

Biomarkers in Alzheimer's, Frontotemporal, Lewy Body, and Vascular Dementias

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This article reviews the current evidence base for biomarkers of the most common causes of dementia in later life: Alzheimer's disease (AD), frontotemporal lobar degenerations, Lewy body dementias, and vascular cognitive impairment and dementia. Biomarkers are objectively measurable indicators of normal physiology, pathological processes, or response to an intervention. Ideally, they are sensitive, specific, easy to obtain, and closely reflect the underlying biological processes of interest. While such markers are well established and in broad clinical use for common disorders in general medicine (e.g., thallium stress tests for coronary artery disease or serum blood urea nitrogen and creatinine for renal failure), analogous, validated markers for AD or other common dementias are limited, although biomarkers in research settings and specialty dementia clinics are progressing toward clinical use. By way of introducing current and future biomarkers for dementias of later life, this article will benefit the practicing clinician by increasing awareness of the availability and utility of current and emerging biomarkers in dementia diagnosis and prognosis and for monitoring new disease-modifying therapeutics that arrive in the clinic over the coming decade.

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Dementia is defined as a decline in cognitive abilities severe enough to interfere with everyday activities, and may result from a number of etiologies. The *DSM-5* defines *dementia*—or major neurocognitive disorder—as significant cognitive impairment in at least one of the following cognitive domains, representing decline from a previous level of functioning: learning and memory, language, executive function, complex attention, perceptual-motor function, and social cognition (1). By far, the most common cause of dementia in later life is Alzheimer's disease (AD), a slow and insidious disorder that affects memory first and foremost, followed by decline in other domains as the disease progresses. After AD, other important neurodegenerative dementias include frontotemporal lobar dementias (FTLDs), Lewy body dementias (LBDs), and vascular cognitive impairment and dementia (VCID). From a clinical perspective, a fair degree of overlap exists across these disorders. Moreover, the brains of individuals demonstrating even “classic” clinical phenotypes of these syndromes will often reveal mixed pathologies at autopsy (e.g. AD with evidence of cerebrovascular disease).

The NIH Biomarkers Definitions Working Group defines *biomarkers* as markers that are “objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (2). Definitive diagnosis of AD, FTLD, LBD, and VCID can only be made by an examination of brain tissue at autopsy. However, biomarkers are rapidly improving in their ability to indicate the presence of brain pathology. Given the clinical and pathophysiological overlap of the

dementias, clinicians and researchers alike are increasingly recognizing that validated biomarkers are needed to accurately diagnosis these conditions in living humans, particularly at early stages in which disease-modifying treatments are likely to be of greatest utility. Furthermore, whereas disease-modifying therapeutics for the dementias have yet to reach the clinic, biomarkers have already proven their usefulness in the diagnosis of biological processes underlying these clinically heterogeneous conditions (Table 1).

In this brief review, we focus on the four most prevalent dementias in older adults: AD, representing about 60%–80% of dementia cases, as well as FTLD, LBD, and VCID, each representing roughly 5%–10% of dementia cases in later life (3, 4).

Dementia biomarkers can be broadly categorized as “imaging based,” “biofluid based,” or electrophysiological. Currently, imaging-based markers include measurements derived mostly from magnetic resonance imaging (MRI) and positron emission tomography (PET) but also derived from computed tomography (CT), single-photon emission computed tomography (SPECT), and infrared optical imaging. Biofluid-based markers are measured in biological samples such as blood, cerebrospinal fluid (CSF), saliva, or urine. Electrophysiological biomarkers principally include electroencephalography (EEG) and EEG-based event-related potentials (ERPs), as well as magnetoencephalography. While still under intense investigation for their performance characteristics in different disease states, these biomarkers are playing growing roles in clinical diagnosis, monitoring disease progression, and even identifying at-risk individuals prior to the manifestation of symptoms.

