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Fluid Biomarkers in Dementia Diagnosis

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RELATIONSHIP DISCLOSURE:
Dr Schindler has received personal compensation in the range of $0 to $499 for serving as a member of the Biospecimen Review Committee with the National Centralized Repository for Alzheimer Disease and in the range of $500 to $4999 for serving as a member of the Alzheimer Disease Center Clinical Task Force with the University of Washington and as a presenter/panelist with the University of Wisconsin. Dr Schindler has a noncompensated relationship as a board member with the Greater Missouri Alzheimer's Association that is relevant to AAN interests or activities. The institution of Dr Schindler has received research support from the National Institute on Aging. Dr Schindler has analyzed blood-based biomarker data provided by C2N Diagnostics to Washington University. The blood-based amyloid test is licensed by C2N and was cofounded by colleagues of Dr Schindler. Washington University will receive royalties from this test, but Dr Schindler will not receive personal compensation from it.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Schindler discusses the unlabeled/investigational use of CSF and blood tests for the diagnosis of dementia.

ABSTRACT

PURPOSE OF REVIEW: This article discusses how fluid biomarkers can augment the routine dementia evaluation and improve diagnostic accuracy. The tests that are currently available and the indications for their use are described. Further, tests that are under development and likely to be used in the future are identified.

RECENT FINDINGS: Technical improvements in assay sensitivity and precision have led to the rapid development of blood-based biomarkers for Alzheimer disease (AD) over the past several years. Studies have found that the ratio of amyloid-β (Aβ) peptides (Aβ42/Aβ40) and concentrations of phosphorylated tau isoforms in plasma can identify individuals with AD brain pathology. Blood-based tests may enable much broader use of AD biomarkers in the evaluation of patients with cognitive impairment.

SUMMARY: Even after a detailed history, examination, routine laboratory testing, and brain imaging, the cause of dementia sometimes remains unclear. CSF and blood-based biomarkers can evaluate for a range of neurologic disorders that are associated with dementia, including AD. Integrating data from fluid biomarker tests and the routine dementia evaluation may improve the accuracy of dementia diagnosis.

INTRODUCTION

A diagnosis of dementia has a profound impact on patients and their families. Determining the cause of dementia is important because this etiologic diagnosis directs treatment and management decisions and provides patients and their families with prognostic information; however, determining the etiology of dementia may be difficult. Dementia symptoms can be caused by numerous conditions, including neurologic disorders, medical conditions, medications, or a combination of factors. Although certain clinical features may be associated with specific neurologic diseases, substantial discordance exists between dementia syndromes and neuropathologic diagnoses.[1] Even after a thorough evaluation, the etiologic diagnosis may remain unclear or be inaccurate, which could negatively affect patients and their caregivers.

The most common etiology of dementia in older individuals is Alzheimer disease (AD). Dementia and AD are sometimes conflated, although they have very different meanings. Dementia refers to significant cognitive impairment

that may be caused by many different conditions, whereas AD refers to a specific neurodegenerative disease that is defined by the characteristic neuropathology of amyloid plaques and tau tangles. Dementia caused by AD brain pathology is termed *AD dementia*. Over the past 20 years, a variety of brain imaging and fluid biomarker tests have been developed that reflect AD brain pathology. AD biomarkers can be used to evaluate whether a patient with cognitive impairment has AD brain pathology, which could influence their etiologic diagnosis. In a large study of individuals with an uncertain dementia etiology, the leading diagnosis changed in 36% of cases following AD biomarker testing.[2] Importantly, AD biomarkers do not provide a definitive etiologic diagnosis for dementia, because copathologies and other conditions may cause or contribute to dementia symptoms. For example, if an initially cognitively normal patient with low levels of AD brain pathology had a stroke that impaired cognition, AD biomarkers may be positive, but the correct diagnosis for the primary etiology of dementia would be cerebrovascular disease. Therefore, AD biomarkers must be integrated with data from the routine dementia evaluation to provide an etiologic diagnosis. Given that dementia symptoms can be caused by numerous conditions, biomarkers may improve the accuracy of dementia diagnosis, enabling clinicians to make more appropriate treatment and management decisions and allowing patients and families to better plan for their future.

