"Senior Moments" or More? Diagnostic Evaluation of Cognitive Complaints in Older Adults and the Role of Cerebrospinal Fluid Biomarkers

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CASE DESCRIPTION

A 76-year-old male, retired professional without any medical history other than gastroesophageal reflux presented to the emergency room for evaluation of a memory lapse. While driving to a routine business meeting, he temporarily lost his way and felt the route was unfamiliar. He recovered his bearings, made it to the meeting, but felt flustered in his attention to the business. He reported this to his primary care provider, and because he was about to leave for lengthy travel overseas, he was advised to seek evaluation at the emergency room. There, he and his wife reported a year or 2 of "senior moments." He had frequent trouble remembering key dates, upcoming plans, and details of conversations, as well as difficulty grasping concepts and figuring out technology, e.g., new smartphone apps, which had always been a strength. An extensive review of systems was unremarkable. His only medication was ranitidine. He was alert and fully oriented to person, place, and time. His general physical and general neurological examinations were entirely normal. Laboratory evaluation for metabolic contributions to mental status changes included a basic metabolic panel, liver function tests, and complete blood count, all of which were normal. A cranial computed tomography scan to rule out mass or subdural hematoma was interpreted as showing periventricular white matter hypodensity, likely representing chronic microangiopathic disease, and mild generalized parenchymal volume loss. He was reassured for travel and referred for specialty evaluation.

At the Massachusetts General Hospital Memory Disorders Unit outpatient evaluation, the patient and wife recapitulated the above history and added that for about 1.5 years he had been slow in his tax preparation, had difficulty filing and finding papers in his home office, was quieter and less engaged in social settings, and although he denied depressive symptoms, he did not seem as happy. He was independent in all his daily functioning, including self-care, shopping, driving, tennis, and exercise workouts at the gym. His family health history was notable for a mother who died at 89 with Parkinson disease and dementia, a maternal uncle who had dementia in late life, a father who was well until his nineties when he died after a fall, and a sister who was alive and well without

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[2] **Nonstandard abbreviations:** CSF, cerebrospinal fluid; AD, Alzheimer disease; MCI, mild cognitive impairment; PET, positron emission tomography; TDP-43, transactive response DNA binding protein 43 kDa; sTREM, soluble cleaved ectodomain of triggering receptor expressed on myeloid cells.

cognitive complaints. Mental status examination included a Montreal Cognitive Assessment, a 30-point cognitive screening instrument. This was notable for a total score of 25 (normal, ≥26), with difficulty in delayed recall of a short list of words and failure to recall the exact date. Mood, affect, and psychiatric functioning appeared normal. His general neurological examination for cranial nerves, motor, sensory, reflex, coordination, and gait functioning was completely normal.

A neuropsychological assessment further depicted his cognitive dysfunction. The most significant difficulties were in the domain of memory, both verbal and visual, with mild difficulty encoding information and greater difficulty retaining information. He also demonstrated mild weaknesses in semantic fluency, verbal and visual reasoning, attention span, working memory, and category set-shifting. Overall, the pattern of performance suggested primary involvement of medial temporal lobe structures given the predominant difficulties in memory, while mild weaknesses with reasoning and working memory also suggested frontal network involvement.

Additional laboratory testing screened for possible metabolic contributors to cerebral dysfunction and included thyroid function tests, vitamin B_{12}, 25-OH vitamin D3, erythrocyte sedimentation rate, high-sensitivity C-reactive protein, and Lyme IgG/IgM antibodies. All were within normal ranges. A brain MRI scan showed evidence of chronic small-vessel ischemic changes and nonspecific parenchymal loss.

A lumbar puncture was conducted for cerebrospinal fluid (CSF)[2] analysis. CSF was clear with 0 red blood cells/μL and 0 nucleated cells/μL and a total protein of 29 mg/dL (reference, 5–55 mg/dL). Athena ADmark® assays yielded values for amyloid-β_{42} of 452.85 pg/mL and total τ of 649.5 g/L for a calculated abnormally reduced amyloid-β_{42} to total τ index of 0.45 (normal, >1), and an abnormally increased phosphorylated τ level of 99.3 pg/mL. The results were interpreted as consistent with a diagnosis of Alzheimer disease (AD). The patient was subsequently treated with a cholinesterase inhibitor for symptomatic benefit, and he entered a clinical research trial for a novel immunotherapy targeting AD pathology.