Neuroimaging methods have rapidly advanced in their utility for assessing brain changes associated with dementia (Table 1). Different MRI techniques in high-field-strength MRI scanners provide insight into the structural integrity of brain tissue, enabling the identification of patterns of cerebral atrophy, white matter tract abnormalities, and degenerative and vascular-related tissue damage. Functional neuroimaging approaches (e.g., arterial spin labeling [ASL] and blood-oxygen-level-dependent MRI and fluorodeoxyglucose [FDG]-PET), on the other hand, provide information about regional patterns of normal and abnormal blood flow and cellular metabolism, and PET with new radioligands can estimate neuropathological burden through radioligands' selective binding to pathological proteins in the brain.

A simple blood-based test that is inexpensive, easy to obtain, and accurate (with high sensitivity and specificity) might be an ideal biofluid biomarker for AD or other dementias. However, unlike systemic diseases, neurodegenerative disease pathology resides behind the blood-brain barrier (BBB), a highly selective semipermeable membrane barrier that separates circulating blood from brain extracellular fluid and cerebrospinal fluid. Furthermore, brain-specific molecules that do leak out into the large volume of peripheral blood are highly diluted and often rapidly metabolized or excreted. These factors present major challenges in the quest to identify markers in the blood that reflect molecular pathological processes in the brain, and as such, the best validated biofluid markers currently available are those collected from the central nervous system (CNS) directly—namely, CSF obtained by lumbar puncture.

In contrast to biofluid- and imaging-based markers, electrophysiological biomarkers utilize sensors to measure electrical signals from the body's normal and aberrant physiological processes. These markers are noninvasive, they have the potential to be cost effective and offer easily accessible techniques capable of detecting subclinical changes in brain or body activity, and they have the added advantage of being deployable in office- or home-based settings.

AD

AD is a neurodegenerative condition clinically characterized by progressive loss of memory and other cognitive functions (5) and is pathologically defined by the presence of abundant amyloid- β (A β) neuritic plaques

and PHF (paired helical filaments)-tau neurofibrillary tangles in the cerebral cortex. AD can be difficult to recognize in its earliest stages, in which the principal complaint is an increase in “forgetfulness” but preservation of daily functioning (often referred to as “prodromal” AD or mild cognitive impairment [MCI]). The diagnosis of dementia due to AD becomes clinically apparent as episodes of forgetfulness increase and progressive loss of other cognitive domains begins to affect daily functioning. As the symptoms of AD worsen, patients may become incapable of attending to basic needs such as feeding, dressing, and self-care. Progression from the first warning signs to the final stages of the disease can span a decade or more, creating a vast social and financial burden on society and extracting an immeasurable emotional toll on family members.

TABLE 1. Imaging and Biofluid Biomarkers for Common Dementias

Imaging	Characteristics
Alzheimer's disease (AD)	
Structural imaging	Disproportionate atrophy of hippocampus and medial temporal lobe, with relative sparing of primary visual and motor cortices
Functional imaging	FDG-PET ^a : decreased glucose uptake of temporal and parietal lobes
Cerebrospinal fluid	Low levels of A β ₄₂ , elevated total and phosphorylated tau
Frontotemporal dementias (FTD)	
Structural imaging	Behavioral-variant FTD: frontal, insular, and anterior temporal lobe atrophy Semantic dementia: anterior and inferior temporal lobe atrophy, including amygdala and hippocampus Progressive non-fluent aphasia: left inferior frontal gyrus and dorsolateral prefrontal cortex atrophy
Functional imaging	FDG-PET: Hypometabolism of regions corresponding with cortical atrophy
Cerebrospinal fluid	Unlikely to see reduction of A β ₄₂ proteins in CSF
Lewy body dementia (LBD)	
Structural imaging	Reduced amygdala volume
Functional imaging	SPECT ^b /PET: abnormal glucose metabolism and perfusion in parietal and occipital regions
Cerebrospinal fluid	No biofluid-based biomarkers; some LBD cases show low levels of CSF A β ₄₂
Vascular cognitive impairment and dementia	
Structural imaging	T2-FLAIR ^c : extensive deep white matter hyperintensities, leukoaraiosis, and/or lacunar infarcts SWI ^d : older hemorrhagic lesions
Cerebrospinal fluid	Less likely to see reduction of A β ₄₂ proteins in CSF, unless mixed dementia with AD

^aFDG-PET, fluorodeoxyglucose-positron emission tomography.

