilized a sample based on blood, saliva or urine, and if there was some evidence of use in clinical trials in cohorts of patients with AD. Biomarkers were excluded if they were used to identify an individual's genetic risk, were used concurrently with imaging techniques e.g. MRI or CT scanning, or were used with more invasive samples, e.g. CSF.

For each included biomarker test we attempted to identify the relevant commercial or academic institutes developing the test and compile information about completed or ongoing clinical trials. For those tests licensed for use in a clinical or research setting we requested additional information from each company on the test's intended place of use and availability in Europe or European commercialisation plans. Companies that did not respond to our initial email were chased twice by email or phone where possible. Tests that were confirmed by the company as no longer in development for AD were excluded. The final cut-off for obtaining information was the end of December 2011. We also searched for published evidence of test accuracy for each available test.

Online sources searched to identify biomarker-based diagnostic tests in development

- Technology databases of horizon scanning and health technology assessment organisations, e.g., UK-National Institute for Health Research Horizon Scanning Centre (NIHR HSC), ECRI, and the EuroScan International Network. (*EuroScan is the International Information Network on New and Emerging Health technologies*

(http://euroscan.org.uk). *It has 20 members from Australia, Canada, Europe and Israel.*)

- Clinical trial databases of ongoing research, e.g. clinicaltrials.gov
- Biographic databases: Medline, ScienceDirect
- Internet search engine: Google and Google Scholar

Results

We identified 6 biomarker-based tests that appeared to be available commercially for clinical or research use (Table 1) and over 21 academic centres or groups of centres investigating the same or other biomarkers. On investigation, tests from all but 6 of these centres were excluded because there was no evidence to suggest that they were in clinical trials in cohorts of patients with AD. Table 2 includes details of the biomarkers under development by the remaining 6 centres.

Tests nearer to clinical use

We successfully contacted all of the companies associated with the reportedly research-available tests. The test closest to the clinical market is AclarusDX™ (ExonHit Therapeutics) which uses a gene expression signature including inflammatory and immune markers. We were not provided with, nor could we find, information about the range of gene markers included. The company reports that, although the test is being used in an observational trial in French specialist memory clinics, it is not likely to be available in the UK until 2014 at the earliest [15]. Although test accuracy values are reported in company press releases (Table 1), details are not publicly available. The second test that may become available for clinical use in the foreseeable future is INNO-BIA plasma Aβ forms assay (Innogenetics N.V.) which measures levels of Aβ40 and Aβ42, and may be put forward for CE marking and clinical use in 2015 [personal information]. We could identify no information about test accuracy, although the test has been used in proof of concept-type trials. The only other test which we know to be undertaking clinical development is Milliplex multi-analyst profiling kits (Merck Millipore) that measures levels of 21 markers including Aβ42, Aβ40, phospho-tau, a non-Aβ component of amyloid – alpha synuclein, clusterin, complement factor H and α2 macroglobulin. The other 2 tests for which we could find information (AlzheimAlert™ and ADtect®) were reported to be either not in development in the present format or the company had no plans for launch or development in the UK.

All the tests nearer to the market are blood-based tests which could potentially be developed and marketed for use in specialist, generalist and community settings. However, the level of evidence for the clinical utility of any test was very limited, if not non-existent. Test accuracy information was available for 3 of the tests and reported sensitivities in the range of 56.3% to 92.3%, and specificities in the range of 57.7% to 96.8%. There was no information available on the time taken to process samples or to receive results, or on likely costs.

Promising biomarkers

Of the biomarkers under evaluation in academic centres, many are the same biomarkers as used in the commercial tests nearer the clinical market. New biomarkers include pregnenolone sulphate, a steroid hormone involved in the production of sex steroids, mineralocorticoids and glucocorticoids; N-glycans, a form of glycoprotein; and lipid profiles. These markers are all in the proof of concept stages.

Discussion

Summary of main findings

We identified 6 tests or biomarkers in the later stages of development for the early diagnosis of AD, however only 3 could be confirmed as undergoing some form of clinical, as opposed to basic research, development or use. No identified test for distinguishing between patients with non-pathological MCI and early AD or other dementias was currently available, or even near to the market, for clinical use in the UK. The test nearest the market (AclarusDx™) has a reported sensitivity of 81% and specificity of 67%. This equates to a positive likelihood ratio of 2.45, and a negative likelihood ratio of 0.28; indicating a test that is poor at distinguishing those with disease from those without. Any proposed test would need to be much more accurate and have substantially more evidence of benefit before it could be recommended for use in specialist health care, let alone in primary care where it would be used in a less selected population. At this stage of development there is no information available on the likely cost of the tests, but costs will play a significant part in acceptance for use in primary care and cost-effectiveness will need evaluation after clinical utility is proven.