As potentially disease-modifying treatments for AD start to enter the clinic, biomarker testing will become increasingly important to identify patients who may be candidates for treatment. The recent development of blood-based biomarkers for AD (including a test based on plasma amyloid-β [Aβ]42/Aβ40, age, and apolipoprotein E proteotype that is now available for clinical use[3,4]) may enable broader and more rapid AD biomarker testing for patients presenting with cognitive impairment. In addition, promising new CSF tests for synucleinopathies may soon allow for testing of a second major category of neurodegenerative diseases. In the future, an increasing array of biomarker tests will improve the accuracy of dementia diagnosis.

ROUTINE DIAGNOSTIC EVALUATION

When a patient presents for evaluation of memory and thinking concerns, the first task is to determine the presence or absence of dementia and, when present, to grade its severity. Since individuals vary greatly in their baseline abilities and habits, the clinical history should assess for changes in the patient's memory, thinking, behavior, and function relative to previously attained abilities. The history typically is collected not only from the patient but also from an individual who knows the patient well, because memory and thinking problems may distort the patient's insight and reporting accuracy. Objective cognitive testing is performed to evaluate for evidence of cognitive impairment and may include instruments such as the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA). The Clinical Dementia Rating (CDR) is frequently used to evaluate dementia severity based on clinical assessment of cognition and functioning in six subdomains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.[5]

After determining that dementia is present and rating its severity, a thorough evaluation should be performed to determine its cause or causes. Numerous conditions, including some that are treatable, can cause cognitive impairment. Further, many patients have more than one condition contributing to their

KEY POINTS

- The routine dementia evaluation includes a comprehensive history and neurologic examination, laboratory testing, and brain imaging.
- The cause or causes of dementia may be unclear despite a thorough evaluation.
- Advanced diagnostic testing may improve the accuracy of dementia diagnosis.
- Confirmation of Alzheimer disease brain pathology is essential before initiating treatment with amyloid-lowering medications.
- One blood-based test for Alzheimer disease is available for clinical use, and more tests are undergoing rapid development.

cognitive impairment (CASE 8-1). Scrutinizing the patient's medication list for drugs associated with cognitive dysfunction, screening for sleep disorders, and asking questions about mood and behavior can be helpful in identifying conditions that are causing or contributing to cognitive impairment. A review of the patient's medical history and family history can also suggest potential causes of cognitive impairment. A neurologic examination may reveal focal signs that could indicate a central nervous system lesion (such as a stroke) or signs of parkinsonism (such as decreased facial expression, slowness, rigidity, resting tremor, decreased amplitude of movements, postural instability, or gait difficulties).

Patients with objective evidence of cognitive impairment should undergo laboratory testing and brain imaging to evaluate for potentially treatable causes of dementia.[6] Routine laboratory testing includes blood chemistries, renal and liver function studies, blood cell counts, thyroid studies, and vitamin B_{12} level. In patients with early-onset dementia, atypical dementia, or risk factors for sexually transmitted or blood-borne infections, it may be appropriate to perform rapid

CASE 8-1

A 63-year-old man with no family history of dementia presented for evaluation of progressive difficulties with memory and thinking over the past year. His wife had become concerned following multiple reports from coworkers that he had made major errors at his work as a car salesman. She said he frequently forgot their conversations, but this was a long-standing problem and she assumed that he was not paying attention to her. She had always performed most of the chores and managed the household finances, so she was uncertain about whether his abilities had declined in these areas. On further questioning, she reported that the patient snored and seemed lethargic during the day. He was taking gabapentin 600 mg 3 times a day for peripheral neuropathy and cyclobenzaprine 10 mg 2 times a day for chronic back pain.