At follow-up almost 2 years after the initial evaluation, the patient showed mild progression. His wife reported worsened forgetfulness, and she took over all their financial affairs. He stopped using the computer completely owing to frustration at not remembering his passwords and often forgot where things go in the kitchen. He continued to prepare some meals, do housework, and run simple errands independently. His Montreal Cognitive Assessment score dropped marginally to 23 of 30.

Case discussion

Occasional minor memory lapses, such as forgetting names or why one walked into a room, are universal and increase in frequency with age. Indeed, large cross-sectional studies of healthy adults find that performance in standardized assessments of most all cognitive abilities peaks in young adulthood and steadily declines across the life span, accelerating in old age (*1*, *2*). This average decline of about 2 SDs over the life span is highly variable among individuals, and, overall, it is modest enough that independent function in life's daily activities can be maintained into the oldest ages. Concern for a disease affecting brain function arises when an individual exhibits a "significant" decline from their personal baseline of cognitive abilities. If there is measurable cognitive impairment compared with a person's previous functioning or age and education-based normative values but the individual is able to carry out most of their daily activities independently, this is called mild cognitive impairment (MCI). If cognition is impaired to the point that a person needs assistance in daily independent, instrumental, or basic living activities, this is called dementia.

While AD is the most common cause of MCI and dementia in older adults (60%–80%), as in the case

described above, there are many other possible causes and contributors that need to be assessed. After clinical examination and neuroimaging (head computed tomography or MRI) to exclude abnormalities that might indicate focal brain lesions, parkinsonism, or other encephalopathic conditions, the American Academy of Neurology guidelines advise additional laboratory evaluation consisting of a complete blood count, serum electrolytes, blood urea nitrogen, creatinine, glucose, liver function tests, thyroid function tests, and vitamin B_{12} (*3*). These screen for most other systemic or metabolic diseases that could contribute to cognitive impairment.

A clinical diagnosis of "probable" AD has been, until recently, a diagnosis of exclusion. If someone developed insidious and slowly progressive memory-predominant cognitive impairment and all major alternative explanations were excluded through the aforementioned evaluation, then the likelihood of AD pathology as the basis for the dementia was considered high and a diagnosis of AD was made. The diagnosis of "definite" AD was made only after postmortem neuropathological examination showed abundant amyloid-β-containing neuritic plaques and paired helical filament τ-containing neurofibrillary tangles in the cerebral cortex (*4*, *5*).

The accuracy of a clinical diagnosis using current guidelines for predicting neuropathological diagnosis is modest, even at dementia specialty centers. Indeed, among National Institute on Aging Alzheimer's Disease Centers, the sensitivity of antemortem diagnosis of AD ranged from 70.9% to 87.3% and the specificity from 44.3% to 70.8% (*6*). Inaccurately diagnosed patients were found to have argyrophilic grain disease or other tauopathies, frontotemporal lobar degeneration, cerebrovascular disease, Lewy body diseases, hippocampal sclerosis, and other rare conditions as their primary etiology.

Biomarkers are transforming the diagnostic landscape of dementia, making AD a diagnosis of inclusion rather than exclusion and extending our ability to prognose, track, and understand mechanisms of disease (Table 1). With the refinement of assays for CSF amyloid-β_{42}, total τ, and phospho-τ and establishment of brain amyloid-β positron emission tomography (PET) (and emerging τ PET) as molecular biomarkers, antemortem determination of AD pathology in people with or without dementia is much improved, now with 89% to 100% accuracy (*7*, *8*). Other biomarkers, such as structural volumetric MRI and ^{18}F-fluorodeoxyglucose PET scanning, also provide useful data for assessing the degree and topography of atrophy/neurodegeneration that can help with diagnosis, staging, and prognosis (*9*), although their sensitivity and specificity for positive identification of AD vs other dementia causes are modest. With the success of these biomarkers, the new "ATN" research framework criteria for the antemortem biological diagnosis of AD classify AD according to the presence of amyloid-β (A), pathological τ (T), and neurodegeneration (N) biomarkers (*10*).

