Blood and Cerebrospinal Fluid Biomarkers in Vascular Dementia and Alzheimer's Disease

A Brief Review

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KEYWORDS

• Biomarkers • Blood • Cerebrospinal fluid (CSF) • Amyloid beta (Aβ) • Tau

KEY POINTS

- A biomarker is as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention.
- Biomarkers for the dementias are primarily a research tool that has more recently begun to be utilized in clinical practice.
- Key biomarkers for Alzheimer's disease include cerebrospinal fluid and blood measures of amyloid beta (Aβ) and tau, and Aβ-PET, tau-PET, and fluorodeoxyglucose-PET scan measures.
- Elucidation of key fluid and other biomarkers for vascular cognitive impairment are currently under study.
- Biomarkers must be interpreted within the context of the clinical dementia phenotype.

INTRODUCTION

The maintenance of brain health is a lifelong process whereby potentially deleterious exposures such as cardiovascular risks, amyloid beta (Aβ), and phosphorylated tau (p-tau) may adversely affect the brain decades before there are clinical manifestations.[1,2] Thus, the early structural and neuropathological foundation for the development of cognitive impairment and its allied features later in life may provide precursor targets such that interventions may be applied to prevent or slow cognitively impairing processes if the underlying mechanism(s) can be addressed in time. In addition, there seems to be a reciprocal relationship between cerebrovascular disease, a currently preventable and modifiable disorder, and neurodegeneration. In fact, one of the earliest changes in

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Alzheimer's disease (AD) may be dysfunction of the blood–brain barrier leading to alterations in cerebral blood flow.[2] Vascular dysfunction in AD has been referred to as a potentially important but "disregarded partner."[3] As such vascular advocates have argued that vascular biomarkers should be incorporated into the AD research framework.[3] In 2018, the US National Institutes of Health (NIH) introduced a new research framework moving the definition of AD from clinical consequences of disease (ie, signs and symptoms) to a biological construct.[4] Specifically, the new focus for the diagnosis of AD included biomarkers grouped according to the following scheme: ATN (A for Aβ accumulation in the brain; T for tau deposits; and N for neurodegeneration).[4] The proposed research framework has now spilled over into clinical practice where blood and cerebrospinal fluid (CSF) biomarkers are being used by health care providers for the purpose of prevention, diagnosis, and treatment.

In this discussion, the author reviews (1) the definition of a biomarker; (2) common biomarkers to consider in the more frequent causes of dementia, vascular cognitive impairment (VCI) or vascular cognitive disorder (VCD), and AD; and (3) limitations of biomarkers and their clinical relevance in practice. Biomarkers hold promise to improve the diagnosis and care of persons at risk of or who have cognitive impairment, especially in the early stages. In this brief review, the author provides guidance for health care providers who may be considering use of biomarkers in the diagnosis and management of patients with cognitive impairment.

DEFINITION OF A BIOMARKER

In 2016, a US Federal Drug Agency-NIH work group created a source reference text on biomarkers called, *BEST (Biomarkers, Endpoints, and Other Tools) Resource*.[5] In the reference resource, the following definition of a biomarker was provided: a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.[5] In addition, biomarkers were classified by type (molecular, histologic, radiographic, and physiologic) and category (safety, diagnostic, prognostic, monitoring, and others).[5] The reference resource includes other topics of interest such as validation of biomarkers, surrogate endpoints, and biomarker qualification and context of use.[5]

In the domain of dementia and related disorders, underlying mechanisms of cognitive impairment are thought to be linked to factors such as cardiovascular risks, misfolded proteins (eg, Aβ), oxidative stress, and neuroinflammation. Therefore, the focus of biomarker discovery, for example, in AD, has been Aβ, tau, and neuroimaging markers of neuronal degeneration (eg, localized brain atrophy). Underlying biological mechanisms for brain injury in cognitive impairment are reviewed in more detail in Betul Kara and colleagues' article, "Vascular and Non-vascular Mechanisms of Cognitive Impairment and Dementia," in this issue.

