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Biomarkers for cognitive impairment and dementia in elderly people

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Abstract

The threat of a looming pandemic of dementia in elderly people highlights the compelling need for the development and validation of biomarkers that can be used to identify pre-clinical and prodromal stages of disease in addition to fully symptomatic dementia. Although predictive risk factors and correlative neuroimaging measures will have important roles in these efforts, this Review describes recent progress in the discovery, validation, and standardization of molecular biomarkers – small molecules and macromolecules whose concentration in brain or biological fluids can aid in diagnosis at different stages of the more common dementing diseases and in the assessment of disease progression and response to therapeutics. An approach that efficiently combines independent information from risk factor assessment, neuroimaging measures, and biomarkers may soon guide clinicians in the early diagnosis and management of cognitive impairment in elderly people.

INTRODUCTION

Cognitive impairment and dementia in elderly people represent a burgeoning public health problem that already causes untold suffering and threatens to overwhelm health care delivery systems in the coming decades. One response to the looming pandemic of dementing illness is the development of biomarkers that can aid in diagnosis, prognosis, selection for clinical trials, and objective assessment of therapeutic response. Here we review the current level of knowledge for biomarkers of the common dementing illnesses, paying particular attention to their applicability at different stages of disease progression and to the quality of the current evidence.

PATHOGENESIS OF COGNITIVE IMPAIRMENT

Progressive decline in cognitive function among elderly people results mostly from Alzheimer's disease (AD) and vascular cognitive impairment (VCI),[1] and less frequently from Lewy body disease (LBD)[2] or frontotemporal dementia (FTD);[3] these forms of dementia combine to varying extents in individual patients.[4–9] The cellular and molecular pathogenesis of the common dementing illnesses is known only in part. For AD, LBD and FTD, complex molecular cascades seem to derive from the accumulation of abnormal forms of proteins or

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peptides, which suggests a proposed class of protein-misfolding diseases or so called proteinopathies.[10,11] Key among these proteins are amyloid β (Aβ) peptides and tau in AD, α-synuclein in LBD, and tau or TAR DNA-binding protein (TARDBP; alias TDP-43) in forms of FTD. Important pathogenic components in these diseases include innate immune activation, excitotoxicity, mitochondrial dysfunction, and oxidative damage, all of which may lead to regional loss of synapses and, ultimately, to loss of neurons.

STAGES OF DISEASE PROGRESSION

More than 30 years ago, Robert Katzman[12] proposed a chronic disease model for AD that suggests that the disease progresses from a preclinical or latent stage with some structural or molecular damage but no functional or behavioral changes, through a prodromal stage with greater damage and mild functional or behavioral changes, to fully expressed clinical syndrome of dementia, typically provoked by substantial and irreversible damage. This perspective is now supported strongly by clinical, neuroimaging and autopsy data.[4–9,13–19] Although they are less complete, emerging data similarly indicate that a chronic disease model may apply to VCI, LBD, and FTD.[1,4,5,18,19] Although these theoretical disease stages are evident in longitudinal studies, they are less apparent in cross-sectional designs. Table 1 shows some of the approaches commonly used to categorize patients into different stages of dementing illnesses in cross-sectional biomarker studies. One approach uses measures such as the clinical dementia rating scale.[24] Another is ascertainment of discrete categories that mainly compromise individuals with disease at different stages. For example, amnestic mild cognitive impairment (MCI) seems to constitute a group that largely consists of patients with prodromal AD,[20] whereas non-amnestic MCI is a proposed, but less accurate, indicator of prodromal VCI.[25] Finally, there are several subtypes of the dementia syndrome with established clinical criteria that have varying levels of sensitivity and specificity for the underlying disease process. For example, vascular dementia (VaD) is a clinically defined category that mainly inlcudes patients with dementia-stage illness from VCI. Similarly, as applied in several biomarker studies, dementia with Lewy bodies (DLB) is evolving as a separate, clinically-defined category for patients with dementia-stage illness from that of LBD.

RISK FACTORS, BIOMARKERS AND DISEASE SURROGATES

Risk factors are identifiable events or conditions associated with an increased probability of disease. For example, advanced age is a risk factor for AD. Genes can also be risk factors, as is shown dramatically by heritability estimates of 0.6 or higher from recent twin studies of AD.[13] Inheritance of the ε4 allele of the apolipoprotein E gene (*APOE*) is associated with earlier age of onset of AD than is inheritance of the other two common alleles of this gene.[26] Accordingly, age and inheritance of the ε4 allelehave been used in biomarker studies to increase of including individuals with pre-clinical AD (see Table 1 and Table 2). We define biomarkers as molecules whose concentration in brain or biological fluids aids diagnosis, assessment of disease progression, or response to therapeutics. Thus, biomarker research in geriatric dementia focuses on quantification of specific molecules using techniques that range from PET ligand binding to gene expression microarrays. Under this definition, structural and functional neuroimaging do not qualify as biomarkers, even though they contribute important information to the assessment of cognitively impaired patients. Disease surrogate is a concept from clinical trials that describes a trait or measure used as a substitute for the clinical endpoint of interest, often because the latter is difficult or unethical to obtain.