CSF can be a particularly informative fluid for biochemical analysis of brain disorders, given its continuity with the brain's interstitial fluid. Assays for the core AD biomarkers—amyloid-β_{42}, total τ, and phospho-τ—respectively reflecting amyloid plaque deposition, neuronal damage, and pathological τ, have matured to the point of clinical utility. A critical challenge in laboratory medicine has been the harmonization and standardization of preanalytic collection protocols, automation of assays, and the production of certified reference materials. These efforts are ongoing but have yielded 3 platforms so far (Euroimmun/ADx, Fujirebio Lumipulse G, and Roche Elecsys) that are poised for agency certification for distributed clinical laboratory implementation (*11*–*13*).

One major issue that the dementia field continues to grapple with is the comorbidity of

Table 1. Established and developing CSF protein biomarkers for use in AD and related dementias.

Biomarker protein	Comments
AD	
Amyloid-β_{42}	Low levels indicate presence of amyloid-β plaque pathology in brain. Established value for diagnosis.
Amyloid-β_{40}	Useful in ratio with amyloid-β42, as the ratio attenuates variability from preanalytic factors.
Other APP[a] fragments and oligomeric amyloid-β	Under investigation to improve AD diagnosis, staging, and research.
BACE1	β-Secretase enzyme that cleaves amyloid precursor protein. Under investigation, as high levels reported in CSF in AD.
Total τ	High levels indicate AD neurofibrillary pathology in brain. Established value in diagnosis of AD, although also elevated in other brain diseases and injuries; also considered to reflect general neurodegeneration and neural injury.
Phospho-τ (pThr181)	High levels indicate AD neurofibrillary pathology in brain. Established value in diagnosis of AD. Considered to be specific for AD.
Novel τ fragments	Under investigation to improve AD diagnosis, staging, and research.
τ seeding assays	Under investigation to improve AD diagnosis, staging, and research.
Lewy body diseases	
α-Synuclein	Presynaptic terminal protein that aggregates in perikarya and neurites in Lewy body diseases. Various assays under investigation with increases reported in AD, decreases in Lewy body diseases, although inconsistent so far.
a-Synuclein seeding assays	Under investigation to improve AD diagnosis, staging, and research.
ALS–FTLD spectrum	
Total TDP-43	Transcriptional repressor, DNA and RNA binding protein in nucleus that aggregates into extranuclear inclusions in neurons in ALS, some FTLD, and to varying degrees in AD and other disorders.
Phosphorylated TDP-43	Under investigation to improve ALS-FTLD spectrum diagnosis, staging, and research.
General neurodegeneration and neural injury	
NfL	Neuron-specific intermediate filament protein released into CSF with axonal injury. Shows good performance characteristics as biomarker of neurodegeneration and neural injury in CSF in various diseases and is an emerging biomarker in blood using ultrasensitive immunoassays.
pNfH	Neuron-specific intermediate filament protein released into CSF with axonal injury. Best studied in ALS, less so in AD. Phosphorylation of NFH makes it less vulnerable to protease degradation. Also measurable in blood.
Neurogranin	Calmodulin-binding protein enriched in dendritic spines. Under investigation as a marker of synaptic degeneration and injury elevated in various disease.
SNAP-25	t-SNARE complex protein enriched in presynaptic terminals. Under investigation as a marker of synaptic degeneration and injury elevated in various disease.
Neuroinflammation	
YKL-40	Also known as Chitnase-3-like protein 1, YKL-40 is expressed and secreted by astrocytes, thought to be involved in inflammation and tissue remodeling. In development as a biomarker, as elevated CSF levels may reflect reactive astrocytosis in AD and other neurodegenerative diseases.
sTREM2	Soluble cleaved ectodomain of TREM2, innate immune receptor expressed in microglia. Under investigation as biomarker of microglial activity.
Neuroinflammatory panels (various)	Various commercially available cytokine/chemokine panels are under investigation for monitoring neuroinflammation in neurodegenerative diseases. α1-ACT, CRP, IL-6, IL-10, IL-15. MCP-1, sCD40L are among the better performers for disease/normal comparisons.
Neurovascular injury	
Vascular injury panels	Various commercially available vascular, endothelial, and tissue remodeling protein panels are under investigation to monitor neurovascular injury in CSF. Flt-1, ICAM-1, several MMPs, PLGF, and VCAM-1 are among those with early interest.