On examination, the patient was obese. He had difficulty describing his cognitive issues and said, "I'm just getting old." His neurologic examination was normal except for tangential answers to questions. Brief cognitive testing showed mild to moderate impairment on tasks of episodic memory and attention. The patient's blood counts, blood chemistries, and vitamin B_{12} level were normal. His thyroid-stimulating hormone (TSH) was elevated, and his free T4 was low. A brain MRI showed mild diffuse atrophy with indicators of mild small vessel disease.

The differential diagnosis included hypothyroidism, obstructive sleep apnea, and medication-induced cognitive dysfunction. The patient's internal medicine physician started treatment for hypothyroidism and weaned him off gabapentin and cyclobenzaprine. He underwent a sleep study, which found moderate obstructive sleep apnea. After initially using continuous positive airway pressure (CPAP) nightly for 2 months, he stopped using it because the mask was too uncomfortable. His performance at work continued to decline, and he was terminated. One year after his initial appointment, his wife reported, "His short-term memory is just gone," and said that she needed to manage his

plasma reagin (RPR) and human immunodeficiency virus (HIV) antibody tests. Structural brain imaging may identify cerebrovascular disease,[7] patterns of atrophy,[8] or other findings that may inform diagnosis. Additional tests may be indicated for some patients, such as a sleep study for patients with excessive daytime sleepiness or an EEG in patients with fluctuating cognitive impairment.

INDICATIONS FOR ADVANCED DIAGNOSTIC TESTING

After completion of a comprehensive history and neurologic examination, routine laboratory testing, and brain imaging, additional testing may be helpful in establishing an accurate etiologic diagnosis.[9,10] Advanced diagnostic testing is not stand-alone testing but instead is meant to augment the data obtained in the routine diagnostic evaluation. Clinicians formulate a differential diagnosis following the routine diagnostic evaluation, and advanced diagnostic testing may confirm or change the initial differential diagnosis. Advanced diagnostic testing for dementia may include CSF or blood tests or imaging procedures such as

medications and appointments, which was a change from the past. Brief cognitive testing showed worse performance on tasks of episodic memory compared with his baseline performance. The differential diagnosis included untreated obstructive sleep apnea, and, given his continued decline, Alzheimer disease (AD) became an important consideration.

The patient underwent CSF testing to evaluate for AD. His CSF had normal cell counts, protein, and glucose. AD biomarker testing revealed an elevated ratio of phosphorylated tau at position 181 (p-tau181) to amyloid-β (Aβ)42. The primary etiology of his progressive cognitive decline was diagnosed as AD, with a secondary contribution from untreated obstructive sleep apnea. He was started on an acetylcholinesterase inhibitor and was encouraged to see his sleep doctor to find a more comfortable mask. He was also told to follow up with his internal medicine physician for treatment of his thyroid disease. His wife was referred to supportive services for caregivers. His diagnosis of AD, supported by CSF biomarkers, strengthened his application for disability benefits.

COMMENT

At his initial presentation, the patient had multiple potential etiologies for cognitive impairment, including hypothyroidism, untreated obstructive sleep apnea, and cognitively impairing medications. However, his cognitive and functional impairment worsened despite addressing some of these potential etiologies, raising concern for an underlying neurodegenerative process. His elevated CSF p-tau181/Aβ42 indicated the presence of significant AD brain pathology. His biomarker abnormalities in combination with his amnestic symptoms supported AD as the primary etiology of his cognitive impairment with untreated obstructive sleep apnea as a secondary cause.

positron emission tomography (PET) and may be particularly helpful to patients, caregivers, and clinicians in several scenarios[9,10]:

- **Early-onset, atypical, and/or rapidly progressive dementia. Some disorders that present with these features have available diagnostic tests that enable a clear diagnosis. For example, rapidly progressive dementia may be caused by Creutzfeldt-Jakob disease (CJD), and highly accurate CSF tests for CJD are available. For more information on CJD and available testing, refer to the article "Rapidly Progressive Dementia" by Gregory S. Day, MD, MSc, MSCI, FAAN,[11] in this issue of *Continuum*.**
- **Uncertain dementia. Patients may have an unclear diagnosis even after a thorough evaluation. This is often true for patients with relatively mild impairment, which can be associated with numerous treatable etiologies, and for patients who have multiple conditions that could potentially cause cognitive impairment. Because AD is the most common cause of dementia in older adults, it is often a diagnostic possibility in uncertain dementia, and therefore AD biomarker testing may be helpful in formulating the differential diagnosis.**
- **Typical dementia syndrome. Although the clinical syndrome may be consistent with a particular etiology such as AD, some patients and their families may pursue confirmatory testing because the diagnosis is expected to alter their personal decision making, such as whether to retire or move.**
- **Consideration of treatment with a potentially disease-modifying AD medication. Because the routine diagnostic evaluation results in a significant rate of AD dementia misdiagnosis, patients who are considering treatment with potentially disease-modifying AD medications, such as amyloid-lowering antibodies, should undergo AD biomarker testing to confirm the presence of AD brain pathology before initiating treatment.[12]**

ANALYSIS OF CSF

Analysis of CSF is performed routinely in inpatient and outpatient settings as part of the diagnostic workup for numerous conditions that affect the central nervous system, including infectious diseases (eg, bacterial, fungal, or viral meningitis), neuroinflammatory conditions (eg, multiple sclerosis), and neoplastic conditions (eg, leptomeningeal carcinomatosis). A patient being considered for lumbar puncture (LP) should be evaluated for potential contraindications, which include a space-occupying lesion, certain anticoagulant medications, disorders of blood clotting, and abnormalities at the LP site, such as a local skin infection. If no contraindications are present, a spinal needle is inserted into the subarachnoid space of the lumbar sac below the termination of

TABLE 8-1 **Changes in CSF Biomarkers Associated With Alzheimer Disease Brain Pathology**

Biomarker	Biomarker change in Alzheimer disease
Aβ42, Aβ42/Aβ40	Reduced
t-tau, t-tau/Aβ42	Elevated
p-tau181, p-tau181/Aβ42	Elevated

Aβ = amyloid-β; CSF = cerebrospinal fluid; p-tau181 = phosphorylated tau at position 181; t-tau = total tau.

the spinal cord. If indicated, the CSF pressure can be measured. Some tests require the use of specific tubes for CSF collection, such as a polypropylene tube for AD biomarker testing. Patients typically tolerate LP well, with no major complications. However, occasionally patients develop a post-LP headache that can be managed conservatively with rest and caffeine or more aggressively with an epidural blood patch.[13] The risk of post-LP headache is highest for individuals with a history of headache, women, and younger individuals and can be reduced by using an atraumatic needle (eg, a Sprotte needle).[13,14]

CSF studies can rule out many potential diagnoses, which is particularly helpful in complex and atypical dementia cases in which many etiologies are under consideration. Commonly ordered CSF studies include the number of red blood cells, the number and type of white blood cells, the protein level, and the glucose level. If these routine tests have normal results, infectious and autoimmune causes of neurologic symptoms are less likely.[15] If these routine tests have abnormal results or suspicion for infectious or inflammatory diseases is high, additional tests can be performed. Tests for infectious diseases include various techniques to detect spirochetes (eg, Lyme disease and syphilis), a myriad of viruses, and other pathogens.[16] Tests for neuroinflammatory disorders, such as multiple sclerosis, include an immunoglobulin profile, oligoclonal bands, and serum and CSF autoantibody panels.[17] If clinically indicated, cytology and flow cytometry can be performed to evaluate for neoplastic conditions.[18] Several tests can be used to evaluate for CJD, including total tau (t-tau), 14-3-3 protein, and the real-time quaking-induced conversion (RT-QuIC) assay for the pathogenic form of prion protein, a highly sensitive and specific test for CJD.[19]