BIOMARKERS TO CONSIDER IN COMMON CAUSES OF DEMENTIA

Vascular Cognitive Impairment or Vascular Cognitive Disorder

In the ensuing discussion, the author uses the terms VCI and VCD synonymously as a means to refer to cognitive disorders with mechanistic underpinnings of cerebrovascular disease, although there are nuances which separate the definition of the clinical terms VCI and VCD that are addressed elsewhere.[6] For sake of simplicity of language, the author uses the term VCI going forward.

In the 1970s, Dr Gary Rosenberg, a pioneer in biomarkers for VCI, studied patients with a cerebrovascular condition referred to as subcortical arteriosclerotic

encephalopathy of Binswanger.[7] The condition was characterized clinically by subcortical strokes, hypertension, dementia, spasticity, syncope, and seizures, and neuropathologically by diffuse demyelination of brain white matter or foci of necrosis plus arteriosclerotic and hypertensive vasculopathy.[7] In this condition, cranial computed tomography (CT) or MRI of the brain traditionally shows substantial white matter disease (ie, white matter hyperintensities or leukoaraiosis [rarefaction of the white matter]). In the encephalopathy of Binswanger, Rosenberg was one of the clinical scientists to call to attention the possible role of neuroinflammation as a factor underlying damage to cerebral white matter.[8] In addition, he emphasized the potential role of matrix metalloproteinases (MMPs) which may injure (1) tight junctions of the blood–brain barrier leading to leakage of toxic blood compartment components into brain white matter and (2) myelin, leading to a loss of its integrity.[8] These observations helped to establish a foundation for the future application of biomarkers for inflammation and MMPs as mechanistic targets for intervention in persons with cerebral subcortical small vessel disease (SSVD).[8]

There are a number of studies, many of which are small or remain unvalidated, and reviews on the topic of biomarkers for VCI. Some of the research addresses the overlap between VCI and AD. In the realm of VCI, there is considerable interest in SSVD as this condition seems to be the most common form of cerebrovascular disease associated with cognitive impairment. In one review, Wallin and colleagues[9] carried out a comprehensive literature search of biomarkers for VCI-SSVD. Based on their review, common mechanistic themes emerged. There were biomarkers related to disruption of blood-CSF and the blood–brain barrier, breakdown of brain white matter and the extracellular matrix, and blood and brain inflammatory markers.[9] Specifically, elevated CSF/blood albumin ratio, a marker of blood-CSF and blood–brain barrier disruption; altered CSF MMPs, reflecting extracellular matrix breakdown; CSF neurofilament, a marker of axonal damage; and blood inflammatory cytokines and adhesion molecules, were identified. The investigators suggested that the profile of SSVD biomarkers contrasted with the characteristic CSF profile of AD (ie, Aβ peptide and increased phosphorylated and total tau [t-tau]).[9] One should keep in mind that neuropathological findings of AD and cerebrovascular disease frequently coexist in older community populations, and thus, one may anticipate a mixed picture of cerebrovascular and neurodegenerative biomarkers.

In a review by Hosoki and colleagues,[10] similarities between biomarkers in acute ischemic stroke and vascular dementia were discussed. Biomarkers of oxidative stress, endothelial dysfunction, inflammation, and neuronal injury were emphasized.[10] Also, there was mention of the importance of identification of reliable markers of brain tissue damage, microRNAs, and long noncoding RNAs. MicroRNAs may be of relevance mechanistically as regulators of function of the blood–brain barrier, influencers of apoptosis and oxidative stress, and modulators of neuroinflammation. In another review on emerging biomarkers in VCI and dementia, Cipollini and colleagues[11] discussed the pathophysiology of endothelial dysfunction, blood–brain barrier disruption, and neuroinflammation, and in addition reference biomarkers of coagulation and thrombosis, and circulating microRNAs.