^bSPECT, single-photon emission computed tomography.

^cT2-FLAIR, T2-weighted fluid-attenuated inversion recovery.

^dSWI, susceptibility-weighted imaging.

Imaging-Based Biomarkers

The most common neuroimaging finding in AD is cerebral atrophy, preferentially affecting the hippocampus and adjacent regions of the medial temporal lobes. In more advanced stages of the disease, atrophy extends into parietal and frontal association regions, with relative sparing of primary cortices such as motor and visual regions (6). Longitudinal studies have demonstrated that the rate and degree of gray matter atrophy are strongly associated with clinical indicators of AD severity and progression, with rates of cortical thinning in the inferior and medial temporal lobe and volume loss in the hippocampus serving as reliable indicators of conversion from MCI to AD upon repeat assessment (7–9). The rate of hippocampal volume loss is around 4.5% per year among patients with AD, 3.0% per year among those with MCI, and about 1.0% annual decline in healthy older adults (10).

Functional neuroimaging demonstrates patterns of reduced cellular metabolism in AD, often in the same regions in which atrophy occurs. One PET approach uses uptake of FDG as an indicator of glucose metabolism and closely associated neuronal activity. Patients with AD show significantly reduced cerebral glucose utilization in a characteristic pattern in the parietal and temporal lobes (11). Like cortical atrophy, the degree of hypometabolism correlates with disease severity, so that patients in the early stages of AD show reduced glucose uptake primarily circumscribed to temporal regions, which then extends into parietal and then also to frontal lobes and, ultimately, globally as the disease progresses (12–15).

PET ligands have also been developed that identify the two molecular neuropathological hallmarks of AD—amyloid plaques and neurofibrillary tangles. Pittsburgh Compound B (PiB) and now other, clinically available fluorinated ligands, including florbetapir, flutemetamol, and florbetaben, have been shown to specifically bind cerebral tissue with high levels of amyloid deposition, as verified by neuropathological studies (16, 17). The presence of amyloid is the sine qua non of AD, with >96% of probable AD patients demonstrating significant amyloid accumulation, later verified at autopsy (18). However, amyloid is a poor indicator of disease progression, as the accumulation of plaques occurs early in the disease process, before observable cognitive decline (19). Cerebral amyloid burden has also been reported in the setting of dementia with Lewy bodies and Parkinson's disease with dementia, with the former having a higher mean amyloid deposition (20, 21). Thus, although amyloid burden is necessary for the diagnosis of AD, it is not always specific to AD. More recently, novel PET ligands have been developed to specifically target tau (22). Interestingly, to date, tracers only appear to bind tau in AD and not tau in other tauopathies such as some FTLDs. As new and better tau ligands emerge that bind all forms of tau, regional distribution of tau tracer uptake may begin to serve as a diagnostic indicator of AD with perhaps greater specificity than amyloid deposition (23).