[a] APP, amyloid precursor protein; BACE1, β-secretase 1; ALS, amyotrophic lateral sclerosis; FTLD, frontotemporal lobar degeneration; NfL, neurofilament light chain polypeptide; pNfH, phosphorylated neurofilament heavy chain polypeptide; SNAP-25, synaptosomal nerve-associated protein 25; sTREM2, soluble cleaved ectodomain of triggering receptor expressed on myeloid cells 2; ACT, antichymotrypsin; CRP, C-reactive protein; MCP-1, monocyte chemoattractant protein-1; sCD40L, soluble CD40 ligand; Flt-1, fms related tyrosine kinase 1 [also known as vascular endothelial growth factor receptor 1 (VEGFR1)]; ICAM-1, intercellular adhesion molecule-1; MMP, matrix metalloproteinase; PLGF, placental growth factor; VCAM, vascular cell adhesion molecule.

pathologies. The majority of brains from patients with dementia attributed to AD also exhibit varying amounts of cerebrovascular disease and/or cortical α-synuclein, other τ, or transactive response DNA binding protein 43 kDa (TDP-43) lesions (*14*, *15*). The degree to which a given patient's cognitive impairments can be attributed to one pathology or another is hard to know.

Another major issue is the modest relationship of clinical dementia features with the extent of AD pathology or biomarker levels of amyloid-β and τ. For CSF biomarkers especially, cutoff values for amyloid-β and τ may perform well enough for dichotomizing people into those with or without AD pathology but perform poorly for staging severity or tracking disease progression. Even in postmortem studies, the densities of pathological lesions measured correlate relatively poorly with severity of cognitive impairment. In large clinicopathological correlation studies, as well as in biomarker studies, it is seen that some persons with extensive AD pathology may have little or even no discernible cognitive decline (*16*, *17*). The factors that constitute this "cerebral reserve" or "resilience" despite pathological lesions are of intense interest, with a focus on immune, metabolic, proteostatic, and synaptic response in AD.

It is increasingly evident that other pathophysiological processes beyond amyloid-β and τ are important in MCI and dementia, disease expression, and progression. Emerging biomarkers showing varying degrees of promise to address these issues include different α-synuclein, TDP-43, and amyloid-β and τ fragment biomarkers of pathological lesions to help with differential diagnosis, neurofilament proteins and neurogranin, reflecting axonal and synaptic damage, respectively, as general markers of neural injury and neurodegeneration, YKL-40, soluble cleaved ectodomain of triggering receptor expressed on myeloid cells (sTREM), and inflammatory cytokine/chemokine panels to gauge inflammation and immune response, and others (*18–20*). These and other novel biomarkers will contribute to a better understanding and measurement of AD and related disorders.

TAKEAWAYS

- AD is the most common cause of dementia, but diagnosis based on clinical features and excluding other identifiable medical conditions is inadequate.
- The implementation of amyloid-β and τ molecular biomarkers via either CSF immunoassays or PET scans allows positive diagnosis of AD pathology in the brain with high accuracy.
- Common comorbid pathologies in older adults such as cerebrovascular disease, α-synuclein, TDP-43, and/or other τ proteinopathies, and varying degrees of inflammatory and plasticity responses, present a challenge for understanding the relative contributions of different diseases to dementia. Efforts are ongoing to develop biofluid assays to measure these phenomena, and, when successful, these will further improve diagnosis, prognosis, and management in clinical research and clinical care.

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