Before reviewing the existing biomarkers for geriatric dementia, we must discuss the nature and quality of the data. We suggest a hierarchy of biomarker development, progressing from discovery of initial associations, to confirmation in a larger or more complex independent sample, to validation with a standardized quantitative assay in other laboratories, and finally

to *widespread* clinical application of that assay. Whereas initial studies might appropriately use bespoke assays to discover initial associations, validation requires uniform assays with authentic standards, quality assurance, and known performance characteristics. To this evidence, then, must be added knowledge of potential effects of other common illnesses and commonly used drugs or supplements,[14,15] age,[16,17] sex,[62] diet, level of physical activity, and circadian variation.[63] With standardization and rigorous quality control, markers may finally be adopted for widespread application in clinical laboratories.

BIOMARKERS FOR ALZHEIMER'S DISEASE

Most data for biomarkers of geriatric dementia are for AD, usually diagnosed as "probable AD" by expert physicians and neuropsychologists in tertiary medical centers.[21] Many of these centers have active research programs that include autopsy and neuropathologic classification of dementing disorders. Therefore, the performance characteristics for expert clinical diagnosis of AD dementia are known. In general, the sensitivity and positive predictive value (*vs* neuropathological confirmation) for a clinical diagnosis of "probable AD" are about 90 to 95%, but specificity is lower (about 50 to 60%) because commonly co-morbid VCI and LDB are often difficult to discern clinically. This limitation of specificity presents an important problem for the interpretation of biomarker studies that have relied on expert clinical diagnosis: the probable AD group is almost always a mixture of patients with dementia that derives from AD alone and a substantial group that has additional dementing illnesses, most often VCI or LBD. One method of addressing this problem is the limitation of biomarker studies to individuals who subsequently undergo autopsy for "gold standard" classification of dementing illnesses.[64–66] Besides greatly limiting the number of cases, this approach assumes that each neuropathologic process present at the time of death was also present earlier when the biomarker was quantified. Considering these limitations, we have summarized current knowledge about biomarkers for AD identified in (**A**) cross-sectional and (**B**) longitudinal studies (table 2). Although direct comparison of the results from different laboratories is difficult, the similarity of outcomes across studies conveys the extent of validation at each stage of disease. .

CSF Biomarkers

Investigations of biomarkers for AD are dominated by cross-sectional studies for CSF $A\beta_{42}$ and tau species at each stage of disease. These markers have achieved widespread application in AD dementia and are currently being validated in prodromal AD or MCI. However, in pre-clinical AD, research is still at the stage of discovery.

CSF $A\beta_{42}$ concentrations are decreased by about 50% in patients with AD dementia or MCI, compared with (typically age-matched) controls.[67] This decrease has been associated with enhanced deposition of $A\beta_{42}$ in the brain.[28] By contrast, CSF total tau (T-tau) is increased on average by two to three times in AD dementia and MCI, whereas some phosphorylated tau (tau-P) species, (*e.g.*, tau-P231 or tau-P181) can be increased by one or two orders of magnitude when compared to control levels.[29,31,34,38,39] Since reduced CSF $A\beta_{42}$ and increased CSF tau are both characteristic changes for prodrome AD and dementia, investigators often combine the results of both assays.[33,67] Indeed, the CSF tau/$A\beta_{42}$ ratio seems to distinguish patients with very slight cognitive impairment from controls.[28] Unfortunately, none of these changes in CSF protein concentration is specific to AD,[68] and the biomarker levels are highly variable across individuals such that nearly all studies show substantial overlap in CSF values among controls and patient groups.[30–32,34,38,39,64,69] Moreover, especially for CSF tau species, the relationship between the concentration of these CSF proteins and the actual burden of disease is unclear.[70] The extent to which these limitations indicate misclassifications of patients versus true discrepancies cannot be resolved at this point and can be addressed only partially with autopsy classification, as noted above.

