Alzheimer Dementia Confirmed by FDG-PET After Negative Neuropsychological Testing:

A Case Series

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Major neurocognitive disorder, including dementia, is a significant cause of functional impairment in the older adult population.[1–4] According to the *DSM-5*, major neurocognitive disorder is diagnosed based on the presence of cognitive deficits that (1) represent a significant decline from baseline in at least 1 cognitive domain, (2) are severe enough to interfere with daily function, (3) do not occur exclusively in the context of delirium, and (4) are not primarily attributable to another mental disorder.[1] An initial neurocognitive assessment typically includes a clinical interview with the patient and caregiver/family, mental status examination, brief in-office cognitive screening tests (such as the Mini-Cog,[5] Mini-Mental State Examination,[6] Montreal Cognitive Assessment [MoCA],[7] or Saint Louis University Mental Status Examination[8]), laboratory testing (such as chemistry panel, thyroid panel, and vitamin B_{12}),[2–4,9] and structural brain imaging (such as head magnetic resonance imaging [MRI] or computed tomography [CT]).[2,3,9–13] This may be followed by formal neuropsychological testing, which is widely considered the gold standard diagnostic tool and entails a battery of tests to assess an individual's function across multiple cognitive domains.[1,4,9–12,14–20] In complex cases where there is still uncertainty regarding the diagnosis, specialized imaging studies such as positron emission tomography (PET) can provide further diagnostic clarity by helping differentiate between dementia syndromes such as Alzheimer disease and frontotemporal dementia,[4,9,11,13,21–25] as well as

distinguishing dementia from cognitive impairment due to depression or other etiologies.[13,26]

Despite the various tools available to assess for major neurocognitive disorder, there is still a risk of inaccurate diagnosis. Formal neuropsychological testing is reported to have greater sensitivity and specificity than brief cognitive screening tests,[9,16] although values for sensitivity and specificity can vary significantly depending on cutoff score designations. Standardized neuropsychological interviews for the detection of dementia have been reported to have sensitivity values ranging from 71% to 100% and specificity values from 46% to 90%,[27–30] while various neuropsychological test batteries commonly utilized in dementia diagnosis have exhibited a wide range of sensitivity values from 32.1% to 100% and specificity values from 43% to 100%.[10,11,17–19,31–44] Given the major social, legal, and financial implications associated with a false-positive diagnosis of dementia, previous literature on the topic of dementia misdiagnosis has primarily focused on the risks of false-positive diagnosis where major neurocognitive disorder does not exist[30,39,45–48] and/or the risks of inaccurate diagnosis when only brief cognitive screening tools are utilized without further formal neuropsychological testing.[17,19,49–55] In contrast, less attention has focused on the possibility and risks of a false-negative diagnosis after formal neuropsychological testing. The risks of a false-negative dementia diagnosis may be especially relevant for patients with milder symptoms,[29,56] given that some studies have reported instances

of patients who presented with memory complaints but who had normal neuropsychological test results and did not meet criteria for mild cognitive impairment at the time.[57,58] Overall, the risks of both false-positive and false-negative diagnoses of dementia are important to consider because neuropsychological screening and testing results can potentially be influenced by the evaluator's unconscious biases and application of heuristics.[59]

This case series presents several patients who underwent formal neuropsychological testing that did not diagnose dementia, but whose clinical course and neuroimaging findings turned out to be consistent with dementia. These false-negative diagnoses following neuropsychological testing for dementia contribute an important perspective to the literature on current standards for dementia assessment.

Case 1

Patient 1 is a male veteran. At age 56 years, he reported falling and striking his head. Shortly afterward, he was referred to the mental health clinic for concerns of memory loss, irritability, headache, and inability to complete his community college classes. At the time, CT of the head was normal. A laboratory panel, which included a comprehensive metabolic panel (CMP), complete blood count (CBC), thyroid-stimulating hormone (TSH) level, and vitamin B_{12} level, was unremarkable. On psychiatric evaluation, he was diagnosed with postconcussive syndrome, an unspecified cognitive disorder, and an unspecified anxiety disorder.

findings were thought to be most likely due to MDD instead of dementia, given her concurrent mood symptoms and relative functional independence. Donepezil was then discontinued. The patient was also referred for psychotherapy.