Strengths and limitations of the study

The development of a commercially successful new biomarker-based test is usually a long and complex one. Candidate biomarkers may be initially identified by individuals, academic institutions or small start-up companies who undertake proof-of-concept testing. Those biomarkers and prototype tests most likely to be successful are usually acquired by larger companies prior to final market development and clinical testing. As there have been many candidate biomarkers and combinations of biomarkers proposed for AD reported in research literature, it can be very difficult to determine whether a biomarker is still in active development until it is acquired by a more established company. Even then the sale of rights to any biomarker and the underlying testing technique (which is often a separate commercial entity) can be complex to

Table 1: Commercial tests – biomarker tests currently available for use in a clinical or research setting

Test	Company	Biomarker	Commercial development & availability	Trial information & notes
AclarusDX™	ExonHit Therapeutics	>130 gene RNA expression signature (compared with healthy controls), including genes involved in inflammatory and immune mechanisms. Blood sample.	CE mark March 2011. Test being introduced initially in France in expert memory centres [15]. Will extend to other EU countries in 2014. [personal information]	• French observational study (DIALOG; n=600 planned) in specialist memory centre in patients consulting for the 1st time – commenced December 2011. • US pilot clinical utility study (n=160 planned) in specialist memory clinics, commenced November 2011 [16]. • Sensitivity 81%, specificity 67% in evaluation study involved 164 individuals (company data on file) [17].
AlzheimAlert™	Nymox	Neural thread protein (NTP). Requires purification of NTP in a laboratory. Urine sample.	CE marked 2004, but not marketed in Europe in current format. Licensed for laboratory-testing service USA.	• New test and/or reformatting of current test may be developed. • Sensitivity 89–92.3%, specificity 90–96.8%, positive predictive value 94.8–97.4%, negative predictive value 78.9–91.8% [18].
ADtect®	DiaGenic ASA Quest Diagnostics UK Ltd (Distributor)	96 mRNA transcripts, real-time PCR assay. Sample shipped to laboratory in Belgium. Blood sample.	CE marked. Available in Spain, no current plans for use in the UK.	• Clinical validation in mild to moderate AD: sensitivity 71.9% ±15.6, specificity 71.4% ±13.7 [19]. • Not evaluated to discriminate between underlying causes of dementia, or in patients aged 80 years or over.
INNO-BIA plasma Aβ forms assay	Innogenetics N.V.	Aβ isoforms: Aβ 1-42 and Aβ 1-40, and Aβ 1-42/Aβ 1-40 ratio. Immunoassay using multi-analyte profiling. Blood sample.	Available for research use only from 2007. May be CE marked for clinical use in 2015 [personal information].	• Clinical utility yet to be evaluated.
Milliplex multi-analyte profiling kits (3 kits)	Merck Millipore (with Proteome Sciences and Kings College London)	21 markers including Aβ 1-40 and 1-42, serum amyloid P (SAP), total and phospho-tau (P-tau231), alpha synuclein, clusterin, complement factor H, and α2 macroglobulin. Immunoassay. Serum, plasma or CSF sample.	Available for laboratory-based research only.	• Clinical development and evaluation ongoing in the UK.
NuroPro™	Power3 Medical Products Inc.	57 protein markers. Blood sample.	No information on its used in AD available.	• Test was being evaluated in USA, no results identified. • Licensed out to Amarantus for further development in Parkinson's disease.

Table 2: Diagnostic biomarkers in earlier stages of clinical development

Biomarker	Company or academic institute	Sample	Commercial development & availability, trial information and notes
Aβ oligomers	Multi-centre European study (EDAR), using PCR and ELISA techniques.	CSF, serum	Europe-wide prospective longitudinal study that includes a sub-study of the diagnostic accuracy of Aβ oligomers in early AD (n=100 with AD; n=250 MCI; n=100 with non-AD disease; n=50 controls) [20]. Data collection ongoing.
Aβ 42 dimers	The University of Melbourne	Blood	Proof of concept study published [21].
Pregnenolone sulfate (PREGS)	Assistance Publique – Hôpitaux de Paris	Blood	Proof of concept trial, NCT00912886, STERMEM, planned n=100 with AD; n=100 healthy [22]. Started 2009, still recruiting.
Truncated/extended forms of Aβ peptide	Centre Hospitalier Universitaire de Nice	Blood	Proof of concept study, NCT01128725, planned n=100, started September 2010, still recruiting [23].
N-glycan (NA2F)	Ghent University	Blood	Proof of concept controlled trial published [24].
Plasma lipid profiles	Universities of Cagliari and Florence, Italy.	Blood	Proof of concept controlled study published [25].

track. The methods used in this study rely on information about individual biomarkers being in the public domain, on our ability to track the development of biomarkers into commercial products, and on information from developers on marketing planning. At any stage this complexity may have led to missed biomarkers and missed commercial products.