Because there are no characteristic symptoms in pre-clinical AD, cross-sectional investigations at this stage are challenging. Most investigators have used inherited mutations or risk factors to identify healthy older adults who are nevertheless likely to develop subsequent cognitive impairment. Some,[27] but not all,[37] groups have observed that CSF $A\beta_{42}$ is decreased to dementia-like levels in cognitively normal elderly with an *APOE* ε4 allele. Another group observed an age-related (cross-sectional) decline in CSF $A\beta_{42}$ in cognitively normal individuals beginning in the sixth decade of life, with a notable exaggeration of this decline in those with *APOE* ε4.[16] These results suggest that decreased CSF $A\beta_{42}$ may be a biomarker of pre-clinical AD. By contrast, others recently identified a cognitively normal volunteer with a family history of AD who had exceptionally high CSF $A\beta_{42}$ concentration and was shown to have inherited a disease-causing mutation in *PSEN1* (presenilin 1).[17] These results indicate that pre-clinical AD itself might have different stages (early increased CSF $A\beta_{42}$ with little parenchymal deposition followed by decreased CSF $A\beta_{42}$ secondary to parenchymal deposition). Alternatively, the pattern of changes in CSF biomarkers might differ among those with *APOE* ε4 versus a disease-causing mutation. Some,[37,38] but not all,[27] investigators have observed increased CSF tau or tau-P231 concentrations in cognitively normal older adults who inherited an *APOE* ε4 allele, suggesting that increased CSF tau and tau-P231 could be biomarkers of at least one stage or form of pre-clinical AD.

In longitudinal analyses of CSF $A\beta_{42}$ and tau, many investigators have shown that decreased CSF $A\beta_{42}$ and increased CSF T-tau or phosphorylated tau species predict subsequent conversion from MCI to AD dementia over follow up periods extending to 6 years,[35,36,71–76] while one group has observed similar predictive power for the relative pattern of C-terminal truncated Aβ peptides.[77] Others have reported that patients with MCI or AD dementia show cross-sectional alterations in CSF $A\beta_{42}$, T-tau, and tau-P181 concentrations that far exceed interval changes over a mean follow up period of 21 months.[78] These findings suggest that these measures are not particularly sensitive markers of disease progression at the prodromal or dementia stages of AD. Initial studies of empirically defined CSF tau/$A\beta_{42}$ ratio, however,suggest that these measures could prove helpful in identifying pre-clinical AD.[28,79]

Another extensively studied CSF biomarker is concentration of F_2-isoprostanes. Unlike disease-oriented (if not disease-specific) biomarkers like $A\beta_{42}$ and tau, F_2-IsoPs are mechanism-specific – that is, they are quantitative markers of free radical damage to lipids in vivo. In cross-sectional studies, increased CSF concentrations of this biomarker have been validated in AD dementia,[15,40,42–46] and similar findings have been confirmed in MCI.[40,41] Initial associations have also been made in individuals with an *APOE* ε4 allele.[37] Thus, CSF F_2-isoprostanes could prove to be useful biomarkers at all stages of AD pathogenesis, a possibility that is further supported by results from brain samples from patients who died with AD at prodromal or dementia stages that show increased F_2-isoprostanes or related molecules.[80–82] Longitudinal studies have also found a 1-year interval increase in CSF F_2-isoprostanes concentrations in patients with early AD dementia that might be suppressed by anti-oxidant vitamin supplements.[15,58]

Several groups are now using relatively unbiased discovery approaches to identify CSF biomarkers for neurodegenerative diseases. One method used by several laboratories is proteomics of CSF in cross-sectional studies.[66,83–86] Several partially overlapping ensembles of CSF proteins have been identified from patients with AD dementia. However, the number of patient samples is typically small and only twice have diagnoses been confirmed by autopsy.[66,84] A few groups have confirmed their initial findings.[48–50,87] One group used surface-enhanced laser desorption ionization to identify a panel of 17 potential biomarkers that distinguished a group of patients with MCI who progressed to dementia over 4 to 6 years.[87] Some molecular species in this panel were subsequently confirmed in analyses of separate samples.[50] Similarly, Hu, and colleagues[48] have assembled a proteomics-discovered six

member multi-analyte profile (MAP) of CSF proteins that partially distinguished patients with very mild AD from controls. Another group has developed a CSF proteomics-discovered eight member MAP and confirmed its use in a relatively large number of individuals (n=202) from multiple centers with different neurodegenerative diseases.[49]

In summary, CSF biomarker research in AD remains dominated by cross-sectional studies of Aβ peptides and tau species, which now have extensive validation in both dementia and prodromal stages. CSF F_2-IsoPs are validated in AD dementia and in MCI. Longitudinal studies and application of CSF proteomic approaches are still in discovery or confirmation phases.