Vascular contributions to cognitive impairment are likely to be an important factor in the pathogenesis of cognitive impairment.[12] Studies have shown that early and midlife cardiovascular risk factors are associated with subsequent cognitive impairment, and the trajectory of cognitive decline and incident dementia is related to an accelerated trajectory of cardiovascular risks.[1,13] Furthermore, the aforementioned reviews of VCI[9–11] support a mechanistic landscape of underlying factors such as oxidative stress, endothelial dysfunction, neuroinflammation, and extracellular matrix

breakdown. What has been lacking, however, is a large scale, comprehensive, translational study of VCI biomarker candidates. To answer this question an initiative on vascular contributions to cognitive impairment, MARKVCID (Bio*mark*ers for *V*ascular Contributions to *C*ognitive *I*mpairment and *D*ementia Consortium) has been established and is discussed below.[14]

MARKVCID includes seven original research sites and a coordinating center funded by grants from the US National Institute of Neurological Disorders and Stroke, National Institute on Aging, and BrightFocus Foundation.[14] The initiative is largely focused on SSVD, the most common phenotype of VCI. The initial 5-year mission of the study is to analyze and optimize candidate VCI and dementia biomarkers in years 1 to 2 and develop and carryout a biomarker scaling up, multisite protocol and validation in years 3 to 5.[14] To achieve the goals of the study, the following protocols or procedures have been established: clinical/cognitive measure collection manuals; biospecimen collection best practices; imaging standard operating procedures; patient MRI protocols; phantom MRI protocols; imaging-based biomarker kit protocols; and fluid-based biomarker kit protocols.[14]

The primary focus of the study is identification of brain imaging and blood and CSF biomarkers. For example, the first phase of the study focused on but was not limited to the following imaging biomarkers: MRI FLAIR, diffusion, gradient echo, T2-weighted imaging, and cerebrovascular reactivity to better understand brain white matter volume, progression or regression, and blood vessel stiffness leading to impairment of cerebral autoregulation and perfusion.[14] In relation to blood and CSF biomarkers, the first phase of the study focused on the following fluid biomarkers: (1) angiogenic factors (factors that regulate the growth and development of blood vessels; eg, vascular endothelial growth factor); (2) cytokines (mediators of inflammation; eg, interleukins 6 and 8); and (3) proteases (eg, MMPs). Based on the results of the first phase of human study, the second phase of the study is moving forward with further testing. The MARKVCID Web site includes links to the publications that have come forth from the study thus far, much of which has informed the second phase of the study, but as of yet, the results are not definitive in relation to clinical practice.[14]

Overall and based on MARKVCID findings thus far, biomarker identification for VCI remains a work in progress with promising leads to inform the way forward in relation to potential mechanisms and pathways whereby interventions may be developed to prevent or slow cognitive impairment associated with cerebrovascular disease. We now transition to the status of biomarkers in AD, an area of study that is more advanced in comparison to that for VCI.

KEY BIOMARKERS IN ALZHEIMER'S DISEASE

There have been many recent advances in the discovery and development of biomarkers for AD. Such measures focus on key neuropathological manifestations of AD such as Aβ plaques, tau neurofibrillary tangles (NFTs), and neurodegeneration.[15] Beyond structural changes of the brain in cognitively impairing disorders that may be detected by commercial CT and MRI of the brain, neuroimaging advances such as amyloid-PET, tau-PET, and fluorodeoxyglucose-PET scans are also now available in some regions.[16] However, neuroimaging poses challenges in relation to availability, cost, and tolerance to the procedure. Thus, there has been interest in the development of blood and CSF biomarkers for AD, as these studies, especially when blood based, provide an easy route of access and a potentially more affordable option.[17] The author now explores candidate biomarker tests for AD to provide a simple understanding of the potential role for these tests.