Biofluid-Based Biomarkers

CSF is in intimate exchange with interstitial fluid of the brain and carries molecules secreted by neurons and glia as well as excreted substances, including metabolic waste and refuse. It is clinically accessible through minimally invasive lumbar puncture. Pathological proteins $A\beta_{42}$ and tau can both be measured reliably in the CSF using commercially available assays. Low levels of $A\beta_{42}$ protein and high levels of total and phosphorylated tau proteins are seen in AD (24, 25). Postmortem studies have found an inverse relationship between ventricular $A\beta_{42}$ CSF levels and cortical plaque load (26), leading to the assumption that “lower” $A\beta_{42}$ levels in the CSF are reflective of more extensive AD pathology. Decreased CSF $A\beta_{42}$ concentrations have also been found to relate inversely to high retention of amyloid radiotracer in the in vivo brain imaging of $A\beta_{42}$ pathology (16). The basis for this inverse relationship is presumed to be plaques that function as “sinks,” drawing soluble $A\beta_{42}$ from interstitial fluid that flows into or exchanges with CSF. Reduction in CSF $A\beta_{42}$ begins prior to symptom onset, and as such, normal CSF $A\beta_{42}$ levels in a person with dementia warrant further evaluation and reconsideration of an diagnosis of AD (27). On the other hand, low CSF $A\beta_{42}$ levels do not necessarily reflect brain amyloid deposition and can be seen in other conditions such as multiple sclerosis (27). Other forms of $A\beta$, including $A\beta_{40}$, can also be measured in CSF, and whereas some studies have suggested that the addition of CSF $A\beta_{40}$ to generate a 42/40 ratio may improve diagnostic accuracy in certain circumstances, this has not yet entered clinical practice (27). Microtubule-associated protein tau can also be measured in CSF, with levels of both total and phosphorylated tau found to be increased in AD (28). However, tau levels are also increased in stroke, neuroinflammatory conditions, and other disorders such as Creutzfeldt-Jakob disease. Despite ongoing research and the promise of new targets, the combination of low CSF $A\beta_{42}$ and high CSF tau predicts the presence of AD pathology with, perhaps, the greatest established accuracy of any biomarkers currently available (29, 30).

While CSF $A\beta_{42}$ and tau testing are available for clinical use, lumbar punctures are not routinely performed in dementia evaluations in many settings. Blood is considered a more accessible biofluid, but despite its practical advantages, no blood-based markers have yet found utility in clinical use. This is due, in part, to technical challenges, including that brain-derived proteins are diluted and often metabolized in blood and thus present in lower concentrations than in CSF, below the level of assay detection (31). The search for blood-based correlates of CSF $A\beta_{42}$ and tau levels has been unsuccessful to date—the relationship between plasma and CSF $A\beta_{42}$ levels is tenuous (32), as is that between plasma and CSF tau levels (33). New ultrasensitive assays are showing promise, however. Neurofilament light (NFL)—another neuron-specific cytoskeletal protein (21)—is one example of an emerging biomarker for AD and other neurodegenerative diseases. Results from previous studies suggest that patients with AD

have increased plasma NFL levels, and plasma and CSF NFL levels are known to correlate (22). A recent study by Mattsson and colleagues (33), for example, demonstrated that plasma NFL correlated with CSF NFL, was increased in patients with MCI and AD dementia compared with controls, and had high diagnostic accuracy for patients with dementia, comparable with that of established CSF biomarkers. High plasma NFL also correlated with poor cognition, AD-related atrophy, and brain hypometabolism (18).

Approaches using techniques in which several biomarkers are analyzed simultaneously have identified potential “blood biomarker panels” (19), but findings from studies have unfortunately been hard to replicate (20). Such approaches attempt to leverage the burgeoning “omics” fields of proteomics (large-scale study of proteins), metabolomics (chemical fingerprints or metabolites generated as a result of cellular processes), and lipidomics (lipid pathways and networks). Casanova and colleagues, for example, recently reported using quantitative metabolomics to identify a panel of 10 plasma lipids that were highly predictive of conversion from normal cognition to AD but failed to replicate their findings in two larger datasets (34). Proitsi et al (2015) performed lipidomics on plasma samples from patients with late-onset AD, healthy controls, and individuals with MCI and identified a combination of 10 metabolites that classified patients with AD with 79% accuracy (35). Although one of the largest AD metabolomics studies to date, the sample size remained modest. Using a novel proteomics approach, Shah and colleagues (2016) used serum from patients with AD and matched controls analyzed by capillary liquid chromatography-electrospray ionization-tandem mass spectrometry, discovering 59 novel potential AD biomarkers, with 13 that recurred in more than one multimarker panel (36). These results, too, require replication in other larger, well-characterized cohorts.

Some AD biomarker experts note that a “combinatorial approach” will likely be required to identify a blood-based biomarker panel for AD (37). In the search for blood-based biomarkers, Lovestone notes that, “[S]amples and data matter. We need many samples, well curated and with as many data from other techniques measuring the same analytes as possible.” Moreover, “most ‘omics technologies remain in their infancy,” and there is no technical platform sufficiently superior to others to justify the enthusiasm sometimes expended on them by their supporters” (37).