CSF biomarkers of AD brain pathology have been extensively studied in research cohorts and used in dementia specialty clinics for nearly 2 decades.[10,20] The AD biomarker assays that currently are used for clinical diagnosis provide precise and consistent measurements of CSF proteins, including Aβ42, Aβ40, t-tau, and phosphorylated tau at position 181 (p-tau181).[10,21,22] CSF levels of Aβ42 decrease as amyloid plaques form, potentially because of the sequestration of Aβ42 into amyloid plaques.[23] CSF t-tau and p-tau181 levels start to increase shortly after amyloid plaques form, many years before significant quantities of neurofibrillary tangles are present, and therefore these biomarkers may reflect neuronal dysfunction in response to amyloid plaques rather than tau tangles.[24-26] The pattern of low CSF Aβ42, high t-tau, and high p-tau181 is associated with significant AD brain pathology. Ratios including Aβ42 (Aβ42 to Aβ40, t-tau to Aβ42, and p-tau181 to Aβ42) perform especially well in identifying which individuals have significant levels of AD brain pathology (**TABLE 8-1**).[21,22] Notably, most studies of CSF biomarkers have been performed in non-Hispanic White cohorts, and the performance of CSF biomarkers assays in other racial and ethnic groups is not well established.

High-performance CSF biomarker tests for AD brain pathology are available from multiple clinical laboratories at a current cost of approximately $1000 per test, but when other routine CSF tests and clinician reimbursements are included, the total cost of the LP and testing is often closer to $2000. Although these tests are not yet fully approved by the US Food and Drug Administration (FDA), Medicare and private insurance usually cover the costs of the tests and LP. However, the reimbursement to providers may not be adequate to cover the costs of the LP, which typically include additional staffing.

KEY POINTS

- **CSF testing is helpful in evaluating infectious, inflammatory, neoplastic, and neurodegenerative causes of dementia.**
- **Lower CSF levels of Aβ42 may reflect sequestration of Aβ42 in amyloid plaques.**
- **Higher CSF levels of total tau and phosphorylated tau isoforms may reflect neuronal dysfunction in response to amyloid plaques.**
- **Significant amyloid burden is associated with lower Aβ42 and Aβ42/Aβ40 and higher t-tau, p-tau181, t-tau/Aβ42, and p-tau181/Aβ42.**

BLOOD-BASED BIOMARKERS

Although CSF enables testing for many neurologic disorders, most patients would prefer blood-based tests, if available. Collection of CSF presents a barrier to care in some cases, either because patients perceive LP as invasive or because clinicians have a limited capacity to perform the procedure. Further, some patients have contraindications to LP, such as taking anticoagulant medication, or physical factors (eg, obesity or previous back surgery) that may increase the difficulty of LP. In contrast, blood collection is not perceived as invasive, which may improve the acceptance of biomarker tests by patients, including individuals who have limited trust in the medical system.[27] Additionally, blood collection does not require expensive equipment or highly trained personnel, which may permit a larger scale of biomarker testing than would be possible for tests that require specialized imaging or LP.

Biomarkers of neurologic disorders are typically present at much lower levels in the blood than in CSF, but recent technical improvements in assay sensitivity and precision have led to the rapid development of blood-based biomarkers for neurologic disease. Plasma Aβ42 alone is not an accurate biomarker of AD brain pathology, but the ratio of Aβ42 to Aβ40 predicts which individuals have significant AD brain pathology.[28,29] The first clinical blood test developed for AD uses plasma Aβ42/Aβ40, age, and apolipoprotein E proteotype to stratify the probability of significant AD brain pathology (CASE 8-2).[3,4] As with CSF tests for

CASE 8-2

A 70-year-old woman presented for evaluation of progressively worsening episodes of confusion over the past 3 years. Her mother had developed Alzheimer disease (AD) dementia at age 85, and the patient's husband and children believed that her cognitive changes represented early AD dementia. The patient had anxiety, for which she was seeing a psychiatrist; she also had severe chronic obstructive pulmonary disease (COPD) and was on home oxygen therapy. Her family reported frequent memory lapses and confusion that fluctuated markedly from day to day. Her husband had taken over the finances because she had missed multiple payments, and she had stopped driving after a car accident. Although she used oxygen via nasal cannula during the day, she frequently took it off at night, despite recommendations from physicians to wear it while sleeping. Her family did not insist that she use oxygen at night, at least partly because they believed she had AD dementia and did not wish to subject her to uncomfortable treatments.