Before one considers candidate biomarkers, a brief review of the neuropathological staging of AD is provided. As mentioned in Rupal I. Mehta and Julie A. Schneider's article, "Neuropathology of the Common Forms of Dementia," in this issue, two of the hallmarks of AD neuropathology are deposition of the abnormal proteins, Aβ in the form of extracellular plaques, and irregularly phosphorylated forms of the microtubule-associated protein tau, manifesting as intraneuronal NFTs. Aβ plaques precede the appearance of NFTs in the brain.[17] Initially, NFTs are found in the trans-entorhinal cortex, near to the entorhinal cortex. As disease progresses, NFTs involve the entorhinal cortex, an area that connects the hippocampus to main portions of the cerebral cortex (neocortex), and the hippocampus and neocortical brain regions become involved. Tau may be important in relation to symptoms of AD, as the presence of tau, neurodegeneration, or both may be needed for memory decline to occur, whereas this is not the case for Aβ.[18] It has been argued, however, that amyloid pathology may provide a permissive state or acts as an enabler whereby tau-related hippocampal brain dysfunction may occur.[19] In relation to the deposition of Aβ in the brain, initially it is deposited within the neocortex followed by spread into areas such as the entorhinal cortex and hippocampus and later into subcortical nuclei including the basal ganglia, thalamus, and hypothalamus, and eventually into the brainstem and cerebellum.

Importantly, as AD brain changes progress, the CSF, which serves as a draining system for Aβ outflow from the central nervous system, shows less Aβ, whereas t-tau and p-tau, the major component of NFTs in the brain and a marker of neuronal injury and neurodegeneration, are elevated in the CSF.

Based on the scope of this brief review, select AD biomarkers and studies are discussed below to provide key teaching points.

- *Amyloid Beta*: Aβ may be measured in the plasma or CSF. The ratio of Aβ 42 (the main component of amyloid plaques in the brain) to Aβ 40 has evolved as a useful biomarker of cognitive impairment. For example, in the Atherosclerosis Risk in Communities cohort, the Aβ 42: Aβ 40 plasma ratio was predictive of a 37% reduction in the risk of mild cognitive impairment (MCI) or dementia in later life compared with a 13% reduction with Aβ 42 alone and a 15% increase with Aβ 40 alone.[20] In a head-to-head comparison of different plasma Aβ 42: Aβ 40 assays in AD, mass spectrometry was shown to be the technology of choice.[21] In the CSF, data suggest that Aβ 42: Aβ 40 is also favored over Aβ 42 alone as there is a higher correlation with tau markers.[22]
- *Tau*: Tau may be measured in the plasma or CSF in a number of different forms: t-tau and p-tau with the latter form being the major component of NFTs in the brain.[17] p-tau consists of various subtypes (eg, p-tau231, p-tau217, p-tau181). In the Presymptomatic Evaluation of Experimental or Novel Treatments for Alzheimer Disease cohort, plasma p-tau231 was more strongly linked to PET biomarkers of AD than p-tau181, and the combination of p-tau and Aβ 42: Aβ 40 biomarkers preferentially detected early AD pathologic change and cognitive decline.[23] In addition, in the AD Neuroimaging Initiative, CSF t-tau, and p-tau181 discriminated between autopsy-confirmed AD and other dementias.[24]
- *Neurofilament Light and Glial Acidic Fibrillary Protein*: Plasma neurofilament light chain (NfL) is a protein and general marker of neurodegeneration. As such, it is not specific for AD.[25] Glial acidic fibrillary protein (GFAP) is a marker of astrogliosis (astrocytic activation) or glial–astrocytic injury which increases when there is Aβ pathology or other neurodegenerative brain change, and thus, is not a specific biomarker for AD.[25] NfL may be associated with worse white matter disease of

the brain based on cross-sectional data.[26] In addition, NfL and GFAP in combination have been used in studies to predict risk of AD or other cognitive decline and have generally been shown to be useful biomarkers.[27–29]

Box 1 shows the AD biomarkers that have been approved by the US federal drug administration (FDA) for commercial use as well as additional biomarker tests that are available. The biomarkers are grouped according to neuroimaging and fluid categories and are accompanied by a brief description of their indication.