FTLD

The FTLDS are a heterogeneous family of disorders characterized by progressive behavioral and/or language deficits, with neurodegeneration involving the frontal and temporal lobes. Symptom profiles include changes in personality and behavior, as well as deficits in expressive and/or receptive language. FTLDD is currently classified into three syndromes based on clinical symptoms, including (1) behavioral variant frontotemporal dementia (bvFTD) characterized by changes

in social behavior and conduct (2), semantic dementia characterized by loss of semantic comprehension, and (3) progressive nonfluent aphasia (PNFA) characterized by difficulty with speech production (38, 39). The molecular pathological processes underlying these syndromes are varied, including proteinopathies due to misfolded tau, TDP-43, RNA-binding protein fused in sarcoma (FUS), and atypical AD (40).

Imaging-Based Biomarkers

As with AD, structural imaging such as high-resolution MRI is often undertaken as a first step in an FTLDD workup. Structural MRI differentiates AD from FTLDD by pattern of atrophy with high accuracy (41), with earliest volumetric differences appreciated in the insula and temporal lobes (42). Diffusion tensor imaging, or DTI, is also useful in distinguishing FTLDD from AD, as changes in global white matter microstructure are more widespread in FTLDD than in AD (43–45). bvFTD, characterized by marked behavioral changes and executive dysfunction, demonstrates cortical atrophy primarily involving frontal and lateral temporal lobes, with relative sparing of parietal regions (46). Meta-analyses have suggested that preferential tissue loss in the prefrontal, insular, anterior temporal, and anterior cingulate cortices, as well as volume loss in the thalamus and striatum, may be sensitive markers for distinguishing bvFTD from AD (47, 48). In the language variants of FTLDD (semantic dementia and progressive nonfluent aphasia), cortical regions within the left hemisphere language network are particularly vulnerable to neurodegenerative processes, with distinct regional involvement mapping onto the language deficits unique to each subtype. In semantic dementia, atrophy is generally observed in the anterior and inferior temporal lobe, including the amygdala and hippocampus (49). However, because semantic dementia and AD both share pathology involving temporal lobe integrity, structural imaging is often used in conjunction with functional neuroimaging to facilitate diagnostic clarity. Hypometabolism of parietal regions differentiates AD from semantic dementia with greater specificity than reliance on cortical atrophy patterns alone (50). In progressive nonfluent aphasia, frontal areas involved in speech production are most vulnerable to neurodegeneration, with gray matter loss primarily occurring within the left inferior frontal gyrus and dorsolateral prefrontal cortex, as well as within the superior temporal gyrus and insula (49). Over time, cortical involvement extends to include more dorsal frontal regions, the parietal cortex, and superior temporal regions. Finally, because amyloid deposition is not typically observed in FTLDD, amyloid PET scans can help differentiate between AD and FTLDD (51).

Biofluid-Based Biomarkers

Currently, the most helpful CSF biomarkers for FTLDD are the same as for AD, because AD biomarkers can distinguish AD pathology from non-AD pathology (since reduction of A β ₄₂ would not be expected in FTLDD) (52). Several studies have reported that CSF total tau levels are lower in FTLDD

than in AD but higher than in controls (53, 54). In many FTL cases, however, total tau levels can be normal. Elevated phosphorylated tau levels are typically seen in AD rather than other neurodegenerative diseases, with one study finding that reduced *p*-tau to *t*-tau ratio predicted TDP-43 pathology in FTL (55). CSF A β_{42} and tau are also valuable for differentiating between underlying AD and FTL pathology in the differential diagnosis of primary progressive aphasia, in which an AD-like CSF profile is found in patients with logopenic variant primary progressive aphasia but not in patients with semantic or nonfluent aphasias (40).