Comparison with existing literature

Our results are consistent with the earlier reviews of biomarkers in development, even though our purpose was different. Sonnen et al. identified, in addition to Aβ42, Aβ40, lipoproteins and inflammatory markers; α1-antichymuotrypsin under investigation as a marker of AD. Published research on α1-antichymotrypsin was reported from 1990 to 2000 [12]. We did not find any published research using our more time-restricted searches, suggesting that its potential has not been realized. The only two plasma-biomarkers found by Hampel et al. were APOE status, and Aβ42 and Aβ40 levels [13]. As APOE status is used to assess an individual's genetic risk, it would have been excluded by our review.

Implications for future research or clinical practice

Unless the level of test accuracy reported improves dramatically in ongoing studies, the biomarker-tests identified here are only likely to be of benefit when used as an aid to diagnosis alongside clinical evaluation, rather than as standalone definitive, diagnostic tests. In primary care

these biomarker-tests may also be positioned as decision tools for referral for specialist assessment. However, given the poor effectiveness of current drugs in preventing cognitive decline or in reversing its effects in the long term, individual patients may consider early diagnosis unwelcome and will need careful counselling prior to testing. In addition, although the tests may be of some benefit in predicting future deterioration to AD in people with MCI, the implications of false negative and false positive results are not inconsequential. In people with MCI or early AD a false negative result may lead to more invasive tests to further investigate symptoms, and to a lost opportunity to arrange personal affairs and spend time with family and friends. False positive results may lead to a lost opportunity to treat other causes of symptoms and possibly to unnecessary despair.

New biomarker tests capable of predicting a decline of MCI into AD, may increase the overall number of people diagnosed with AD, and will bring into the diagnosis many more people with early AD. This may increase the number of patients being seen in specialist memory clinics, prescribed disease modifying drugs and monitored for effect, increasing costs. The number of patients with early AD accessing support services is also likely to increase, putting pressure on already pressurised services and potentially limiting service availability for those with severe disease. Other factors that need evaluation before adoption include the costs of the test and the testing equipment. It is highly likely that given the poor predictive value of current tests in development and the cost of providing a diagnostic service, a new diagnostic strategy using these tests will be found cost-ineffective. There is no indication at present that any of the tests will be developed as point

of care tests with analysis in primary or community care, so testing services are likely to be placed in hospital-based or commercial laboratories. As there is little urgency for an ultra-rapid turnaround of results, the time to results is unlikely to be a key feature in the adoption decision. It is debatable whether there will be any cost savings associated with the early diagnosis of AD, but there may be a reduced time to diagnosis and a reduction in referrals for more expensive MRI, SPECT and PET imaging.

All the tests we identified have inadequate data on clinical validity i.e., the accuracy with which they can predict underlying AD or deterioration into AD. In addition, the clinical utility of such an early diagnosis is also uncertain and the value of current treatments to individuals and their carers needs to be evaluated and balanced by the consequences for those with false positive or negative results. This information can only come from larger and longer trials and detailed evaluation of the results.

Conclusions

Although we identified 3 biomarker-tests that are nearing the clinical market, only 2 have demonstrated any analytic validity, and none have demonstrated clinical utility. Although the tests may have a role in the future to help target AD-specific treatment and guide prognosis, they are not yet ready for trials in primary care. It would be informative to repeat our searches in 2–3 years to reassess the status of the biomarkers and tests identified, and to find any new proposed biomarkers.

Notes

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Each author contributed to the study design, data analysis, data interpretation and writing of the final paper. All authors agree on the final version of the paper submitted for publication.

INAHTA Checklist

Checklist for HTA related documents (Attachment 1).

Attachments

Available from
http://www.egms.de/en/journals/hta/2013-9/hta000107.shtml
1. hta000107_INAHTA-Checklist.pdf (85 KB)
    Checklist for HTA related documents

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