Box 1
US FDA approved neuroimaging and fluid biomarkers available for the diagnosis of Alzheimer's disease and other causes of cognitive impairment[a]

Neuroimaging Biomarkers

1. *Florbetapir F 18 Injection* (Amyvid): Radioactive diagnostic agent for PET imaging of the brain to determine β-amyloid neuritic plaque density in adults with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline.
   Reference Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202008Orig1s000Approv.pdf (accessed online July 14, 2022).
2. *Flutemetamol F 18 injection* (Vizamyl): Radioactive diagnostic agent for PET imaging of the brain with a similar indication to #1 above.
   Reference Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203137Orig1s000Approv.pdf (accessed online July 14, 2022)
3. *Florbetaben F18 injection* (Neuraceq): Radioactive diagnostic agent for PET imaging of the brain with a similar indication to #1 above.
   Reference Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204677Orig1s000Approv.pdf (accessed online July 14, 2022).
4. *Flortaucipir F18 injection* (Tauvid): Radioactive diagnostic agent indicated for PET imaging of the brain to determine the density and distribution of aggregated tau neurofibrillary tangles (NFTs) in adult patients with cognitive impairment who are being evaluated for AD.
   Reference Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212123Orig1s000Approv.pdf (accessed online July 14, 2022)

Fluid Biomarkers

5. *β-Amyloid Ratio (1–42/1–40)* (Lumipulse G): Cerebrospinal fluid (CSF) test that combines the results of Lumipulse G P-Amyloid 1-42 and Lumipulse G P-Amyloid 1-40 assays into a ratio of B-amyloid 1_42 to B-amyloid 1_40 concentrations using the LUMIPULSE G 1200 System to be used in adult patients, aged 55 years and older, presenting with cognitive impairment who are being evaluated for AD or other causes of cognitive decline.
   Reference Source: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN200072.pdf (accessed online July 14, 2022)
6. *Phosphorylated Tau (pTau) 181 Protein and Apolipoprotein (APOE) E4 (Elecsys Amyloid Plasma Panel)*: Measures blood plasma pTau and APOE E4 and is used in conjunction with other clinical information in symptomatic patients who are being evaluated for AD and other causes of cognitive decline to ensure better identification of patients that require further confirmatory testing. The test received US FDA Breakthrough Device Designation as did the Elecsys Beta Amyloid (1–42) CSF and Elecsys Phospho-Tau (181P) CSF tests.
   Reference Source: www.roche.com (accessed online July 24, 2022)

[a]Additional tests available to measure biomarkers in AD: A. *Amyloid-beta 42:40 levels and ApoE Isoforms* (PrecivityAD): Amyloid-beta mass spectrometry assay used to monitor amyloid-beta 42:40 levels and ApoE isoforms in the blood. Reference Source: https://precivityad.com/ (accessed online July 15, 2022). B. *Amyloid-beta 42:40 levels* (AD-Detect): Amyloid-beta mass spectrometry assay used to monitor amyloid-beta 42:40 levels in the blood. Reference Source: https://testdirectory.questdiagnostics.com/test/test-guides/TS_AD_Detect_BetaRatioPlasma/quest-ad-detect (accessed online July 15, 2022). C. *Neurofilament Light Chain:* Blood test to assess neuronal damage related to various neurodegenerative diseases. Reference Source: https://www.labcorp.com/tests/140455/neurofilament-light-chain-serum (accessed online, July 15, 2022).

A number of other approaches are being studied in relation to biomarkers for cognitively impairing disorders, and a detailed discussion of these approaches is outside the scope of this article. For example, genomic exploration is being carried out to elucidate genomic susceptibility profiles for cognitive dysfunction.[30] As an example, there are a number of genetic mutations associated with amyloid precursor protein, a potential biomarker target for intervention to reduce Aβ burden in the brain. Furthermore, the presence of an APOE epsilon 4 allele substantially elevates the risk of AD and may be used as a marker to select those persons more likely to have AD changes in the brain and who may be candidates for AD interventions. In addition, epigenetic approaches are being explored to better understand how behavior and environment alter how genes work through methylation of DNA whereby genes are "turned off" and through demethylation of DNA whereby genes are "turned on" to function. In one study, DNA methylation metrics were associated with MRI markers of brain aging whereby blood C-reactive protein was not.[31] Genome-wide association studies and genetic molecular characterization of vascular and perivascular cells in AD support a mechanistic vascular pathological underpinning in AD.[32,33] Finally, digital technology is being applied to AD whereby voice recordings may be used to identify persons with cognitive impairment.[34]