NFL has been of increasing interest as a fluid biomarker for FTL (40). Neurofilaments are a major constituent of the neuroaxonal cytoskeleton and play important roles in axonal transport, with increased NFL levels thought to reflect axonal damage (40). Two recent studies found elevated CSF NFL levels in FTL, and these appeared to correlate with FTD disease severity (56, 57). Such data suggest that NFL may be a good biomarker of neurodegeneration and neural injury in general, rather than in any specific disease. As with AD, there is also considerable interest in inflammatory contributors to FTL, such as proinflammatory cytokines tumor necrosis factor α (TNF- α) and transforming growth factor β (TGF- β), both of which have been found to be significantly increased in CSF in patients with FTL compared with controls (58). While various changes in CSF and/or blood levels of cytokines have been found in FTL, these changes, nevertheless, also seem to reflect nonspecific mechanisms, and many are also present in AD (40). Increased CSF TDP-43 has been reported in FTL, though results of studies to-date have been mixed (40). Elevated TDP-43 is found in amyotrophic lateral sclerosis as well, a TDP-43 proteinopathy that often, though not always, is accompanied by FTL (59).

LBDs

While clinically heterogeneous, characteristic features of LBD include dementia, varying degrees of parkinsonism, fluctuating cognition and alertness, visual hallucinations, autonomic dysfunction, and REM sleep changes. LBD is an umbrella term for two closely related clinical diagnoses: Parkinson's disease dementia (PDD) and dementia with Lewy bodies (60). Its name derives from the signature eosinophilic deposits seen on autopsy: alpha-synuclein containing aggregates termed "Lewy bodies."

Imaging-Based Biomarkers

There is considerable overlap in brain atrophic changes between AD and LBD; thus, the utility of MRI in this setting is limited (61). In a recent study, LBD, but not AD, pathology was associated with reduced amygdala volume in pathologically verified cases, but neither LBD nor AD pathology was associated with volume loss in hippocampus or entorhinal cortex, suggesting that other neuropathological factors accounted for atrophy in these structures (62). Atrophy in other cortical and subcortical structures has also been

reported in LBD, including striatum, hypothalamus, and dorsal midbrain (63). Rates of atrophy in LBD (compared with AD) are mixed, with some studies suggesting higher rates in AD (64) and others suggesting higher rates in LBD (65).

SPECT and PET demonstrate abnormal glucose metabolism and perfusion deficits in parietal and occipital areas in DLB (66, 67). Radioligands such as ^{123}I -FP-CIT have also been developed to track dopamine transporter (DAT) loss with SPECT imaging (68). Reduced binding in the striatum reflects DAT loss in the substantia nigra, a disease process highly specific to LBD (69, 70). Preliminary tau PET studies suggest a gradient of increasing tau binding from cognitively normal Parkinson's disease (absent to lowest) to DLB (intermediate) to AD (highest). However, given the presence of overlapping pathologies, future α -synuclein PET ligands are expected to have the best potential for distinguishing LBD from AD (71).

Biofluid-Based Biomarkers

Currently, there are no blood or CSF markers available for diagnosis of LBD (61). α -synuclein has been studied as a potential CSF biomarker, but results from studies have been mixed. Quantification of CSF α -synuclein may help to differentiate the synucleinopathies (DLB, PD, and multiple system atrophy) from AD, but CSF α -synuclein levels do not appear to differ significantly across the synucleinopathies themselves (72, 73). Others have reported low A β_{42} levels in DLB compared with those in controls (74) and cases of PDD (75), though such levels are also seen in AD. Studies have also suggested that CSF A β_{38} as well as A β_{42} /A β_{40} and A β_{42} /A β_{38} ratios may discriminate AD from DLB, though the evidence base for this remains limited (76, 77).

VCID

VCID refers to a broad spectrum of cognitive and behavioral changes associated with cerebrovascular pathology. Earlier terms for VCID included multi-infarct dementia and Binswanger's disease. Symptomatically protean, this family of disorders is often characterized by attentional and executive impairment ranging from MCI to severe dementia (78). Underlying etiologies can similarly range from symptomatic stroke to subclinical vascular brain injury (79). Cardiovascular disease risk factors, including hypertension, diabetes, hyperlipidemia, smoking, and obesity, dramatically increase the risk for VCID, leading to the development of small vessel disease, atherosclerosis, arterial stiffening, and elevated pulse pressure (80). Deep penetrating small vessels are especially vulnerable to reduced blood perfusion and infarction, particularly in brain areas with limited collateral blood supply ("watershed" regions), such as deep white matter regions, periventricular pathways, and basal ganglia structures (81, 82). Given this, VCID is often conceptualized as a disconnection syndrome (or "subcortical dementia") in that tissue damage primarily accumulates in deep white matter pathways, eventually reaching a clinically significant

threshold causing cognitive decline within the domains of attention, processing speed, and higher order executive functioning (83, 84).