Over the following year, however, her memory symptoms and functional deficits did not improve. About a year after initial neuropsychological testing, reevaluation was conducted by another neuropsychologist, but this was discontinued due to low effort and inconsistent performance, and her symptoms were believed to be due to MDD and generalized anxiety disorder instead of dementia. Afterward, she was switched to another antidepressant due to lack of efficacy. A repeat MRI of the head was also done, which again showed nonspecific chronic microvascular ischemia. Subsequently, her psychiatric diagnosis was updated by her psychologist/psychotherapist to include dependent personality disorder.

About 3 years after the second neuropsychological evaluation, the patient underwent neuropsychological testing again with a third different neuropsychologist, and she was again noted to exhibit low effort and inconsistent performance. Her performance was attributed to dependent personality disorder instead of dementia, with the recommendation for no further neuropsychological testing unless she had a documented medical event.

However, she continued to exhibit memory difficulties, along with worsening functional deficits and increasingly bizarre behaviors, such as not recognizing her own reflection in the mirror, as well as beliefs that inanimate objects were talking to her. A month later, an FDG-PET scan was done and revealed moderate regionally decreased metabolic activity within the bilateral posterior parietal and temporal cortices, posterior cingulate, and precuneus, consistent with Alzheimer disease. With these imaging findings, and the patient's continued significant decline

in cognitive function and cognitive deficits that interfered with everyday activities, her diagnosis was finally changed to major neurocognitive disorder due to Alzheimer disease.

Case 4

Patient 4 is a male veteran with a history of pacemaker placement. At age 63 years, he presented to the mental health clinic for concerns of worsening memory difficulties over the past 2 months, following a mild concussion that had occurred around a year ago. He had been independent with ADLs and semi-independent with IADLs. At the time of the concussion, CT of the head at an outside facility had been reportedly unremarkable. In his initial workup, CMP and CBC were nonexplanatory. His TSH level was within normal limits, and vitamin B_{12} was low-normal. Repeat CT of the head showed no acute abnormality.

He then completed a neuropsychological evaluation. Reduced engagement was noted, and he scored within normal limits (low-average range or higher) on most measures, including those testing memory. He was given a diagnosis of MDD, and no neurocognitive disorder was diagnosed.

About a year later, repeat neuropsychological testing was conducted by a different neuropsychologist, who diagnosed the patient with an unspecified depressive disorder and again attributed his reported memory difficulties to mental illness. At the time, another CT of the head was unremarkable, and the patient was unable to undergo MRI brain imaging due to his pacemaker.

Given the lack of improvement in his memory deficits, there continued to be clinical suspicion for dementia. Less than 2 years later, an FDG-PET scan was done, which showed significantly decreased FDG uptake in the bilateral precuneus, parietal lobes, posterior cingulate gyrus, middle temporal gyrus, and lateral temporal lobes. These imaging findings, as well as the patient's continued significant

decline in cognitive function and cognitive deficits that interfered with everyday activities, were noted to be consistent with major neurocognitive disorder due to Alzheimer disease, and the patient was finally started on donepezil.

Discussion

As these patient cases illustrate (Table 1), there is a risk that neuropsychological evaluation may result in a false-negative diagnosis for dementia. All 4 of these patients initially presented with memory loss together with mood symptoms, and formal neuropsychological testing showed inconsistent or impaired effort, leading to the attribution of memory loss to depression. However, for these patients, a lack of clinical improvement following depression treatment, combined with findings suggestive of dementia on follow-up imaging studies, ultimately led to dementia diagnosis, consistent with the *DSM-5* criteria for neurocognitive disorder due to Alzheimer disease.[1] It should be noted that in these patient cases, the time between neuropsychological evaluation and PET imaging was short, making conversion to dementia between the time of neuropsychological testing and imaging less likely. Further, the false-negative dementia diagnoses were not limited to a single neuropsychologist, as these patients were evaluated by several different neuropsychologists.