On examination, the patient was anxious but had no evidence of language impairment or abnormal neurologic findings. Brief cognitive testing showed mild impairment on tasks of episodic memory and attention. The patient's blood counts, blood chemistries, thyroid function, and vitamin B_{12} level were normal. An EEG was performed and showed mild generalized slowing. She was unable to tolerate a brain MRI or head CT, even after multiple attempts with mild sedation. After two visits, the etiology of her cognitive impairment remained unclear because of her incomplete workup. AD biomarker testing was recommended because the patient and her family wanted a clear diagnosis and because

AD biomarkers, this test is not yet fully approved by the FDA. Medicare and private insurance do not yet reimburse the cost of this test, creating a financial obstacle for many patients, although a sliding scale fee is available for patients who qualify. Additional assays for AD dementia that measure p-tau181 or p-tau217 concentrations also appear very promising[30-34] and will likely be available in the clinic soon. Combining levels of multiple blood-based biomarkers along with individual level factors (eg, age, sex, race) may allow individualized prediction of AD dementia risk.[35] Blood-based biomarkers may also be helpful in evaluating non-AD disorders: serum/plasma neurofilament light chain (NfL) is currently being studied in a variety of neurologic disorders and could be used in the dementia clinic within a couple of years. Studies suggest that both plasma NfL and t-tau could be used as blood-based biomarkers for CJD.[19]

TRENDS

Although AD dementia is often on the differential diagnosis of patients presenting with memory and thinking concerns, AD biomarkers have been performed sparingly, perhaps in less than 5% to 10% of potential AD dementia cases. Perceived risks, high costs, and limited availability of amyloid PET scans and LP have been major contributors to this low rate of testing. In contrast, blood-based tests are not perceived as risky, costs are significantly lower, and blood collection services are widely accessible. Currently, most blood-based AD

they were making decisions with the assumption that she had AD dementia. The patient refused lumbar puncture, but she was willing to provide a blood sample for evaluation of amyloid-β (Aβ)42/Aβ40 and apolipoprotein E proteotype. The results were consistent with no significant brain amyloid. The patient was encouraged to wear her oxygen consistently, especially at night, and to follow up with her pulmonologist for assessment for possible sleep apnea. She was also encouraged to continue close follow-up with her psychiatrist. The etiology of her fluctuating confusion remained uncertain, especially because she was unable to tolerate brain imaging, but her severe COPD with hypoxia and anxiety were likely contributors.

COMMENT

This case illustrates the use of blood-based AD biomarkers to determine whether cognitive impairment is likely to be caused by AD brain pathology. The more established CSF and amyloid positron emission tomography (PET) tests would likely have reached the same conclusion (no significant brain amyloid), but the patient was unwilling to undergo these procedures. This patient may have experienced cognitive impairment at least partly related to her severe COPD and oxygen noncompliance, and her family's belief that her symptoms were related to AD caused them to deemphasize compliance with oxygen therapy. In this case, a negative AD biomarker result encouraged the patient and her family to pursue more aggressive evaluation and treatment of non-AD causes of cognitive impairment.

biomarker tests are still undergoing development and clinical validation (as of this writing, only one AD blood test is available for clinical use), but it seems likely that blood-based AD biomarkers will enable testing of a much larger proportion of the patient population with memory and thinking concerns. Evaluating for AD brain pathology with a blood test early in the diagnostic evaluation would enable more prompt diagnosis of AD dementia in patients with a positive test and consistent clinical findings or would direct clinicians to focus on alternative etiologies in patients with a negative test. The benefits of AD biomarkers have been perceived as low for many patients because effective AD-specific treatments have not been available. However, as potentially disease-modifying treatments start to enter the clinic, AD biomarker testing will likely be required before initiating therapy.[12] Initial screening with an AD blood test followed by confirmation with amyloid PET or CSF biomarkers may increase the efficiency of biomarker testing. If AD blood tests are further optimized and reach very high levels of accuracy, confirmatory testing with amyloid PET and CSF biomarkers may be unnecessary.