Imaging-Based Biomarkers

Neuroimaging that demonstrates tissue damage of a presumed vascular origin defines the core diagnostic feature of VCID. While functional neuroimaging techniques (such as ASL-MRI) are capable of measuring in vivo cerebral blood perfusion, more commonly used clinical indicators of VCID are structural MRI sequences. In MRI, T2-weighted sequences such as fluid-attenuated inversion recovery (FLAIR) scans are most sensitive to vascular-related lesions—often described upon radiological review as deep white matter hyperintensities, periventricular hyperintensities (leukoaraiosis), and lacunar infarcts, as well as susceptibility-weighted imaging (SWI) protocols sensitive to old hemorrhagic lesions common in cerebral amyloid angiopathy. Although the presence of overt stroke is easily captured by structural MRI, it is the more insidious and diffuse ischemic tissue damage resulting from prolonged exposure to hypertension and other vascular risk factors that underlies the bulk of VCID pathophysiology in the absence of larger strokes (80). Among patients presenting with VCID, the quantitative burden of leukoaraiosis is generally related to the severity of cognitive deficits, with the extent of tissue damage correlating with worse cognitive performance and dementia severity. However, the presence of white matter signal abnormalities in older adults is not always an indicator of VCID, as patients can exhibit extensive leukoaraiosis while maintaining generally intact cognition. Indeed, over 96% of community-dwelling older adults over the age of 65 demonstrate white matter signal abnormalities on MRI, though only 20% have a lesion burden that is associated with decreased cognition and/or gait changes (85).

Biofluid-Based Biomarkers

As is the case for FTLT, CSF markers of the greatest interest in VCID include $A\beta_{42}$, total tau, and phospho-tau, primarily to rule out (or rule in) the presence of AD pathology. It is important to note, however, that dementia is often of mixed etiology, particularly so for AD and VCID. $A\beta_{42}$ levels in AD are significantly lower than in “pure” VCID (86), though decreased $A\beta_{42}$ levels within the range of those in AD have also been reported (87). VCID cases with a low incidence of AD-related pathology (e.g., CADASIL) demonstrate $A\beta_{42}$ values falling between those of AD and control cases (87). CSF $A\beta_{40}$ levels have been reported to be lower in VCID when compared with AD and controls, and it has been suggested that the $A\beta_{42}/A\beta_{40}$ ratio may help to discriminate between AD and VCID cases (88).

Cerebrovascular damage seen in VCID may occur through pathways mediated by oxidative stress, inflammation, and the accumulation of advanced glycation end products, among others (89), with BBB alterations likely compromising the cerebral microenvironment (90). As such, markers that capture key drivers of these processes may ultimately have utility as

biomarkers for VCID. The ratio of CSF to serum albumin, a marker of BBB structural and functional integrity, is increased in VCID (91), though this is a nonspecific finding that may not distinguish VCID from AD (92). Increased levels of CSF myelin lipid sulfatide (93) and NFL (94) have also been described in VCID, suggesting mechanisms of demyelination and axonal damage that occur in the setting of cerebrovascular injury.

Apart from CSF, serum C-reactive protein (CRP) and homocysteine levels are nonspecific vascular risk factor biomarkers, and increased levels have been reported in the presence of vascular lesions and VCID (95, 96). Elevated levels of serum homocysteine, however, can also be seen in AD (97), although this may be reflective of comorbid vascular pathology (89).