Plasma or urine biomarkers

Although there is clear rationale for pursuing AD biomarkers by PET probes or in CSF,[69,88] there is no question that a biomarker derived from a peripheral fluid would be vastly more convenient and would probably aid the execution of large clinical trials. Unfortunately, plasma or urine biomarkers remain far less developed than those in CSF. Repeatedly published observations of increased plasma or urine concentrations of F_2-isoprostanes in patients with MCI or AD dementia could not be confirmed by others[89], and the original findings were not replicated by the same investigators using a different sample set.[90]

The data on concentrations of plasma Aβ species are complicated. Increased plasma $A\beta_{42}$ and sometimes $A\beta_{40}$ have been reported in rare autosomal dominant early-onset forms of AD and in patients with Down's syndrome.[91–93] Other investigators have repeatedly observed increased plasma $A\beta_{42}$ but not $A\beta_{40}$ concentrations in patients with late-onset AD dementia;[94–96] however, the usefulness of increased plasma $A\beta_{42}$ as a biomarker for this much more common form of AD is not clear.[97] Indeed, a recent cohort analysis from the Rotterdam Study concluded that increased plasma concentrations of $A\beta_{40}$, especially when combined with reduced plasma levels of $A\beta_{42}$, are associated with a risk of dementia from AD or VaD that is increased by up to ten times.[58] As with CSF, there is substantial overlap in plasma $A\beta_{42}$ concentrations among controls and patients with AD or other forms of dementia in cross sectional studies. One group did longitudinal analysis of cognitively normal older adults and concluded that reduced plasma $A\beta_{42}$:$A\beta_{40}$ ratio is associated with an increased risk of subsequently developing MCI or AD dementia.[59] However, a recent study of plasma Aβ peptides in 1725 men in their seventies concluded that decreased plasma $A\beta_{40}$ predicts incident AD.[60] A recently published 4.5 year longitudinal study of plasma Aβ peptide concentrations in a subset of participants in the Cardiovascular Health Study Cognition Study who were normal (n=242) or had MCI (n=42) concluded that, after controlling for age and other illnesses including cerebrovascular disease, plasma $A\beta_{40}$, $A\beta_{42}$, and their ratio did not seem to be useful biomarkers for AD.[61] A final level of complexity is raised by a recent study which showed ^{11}C-Pittsburgh compound B (PiB)-PET imaging correlates well with CSF $A\beta_{42}$ concentration, but that there is no discernible trend toward correlation with plasma concentrations of Aβ species.[53] Obviously, a deeper understanding is needed of the mechanistic connections among the brain, CSF, and plasma Aβ species in health and disease.

Several other plasma biomarkers for AD have been proposed, mostly related to immune activation or oxidized low-density lipoproteins. The specificity of these peripheral markers of inflammation has not been rigorously studied and they remain mostly in the discovery phase of development.[98–102] Increases in plasma α1-antichymotrypsin has been validated in AD dementia with varying degrees of correlation to disease severity,[103,104] but this finding was not supported by a third study.[105] A recent report identified 18 signaling peptides in plasma (out of 120 candidates), with concentrations that identified patients with AD dementia in a cross-sectional analysis, and progression from prodrome to dementia stage AD.[106] This is a potentially very important study; however, as with previously proposed plasma biomarkers of AD, independent validation of this panel's performance will be key to its future application.

In summary, biomarkers of AD in plasma, serum, or urine are highly desirable and thus are an area of active investigation that is still largely in the discovery phase. Several initially promising discoveries have not withstood attempts at validation, whereas others await validation.

PET for cerebral amyloid

Several amyloid-binding compounds can be synthesized with unstable isotopes compatible with radiotracer imaging. The most widely reported technique has used ^{11}C-labeled Pittsburgh Compound-B (2-[4L'-(methyl-amino)phenyl]-6-hydrobenzothiazole; ^{11}C-PiB) for PET imaging of amyloid binding.[57] The ^{11}C-PiB ligand is distributed rapidly to all grey-matter regions in the brain and is selectively retained in regions where it binds. Typically, data from cerebral regions are normalized to ^{11}C-PiB retention in cerebellum. Average and regional ^{11}C-PiB-PET signals are inversely correlated with MRI volumetric measurements, but do not co-register well with ^{18}F-FDG-PET in the frontal lobe of patients with AD dementia.[55,56] Although some have referred to PiB as a probe for amyloid plaque binding,[53] the ligand binds to amyloid deposits not only in the parenchyma, but also in cerebral blood vessels[107] that apparently can be the major source of signal.[107,108] The mean ^{11}C-PiB-PET signal intensity from multiple cerebral cortical regions is inversely correlated with CSF $A\beta_{42}$ concentrations, but not with CSF $A\beta_{40}$, CSF T-tau, CSF tau-P181, plasma $A\beta_{42}$, or plasma $A\beta_{40}$ in individuals with no cognitive impairment to moderate AD dementia.[53] This important demonstration of the relevance of CSF $A\beta_{42}$ concentrations to the burden of disease in the brain is lacking for other CSF or plasma biomarkers. Along with other reports, these data support the hypothesis that decreased CSF $A\beta_{42}$ is a consequence of increased cerebral deposition that may begin in pre-clinical AD[17,51,53] where it may be associated with diminished (if still normal) episodic memory.[52]