Although neuropsychological testing is considered a gold standard for major neurocognitive disorder diagnosis, it entails a degree of subjective interpretation of the patient's cognitive status and function, leading to the potential for false-negative misdiagnosis. In this case series, 1 factor that may have influenced the interpretation of neuropsychological testing results was the patients' relatively young age at the onset of cognitive symptoms. These patients were still in their 50s or

Table 1.

Patient Cases, Including Their Initial Diagnoses From Neuropsychological Evaluation and Their Final Diagnoses From FDG-PET Imaging

Patient case (initial presentation age)	Neuropsychological evaluation diagnoses	FDG-PET diagnosis
Patient 1 (56 y)	(1) Major depressive disorder, inconclusive for cognitive disorder (2) Major depressive disorder, no cognitive diagnosis (3) Persistent depressive disorder, no cognitive diagnosis	(1) Major neurocognitive disorder due to Alzheimer disease
Patient 2 (65 y)	(1) Major depressive disorder, "rule out" mild neurocognitive disorder	(1) Major neurocognitive disorder due to Alzheimer disease
Patient 3 (67 y)	(1) Major depressive disorder, no cognitive diagnosis (2) Major depressive disorder, generalized anxiety disorder, no cognitive diagnosis (3) Dependent personality disorder, no cognitive diagnosis	(1) Major neurocognitive disorder due to Alzheimer disease
Patient 4 (63 y)	(1) Major depressive disorder, no cognitive diagnosis (2) Unspecified depressive disorder, no cognitive diagnosis	(1) Major neurocognitive disorder due to Alzheimer disease

Abbreviation: FDG-PET = fluorodeoxyglucose-positron emission tomography.

60s at the time of initial presentation and would thus be expected to have a lower baseline probability of dementia compared with the oldest geriatric patients, as dementia risk rises with increasing age.[4,12,15,62] Additionally, younger patients with Alzheimer disease may present with a higher prevalence of atypical symptoms,[63] and individuals in the early stages of Alzheimer disease may be more difficult to identify if neuropsychological testing overemphasizes certain cognitive abilities, such as immediate recall learning, recognition memory, and intrusions.[42] Another consideration for this case series is that patients with dementia and a concurrent psychiatric diagnosis may potentially be at risk of having their memory deficits prematurely attributed to psychiatric illness alone.[15] Dementia risk is noted to be higher in individuals with mental health disorder diagnoses,[4,15,26,64–67] and thus, it is important for clinicians to note that diagnosing mental illness in a patient with memory deficits does not exclude major neurocognitive disorder (or vice versa). In cases where a diagnosis of dementia versus depression is unclear, imaging studies such as brain PET and MRI can provide additional data to help distinguish between dementia and depression[26]; however, imaging findings should always be interpreted with caution and as part of a larger clinical picture, given concerns that overreliance on imaging can still present a risk of false-positive dementia misdiagnosis.[68,69]

Ultimately, this case series adds to the literature on the risk of a false-negative dementia diagnosis after formal neuropsychological testing. Although scientific literature on dementia misdiagnosis has focused primarily on the risks of false-positive diagnosis of major neurocognitive disorder,[30,39,45–48] the significance of avoiding a false-negative diagnosis has received less scholarly attention. It is important to note that a false-negative dementia diagnosis can lead to a patient not receiving the dementia care and support that they need, given that others around them would expect them to function at a higher level than would be appropriate. This could potentially impact a patient's safety, access to resources, interactions with family/caretakers, and ability to function in social settings such as conversations. However, the risks and impacts of a false-negative dementia diagnosis can potentially be reduced with repeated neuropsychological testing and/or screening.[52]

Of note, this case series has several limitations. First, the sample size is small, consisting only of a few cases. In terms of demographics, the individuals in these cases are all veterans who were seen at health care facilities within the Veterans Affairs North Texas Health Care System, limiting generalizability to nonveteran populations. Additionally, although the Veterans Affairs facilities where these patients were seen all had access to PET imaging, not all health care facilities may have PET or other advanced imaging modalities available, and similarly, not all individuals' health care insurance may cover advanced imaging. Finally, all the patients in this case series were ultimately diagnosed with major neurocognitive disorder due to Alzheimer disease, limiting generalizability to patients with non-Alzheimer dementia.

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