ELECTROPHYSIOLOGY-BASED BIOMARKERS: AN EMERGING AREA OF INTEREST

In contrast to biofluid- and imaging-based markers, EEG-based biomarkers record normal and aberrant physiological processes through sensors placed on the scalp. Compared with other commonly utilized functional neuroimaging techniques such as functional MRI and FDG-PET, EEG offers outstanding temporal resolution through the detection of local electrical changes of neuronal cells (with data obtained on the order of milliseconds) that reflect brain activity, including sensory and cognitive processing. However, they have historically had poor spatial resolution: while EEG is adequate in detecting physiological signal in cortical regions positioned directly beneath the skull, it is limited in its ability to capture electrical activity arising from deep subcortical and medial temporal lobe structures (areas that are particularly vulnerable in AD). EEG recordings are also subject to artifacts from muscle contraction, eye movement, and environmental conditions. Nonetheless, with improving technologies and analysis algorithms, EEG is a promising biomarker for dementia, representing a cost-effective and easily accessible technique capable of potentially detecting subclinical changes in local brain activity.

Two major categories of EEG analysis are of potential use as biomarkers of dementia. Quantitative EEG (QEEG) spectral analysis measures EEG waveforms that are classified into distinct bands of increasing frequency, including alpha, beta, theta, delta, and gamma spectra. ERPs are averaged measures of EEG electrical potentials occurring at specified times after repeated sensory or cognitive stimuli (“events”). At present, EEG is primarily used for the diagnosis and management of epilepsy and sleep disorders, with mixed results to date with respect to aiding the diagnosis of dementia. A 2009 meta-analysis of EEG studies, attempting to differentiate between dementia subtypes, concluded that EEG was limited by low specificity and had not yet reached a level of diagnostic validity to be used in routine clinical practice (98). Abnormal QEEG recordings are most frequently seen in AD, characterized by both focal

and diffuse increases in theta and delta wave activity (99). On the other hand, patients with DLB may present with a loss of alpha dominance (typically, the primary frequency observed in awake states), as well as a characteristic pattern of frontal intermittent rhythmic delta activity (100). Less consistent evidence of atypical EEG activity is observed in VCID and FTLT. Advances in EEG processing techniques have bolstered the promise of EEG as an early diagnostic marker of dementia, with recent studies demonstrating that EEG spectral analysis can play an important role in tracking disease progression over time (101), as well as adding predictive power in discriminating between dementia subtypes when combined with standard clinical assessment techniques such as neuropsychological assessment (102). Novel analytic approaches, such as multivariate and functional connectivity methods, as well as new classification models, are continuously being developed with the hope of improving the specificity of EEG metrics in discriminating dementia subtypes (103, 104). There has also been growing interest in ERPs in AD, with improving reliability of equipment, technique, and analyses demonstrating significant differences in AD compared with older adults with normal cognition (105).

CONCLUSIONS

With our increasing awareness that the common neurodegenerative diseases of aging require many years to take root, injure the brain, and manifest clinically, it is clear that identifying individuals at preclinical or early stages of these devastating diseases is of the utmost importance, with the hope of introducing disease-modifying therapies before the point at which disease burden affects cognitive function. This process of early diagnosis depends on biomarkers, many of which remain under development. The imaging- and biofluid-based biomarkers that are currently available—while more accurate, sensitive, and specific than ever—remain expensive and cumbersome and are not widely available, currently precluding their use across large segments of the aging population who have a high likelihood of developing dementia in the coming decade.

While CSF sampling and neuroimaging are currently the best validated modalities to date, the hope remains that inexpensive, less invasive, and more scalable peripheral markers (i.e., blood based or electrophysiological) will emerge in the coming years. Such markers, if validated, will allow screening across large numbers of individuals at risk, enabling diagnosis and interventions that may be delivered in a targeted manner to individuals most at risk. The practice of waiting to treat until symptoms emerge—which has been, to date, largely ineffective—will soon be replaced by a new wave of biomarker-guided, disease-modifying therapeutics. This development, now on the horizon, underscores the need to discover dementia biomarkers that are reproducible, are stable over time, are responsive to treatment, and directly reflect the underlying biological processes that affect the brain's health and functioning.

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