Sensitivity of ^{11}C-PiB-PET against a standard of expert clinical diagnosis of AD dementia is high (about 90%)[51,56] but autopsy investigations will be needed to assess this finding further. Specificity of the ^{11}C-PiB-PET signal for AD and congophilic amyloid angiopathy (*vs* other changes) is currently under investigation. PiB does not seem to bind to cortical Lewy bodies,[109] and PET imaging of ^{11}C-PiB retention in a patient with an autosomal dominant form of prion disease was similar to that in cognitively normal controls.[110] However, PET imaging with another amyloid radiotracer, FDDNP(2-(1-(6-[2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene) malononitrile), showed values between those from controls and AD in a sibling who had the same mutation. The latter observation suggests that different amyloid binding radiotracers may vary in their evaluation of dementing illnesses.[110] Indeed, results with ^{18}F-BAY94-9172, a novel Aβ ligand and PET tracer, were recently reported in 15 controls, 15 patients with AD, and 5 patients with FTD. Blinded reading of PET images correctly distinguished all FTD patients from those with AD and had 100% sensitivity and 90% specificity for the clinical diagnosis of AD or control.[111]

BIOMARKERS FOR VASCULAR COGNITIVE IMPAIRMENT

The same difficulties that surround expert clinical diagnosis of AD also exist also for VCI, perhaps even more so.[1] As we noted above, this limitation in clinical diagnosis can serve as a motivation for biomarker development, but it also imposes a considerable challenge to such work because reliable diagnosis is more dependent on neuropathologic assessment with all its limitations.

VCI spans from local territorial infarcts, for which structural MRI provides unsurpassed insight into lesion size and progression, to widespread small vessel disease, which isnot as easily assessed or distinguished from the consequences of AD by clinical examination or by current standard neuroimaging techniques.[112] Thus, biomarkers could contribute to the assessment

of damage from small vessel disease, whereas neuroimaging is likely toretain its central role in the assessment of ischemic injury from large and medium caliber vessels.

In 2006 the US National Institute for Neurological Disorders and Stroke and the Canadian Stroke Network made expert recommendations for biomarkers in VCI.[22] Increased CSF concentrations of T-tau or phosphorylated tau species, sometimes combined with normal $A\beta_{42}$ concentrations, increased neurofilament protein, and increased CSF:serum albumin ratio all have been reported in patients with dementia in cross-sectional studies.[31,113–117] Unfortunately, all such findings are limited by the broad overlap with values from patients whose clinical appearance suggests AD without VCI (Table 3). CSF sulfatide concentrations seem to be raised in VaD but have been shown only once to differ significantly different from those found in AD dementia.[119,120] CSF matrix metalloproteinase is raised in VaD but not AD dementia or controls.[121] One longitudinal study found that normal CSF tau levels combined with MRI evidence of presumed white matter ischemic injury could be used to identify patients with MCI who are less likely to progress to dementia.[118]

Several plasma-based or serum-based biomarkers for VCI have also been proposed. One recent longitudinal study discovered that increased plasma fibrinogen, but not C-reactive protein was associated with an increased risk for VaD and AD dementia.[100] Another study found that the combination of high C-reactive protein and high interleukin-6 concentrations increased the risk of incident VaD, but not AD dementia.[100,123] As in AD, the evidence for plasma Aβ peptide biomarkers for VCI is not entirely consistent. One recent study found that a 1 SD increase in serum $A\beta_{42}$:$A\beta_{40}$ ratio increased risk for VaD in 70-year-old men but not 77-year-old men.[60] Another group found plasma $A\beta_{40}$ to be increased and the $A\beta_{38}$:$A\beta_{40}$ ratio decreased in VCI.[122] In summary, biomarker development in VCI is less mature than in AD and has not yet identified candidates that are ready for standardization and widespread application.

BIOMARKERS FOR LEWY BODY DISEASE

LBD is characterized by regional intraneuronal accumulation of Lewy bodies composed of several proteins that prominently include α-synuclein. Accumulation of Lewy bodies in neocortical regions of the brain is a strong correlate of dementia.[4] However, clinical criteria that can reliably distinguish DLB from AD dementia are still under development.[23] As a result, biomarker studies of patients without autopsy confirmation of diagnosis are likely to rely on groups that mainly compromise patients with AD or DLB, but with an unknown degree of diagnostic cross-contamination.[114]