POTENTIAL LIMITATIONS OF BIOMARKERS AND APPLICATION IN CLINICAL PRACTICE

In response to the publication reframing the definition of AD based on a biological construct and reliance on biomarkers,[4] an expert panel published a personal view on the limitations of biomarkers and how they may be applied in a clinical setting.[35] When considering a pure biological definition and relying on biomarkers in AD, the investigators highlight specific limitations that one must bear in mind. These include distinction between the presence of AD neuropathology and the complete AD continuum of phenotypic clinical features plus neuropathology; the potential for a low predictive accuracy of biomarkers in AD (eg, in MCI); the co-occurrence of other neuropathological processes in AD patients (eg, Lewy body disease or cerebrovascular disease) which need to be recognized for prognostic and management considerations but may be overlooked; variability in the prognostic value of biomarkers in relation to, for example, cognitive decline; limits of generalizability and accessibility of biomarkers; and other pertinent limitations.[35]

From an application in clinical practice perspective, the panel makes the following key points to inform the health care practitioner about how to apply AD biomarkers in practice[35]:

1. Consider AD as a continuum including its clinical phenotype (ie, signs and symptoms such as amnestic manifestations) and biomarker measures.
2. In persons with common phenotypic manifestations of AD (eg, amnestic syndrome), positivity of Aβ and tau biomarkers establishes a diagnosis.
3. Recommended biomarkers: low CSF Aβ 42, increased CSF Aβ 40-42 ratio (preferable to low CSF Aβ) or high tracer retention for amyloid-PET. For tau, high CSF p-tau or increased ligand retention for tau-PET. If the results of cognitive, biomarker or both tests are of borderline significance, additional investigations may be needed (eg, repeat testing, fluorodeoxyglucose-PET).
4. CSF testing may be preferable for some patients to obtain simultaneous Aβ and tau measure.
5. In routine clinical practice, AD biomarkers are generally not indicated in cognitively unimpaired persons based on the inability of these metrics to predict cognitive trajectories in asymptomatic persons.

6. Biomarker positivity may be ambiguous in cases of concurrent (mixed) neuropathology.
7. Biomarker investigations may be used for screening purposes for interventional and other research studies.
8. It may be propitious to have AD biomarkers selected, ordered, and interpreted by health care providers with special expertise in the field.

In relation to tau biomarkers in AD, a recently published expert review states that only 5% to 10% of Aβ-positive cognitively unimpaired persons and 50% to 67% of Aβ-positive persons with MCI have suprathreshold tau-PET signal in the neocortex, whereas both CSF and plasma p-tau markers may be elevated in early disease stages.[17] However, given key limitations in CSF and fluid tau biomarkers, tau-PET may be the preferred initial biomarker test for the differential diagnosis of dementia syndromes.[17]

CLINICS CARE POINTS

- Biomarkers should be interpreted within the context of the clinical phenotype of the underlying dementia subtype.
- As the Alzheimer's disease (AD) process progresses in the brain, amyloid beta (Aβ) levels drop, and measures of tau increase in the cerebrospinal fluid (CSF).
- A useful biomarker in the CSF and blood is the ratio of Aβ 42: Aβ 40.
- The value of AD biomarkers in asymptomatic persons remains uncertain, is primarily a research tool, and may best be interpreted by persons with special expertise in the field.
- Biomarkers for vascular cognitive impairment are currently under study and are not ready for application in clinical practice.

DISCLOSURE

Dr P.B. Gorelick serves on a Data and Safety Monitoring Board for Novartis in relation to a heart failure and cognition study.

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