Besides additional AD blood tests, diagnostic tests that are likely to enter the clinic in coming years include CSF tests for synucleinopathies and neuroaxonal injury. Assays that permit detection of misfolded α-synuclein, such as RT-QuIC and protein-misfolding cyclic amplification assays, have demonstrated high accuracy in identifying individuals with several neurodegenerative diseases caused by α-synucleinopathies (Parkinson disease, dementia with Lewy bodies, multiple system atrophy, and rapid eye movement [REM] sleep behavior disorder).[36-40] Although these tests are not yet clinically available, given the strong and consistent results, it seems possible that a test will become available within several years. These tests may be helpful in evaluating patients presenting with cognitive symptoms who also have features suggestive of dementia with Lewy bodies or other synucleinopathies (eg, motor and/or autonomic symptoms, fluctuations, visuospatial dysfunction, sleep disturbance). Another analyte that is likely to be used in the clinic is CSF NfL. Many studies have shown that CSF NfL is elevated in most neurologic disorders, including inflammatory (eg, multiple sclerosis) and neurodegenerative diseases (eg, amyotrophic lateral sclerosis and frontotemporal dementia).[41] Although CSF NfL elevation is not specific to a particular neurologic disease, it does indicate the presence of neuroaxonal injury, which may be helpful when a clinician is considering whether a patient has a neurologic or non-neurologic cause of cognitive impairment. A panel of CSF biomarkers that includes NfL may be used for dementia diagnosis in the future.[42]

INTERPRETATION OF BIOMARKER RESULTS

It is critical that biomarkers be used to augment, but not to replace, a thorough diagnostic evaluation for dementia. A worst-case scenario is that a patient has cognitive decline caused by a treatable etiology but because of a positive AD biomarker test, the cognitive impairment is ascribed to AD and the patient never receives appropriate evaluation or treatment. It is also essential that clinicians understand the meaning of biomarker tests. For example, a positive result on an amyloid PET scan or a CSF AD biomarker panel indicates the presence of significant AD brain pathology, but it does not necessarily mean that a patient's cognitive impairment is caused by AD. In contrast, because AD biomarkers are relatively sensitive to AD brain pathology, negative AD biomarkers significantly

decrease the likelihood that AD is the cause of dementia. However, clinicians should consider that no test is 100% accurate and that clinicians should "treat the patient, not the test." The limitations of relevant biomarkers should also be carefully considered as the results are interpreted. For example, autoantibody panels are only positive in some cases of autoimmune encephalopathy, and a negative result does not exclude the diagnosis. Biomarkers can be powerful tools to improve diagnostic accuracy, but clinicians must understand the proper interpretation of each test and always consider that biomarker tests are not perfect.

KEY POINTS

- **Biomarkers augment but do not replace a thorough diagnostic evaluation.**
- **Clinicians must understand the meaning and limitations of diagnostic tests for dementia.**

CONCLUSION

The routine evaluation for dementia, which includes a comprehensive history and neurologic examination, laboratory testing, and brain imaging, assesses for the numerous causes of cognitive impairment that commonly affect patients. Completing this evaluation helps to ensure that treatable causes of dementia are not overlooked, even if they co-occur with neurodegenerative disorders. Indications for advanced diagnostic testing may include clinical features that suggest disorders that can be confirmed by diagnostic testing, uncertainty about the diagnosis, the patient's desire for further confirmation of a suspected diagnosis, or consideration of treatment with a potentially disease-modifying medication for AD. Analysis of CSF allows evaluation for numerous neurologic illnesses that may cause dementia. A blood test for AD is available, and more blood tests are likely to enter the clinic soon. Blood tests are more acceptable to patients and may allow for broader use of biomarkers in the clinic. For both CSF and blood-based AD biomarker tests, a positive result is useful in supporting AD as an etiology of dementia, but a negative result is also useful because it directs clinicians to further evaluate for non-AD causes of dementia. Overall, the development of CSF and blood tests for neurologic disorders is likely to improve the accuracy of diagnosis for patients with cognitive impairment.

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