We are unaware of biomarker studies that focus on prodromal or pre-clinical DLB. One large (> 30 individuals per group) multicenter cross-sectional study of CSF biomarkers for DLB versus AD used commercially available kits to measure CSF $A\beta_{42}$, T-tau, and tau-P181. This study concluded that CSF tau-P181 is the most useful marker for distinguishing DLB from AD dementia, yielding an overall accuracy of 80%.[124] These findings confirmed a smaller previous study.[114] Another group has reported that a relative abundance of $A\beta_{37}$ and $A\beta_{42}$ in CSF discriminates between relatively small samples of patients with DLB and AD dementia.[125] Efforts directed at biomarkers for another form of LBD, Parkinson's disease with dementia, are likely provide insight.[126] Some investigators are using PET to determine amyloid burden, integrity of the cholinergic system, and density of dopamine transporters in the neostriatum.[2] Assays for CSF α-synuclein or plasma oligomers of α-synuclein in Parkinson's disease remain in the discovery phase.[127,128]

BIOMARKERS FOR FRONTOTEMPORAL DEMENTIA

FTD comprises a constellation of neurodegenerative diseases that are currently under active investigation. There are relatively few studies of biomarkers for FTD, and all have focused on

the dementia stage (little is known about preclinical or prodromal stages of this diagnostic group). One study observed that CSF T-tau and $A\beta_{42}$ were changed similarly in FTD (n=34) and AD (n=76) when compared with controls (n=93), but that tau-P181 was significantly increased only in AD.[129] Others could not confirm these findings for FTD, but did observe significantly increased neurofilament protein subtypes in a group of patients with FTD (n = 17) as compared with AD dementia (n = 20) or controls (n = 25).[130] In relatively small sets of CSF samples, some groups have discovered potential protein profiles or MAPs that may prove useful in distinguishing patients with FTD from those with AD or controls.[49,50,131] PET imaging showed that ^{11}C-PiB retention in multiple cerebral regions, including frontal lobes, from patients with FTD was significantly lower than in patients with AD dementia and not significantly different from cognitively normal controls.[54,132] As with CSF biomarkers, 20 to 33% of patients with FTD had ^{11}C-PiB-PET signals that overlapped with values typical for patients with AD; however, this degree of overlap might diminish with improvements in clinical acumen.

CONCLUSIONS AND FUTURE DIRECTIONS

Dementing illnesses in elderly people pose an enormous challenge in the 21st century, and improved tools are urgently needed for diagnosis and monitoring of clinical progress and therapeutic interventions. Biomarker development holds considerable promise for these purposes, but the evidence base is much stronger at present for AD than for VCI and, in particular, for LBD and FTD. In general, the evidence is strongest for the dementia stages of these neurodegenerative diseases, weaker for prodromal illness, and weakest for preclinical stages. The immediate challenge will be to identify combinations of biomarkers that identify the relative contributions of AD, VCI, LBD, FTD, or other disease processes to the different stages of cognitive impairment in older individuals from the general population.[31] The challenge will almost certainly be greatest for pre-clinical illness, for which therapies are most likely to be effective, but the tolerance for toxic effects is lowest.

Critical evaluation of the usefulness of a combination of standardized biomarkers, risk factor assessment, and structural and functional neuroimaging will be central areas of research as the field moves from discovery to validation to widespread clinical application. For example, will CSF tau (or a tau-P) and $A\beta_{42}$ concentrations carry the same, substantially more, or less information than a PET imaging study of amyloid or glucose metabolism? The present challenge of contrasting performance of biomarkers in different studies could be resolved through a cooperative multi-center approach to the identification of markers most useful in widespread clinical application. We speculate that assessment of genetic risk, neuroimaging to determine structural or functional changes, and some ensemble of biomarkers will become part of the standard examination for geriatric dementia over the coming decade. New knowledge from these investigations will propel testing and development of mechanism-specific interventions through the identification of appropriate subgroups for clinical trials and provision of objective measures of disease suppression. Success with new therapies would lead quickly to the widespread application of biomarkers in the clinical management of geriatric cognitive disorders.

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References for this review were identified by searches of PubMed from 1966 until April 2008. Terms used for search included: biomarkers; Alzheimer's disease, mild cognitive impairment; vascular brain injury; vascular cognitive

impairment; vascular dementia; Lewy body; and fronto-temporal dementia. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed.

Contributions:

All authors were involved in the selection of papers to be included in this review and in writing and editing of subsequent drafts.

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Table 1

Some commonly used approaches to categorize groups of individuals at different stages of dementing illnesses for biomarker studies

	Pre-clinical	**Prodrome**	**Dementia**
Alzheimer's disease	*PSEN1* mutations, trisomy 21, *APOE*ε4, family history, age	Amnestic MCI[20]	Probable AD[21]
Vascular cognitive impairment	Risk factors for vascular disease, neuroimaging, clinical and family history, age	Non-amnestic MCI[20]	Vascular dementia[22]
Lewy body disease	nr	nr	Dementia with Lewy bodies[23]
Frontotemporal dementia	nr	nr	¨ Frontotemporal

AD=Alzheimer's disease. MCI=Mild cognitive impairment. nr =not reported.

Table 2

Studies of biomarkers in Alzheimer's disease

	n	Main Outcome	Stage
CSF T-tau or $A\beta_{42}$			
Peskind and co-workers[16]	184	↓ $A\beta_{42}$ in patients aged <50 years, most prominently in *APOE* ε4 carriers	Preclinical
Kauwe and co-workers[17]	191	↓ $A\beta_{42}$ or $A\beta_{42}$: $A\beta_{40}$ was highly correlated with age, CDR of 0–1, and *APOE* ε4; *PSEN1* mutation identified in a patient with greatly increased $A\beta_{40}$ and $A\beta_{42}$ concentrations	Preclinical, prodrome, dementia
Sunderland and co-workers[27]	292	↓ $A\beta_{42}$, but no change in tau in *APOE* ε4 carriers and ↓ $A\beta_{42}$ and ↑ tau in AD dementia	Preclinical, dementia
Fagan and co-workers[28]	139	↓ $A\beta_{42}$ and ↑ tau in patients with CDR ≥0.5	Prodrome, dementia
Lewczuk and co-workers[29]	223	↓ $A\beta_{42}$ and ↑ tau in amnestic MCI and AD dementia compared with non-amnestic MCI; ↑ tau in AD dementia compared with amnestic MCI	Prodrome, dementia
Sunderland and co-workers[30]	203	↓ $A\beta_{42}$ and ↑ tau in AD	Dementia
Andreasen and co-workers[31]	241	↓ $A\beta_{42}$ and ↑ tau in AD dementia; ↑ tau in AD dementia compared with VaD, MCI, DLB, and controls	Prodrome, dementia
Andreasen and co-workers[32]	111	↑ tau in AD and some VaD	Dementia
Galasko and co-workers[33]	216	↓ $A\beta_{42}$ and ↑ tau in AD; *APOE* ε4 gene-dosage effect on $A\beta_{42}$ concentrations	Dementia
Bouwman and co-workers[34]	375	↓$A\beta_{42}$ and ↑ T-tau in AD dementia and ↓ $A\beta_{42}$ in older controls	Dementia
Hansson and co-workers[35] *	137	↓$A\beta_{42}$ and $A\beta_{42}$:$A\beta_{40}$ in MCI that progressed to AD over 4–6 years	Prodrome
Ewers and co-workers[36] *		↑ T-tau:$A\beta_{42}$ predicted progression to MCI or AD dementia over up to 40 months	Preclinical
CSF tau-P181			
Fagan and co-workers[28]	139	↑ in patients with CDR ≥0.5	Prodrome, dementia
Lewczuk and co-workers[29]	223	↑ in amnestic MCI and AD dementia compared with non-amnestic MCI	Prodrome, dementia
Bouwman and co-workers[34]	375	↑ in AD compared with controls and in older controls compared with younger controls	Dementia
CSF tau-P231			
Glodzik-Sobanska and co-workers[37]	78	↑ in *APOE* ε4 carriers	Preclinical
Buerger and co-workers[38]	131	↑ in MCI *APOE* ε4 carriers Prodrome	
Buerger and co-workers[39]	192	↑ in AD compared with controls, FTD, VaD, and DLB	Dementia
Ewers and co-workers[36] *	145	↑ in MCI that converted to AD over 14–28 mos	Prodrome
CSF F2-IsoPs			
Glodzik-Sobanska and co-workers[37]	78	↑ *APOE* ε4 carriers	Preclinical
Pratico and co-workers[40]	63	↑ in MCI and AD	Prodrome, dementia
de Leon and co-workers[41]	16	↑ in MCI	Prodrome
Montine and co-workers[42–45] Pratico and co-workers[46]	14–77	↑ in AD and HD but not in ALS or MSA	Dementia
Quinn and co-workers[15] * de Leon and co-workers[47] *	40,16	↑ over 1 year in patients with CDR 0.5–1	Dementia
CSF MAP			

	n	Main Outcome	Stage
Hu and co-workers[48]	94	6-member proteomics-discovered MAP effective in identifying patients with CDR 0.5–1	Prodrome, dementia
Zhang and co-workers[49]	183	8-member proteomics-discovered MAP moderately effective in identifying AD, strongly effective for PD	Dementia
Simonsen and co-workers[50]	137	15-member proteomics-discovered group validated to differentiate AD from controls	Dementia
^{11}C-PiB-PET			
Mintun and co-workers[51]	51	↑ binding in AD dementia and a subset of asymptomatic individuals	Preclinical, dementia
Pike and co-workers[52]	96	↑ binding in 97% of AD dementia, 61% of MCI, and 22% of controls, and was correlated with objective deficits in episodic memory	Preclinical, prodrome, dementia
Fagan and co-workers[53]	24	↑ binding was correlated with ↓ CSF $A\beta_{42}$ in individuals with CDR of 0–2	Preclinical, prodrome, dementia
Rabinovici and co-workers[54]	27	↑ binding in AD and some FTD cases	Dementia
Archer and co-workers[55]	9	Binding correlated with brain atrophy in AD	Dementia
Edison and co-workers[56]	33	↑ binding in 17 of 19 AD patients and correlated with reduced glucose uptake by FDG-PET in some regions	Dementia
Klunk and co-workers[57]	25	↑ binding in AD	Dementia
$A\beta_{42}$:$A\beta_{40}$ plasma ratio			
van Oijen and co-workers[58]	1756	↓ $A\beta_{42}$:$A\beta_{40}$ associated with increased risk for AD and VaD	Dementia
Graff-Radford and co-workers[59] *	563	↓ ratio at baseline associated with increased risk for conversion to MCI or AD dementia at 3–7 years	Preclinical
Sundelof and co-workers[60] *	1725	↓ $A\beta_{40}$ predicted conversion to AD dementia in 77-year-old men over up to 7.9 years	Preclinical
Lopez and co-workers[61] *	274	↓ $A\beta_{42}$, ↑ $A\beta_{40}$, and ↓ $A\beta_{42}$: $A\beta_{40}$ predicted conversion from control or MCI to AD, but this association was lost in models that corrected for vascular disease risk	Preclinical, prodrome

* Longitudinal studies (all others are cross-sectional studies).

↑=biomarker increased. ↓ =biomarker decreased. Aβ=amyloid β. AD=Alzheimer's disease. ALS=amyotrophic lateral sclerosis. CDR=clinical dementia rating (score). DLB=dementia with Lewy bodies. FDG= fluorodeoxyglucose. FTD=frontotemporal dementia. HD=Huntington's disease. IsoPs=isoprostanes. MAP=multianalyte profile. MCI=mild cognitive impairment. MSA=multisystem atrophy. PD=Parkinson's disease. PiB=Pittsburgh compound B. tau-P=phosphorylated tau. T-tau=total tau. VaD=vascular dementia.

Table 3

Studies of Biomarkers in vascular cognitive impairment

	n	Main outcome	Stage
CSF t-tau and $A\beta_{42}$			
Andreasen and co-workers[31]	241	↑ tau, but normal $A\beta_{42}$ in VaD	Dementia
Stefani and co-workers[113]	110	↓ $A\beta_{42}$ in AD discriminates from VaD Dementia	Dementia
Maruyama and co-workers[118] *	57	Stable MCI was characterized by normal T-tau concentrations and high-grade periventricular white-matter lesions	Prodrome
CSF tau-P181			
Stefani and co-workers[113]	110	↑ in AD dementia discriminates from VaD	Dementia
CSF sulphatide			
Tullberg and co-workers[119]	90	↑ in subcortical arteriosclerotic encephalopathy	Dementia
Fredman and co-workers[120]	83	↑ in VaD	Dementia
CSF neurofilament protein			
Sjogren and co-workers[117]	51	↑ in VaD	Dementia
Wallin and co-workers[116]	43	↑ in patients with dementia with several vascular risk factors or white-matter imaging abnormalities	Dementia
CSF MMP9			
Adair and co-workers[121]	53	↑ in VaD compared with controls and AD dementia	Dementia
CSF:serum albumin ratio			
Skoog and co-workers[115]	65	↑ in VaD and AD compared with controls; ↑ in women (n=3) who progressed to dementia over 3-year follow-up	Preclinical, dementia
Wallin and co-workers[116]	43	↑ in VaD	Dementia
Plasma $A\beta_{40}$			
van Oijen and co-workers[58]	1756	↑ $A\beta_{40}$ (and ↓ $A\beta_{42}$) associated with increased risk for AD dementia and VaD	Dementia
Bibl and co-workers[122]	72	↑ in VCI	Dementia
$A\beta_{38}$:$A\beta_{40}$ plasma ratio			
Bibl and co-workers[122]	72	↓ in VCI	Dementia
$A\beta_{42}$:$A\beta_{40}$ plasma ratio			
Sundelof and co-workers[60] *	1725	1 SD ↑ in $A\beta_{42}$:$A\beta_{40}$ ratio associated with increased risk for VCI in 70-year-old men	Preclinical

* Longitudinal studies (all others are cross-sectional studies).

↑ =biomarker increased. ↓ =biomarker decreased. Aβ=amyloid β. AD=Alzheimer's disease. MCI=mild cognitive