Psychological Masquerade

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CME Background

Original material is selected for credit designation based on an assessment of the educational needs of CME participants, with the purpose of providing readers with a curriculum of CME activities on a variety of topics from volume to volume. This special series of case reports about dementia was deemed valuable for educational purposes by the Publisher, Editor in Chief, and CME Institute Staff. Activities are planned using a process that links identified needs with desired results.

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CME Objective

After studying this case, you should be able to:

- Conduct a differential diagnosis in elderly patients with depression and cognitive impairment.

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Date of Original Release/Review

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Financial Disclosure

All individuals in a position to influence the content of this activity were asked to complete a statement regarding all relevant personal financial relationships between themselves or their spouse/partner and any commercial interest. The CME Institute has resolved any conflicts of interest that were identified. In the past year, Larry Culpepper, MD, MPH, Editor in Chief, has been a consultant for AstraZeneca, Labopharm, Pfizer, and Trovis; has been a member of the speakers/advisory board for Merck; and has held stock in Labopharm. No member of the CME Institute staff reported any relevant personal financial relationships.

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HISTORY OF PRESENT ILLNESS

Ms A, an 81-year-old widow, presented to the Memory Disorders Clinic at Banner Alzheimer's Institute with her son for evaluation of cognitive impairment. Ms A stated that symptoms began approximately a year and a half ago. At that time, Ms A suffered a significant loss in the form of the death of her husband. According to the patient's son, she developed prominent depressive symptoms after his death. Although memory problems and difficulty with concentration were noted then, the family initially attributed these symptoms to Ms A's depression. The patient's son and daughter-in-law had moved in with Ms A to help care for her husband during the last half year of his life. They continued to reside with Ms A and observed her functional abilities.

Ms A noted a gradual progression of symptoms that significantly worsened over the past 6 months. Symptoms included repeating questions and statements in conversations, difficulty with concentration, and trouble completing more complex tasks such as management of finances. Word-finding difficulty was also noted.

Ms A described very limited cognitive and functional impairment. Both she and her family denied any difficulty with judgment or problem-solving. Ms A was still able to manage finances, albeit with some assistance from her son. No significant difficulty with calculation was noted. Ms A continued to participate in pleasurable activities with friends and family including a book club, although she stated that she was unable to remember details of the book she read. No difficulty with household appliances or the computer was noted. Ms A continued to drive without problems; no accidents or confusion on the road were noted by her family. She continued to manage her own medications without errors. No difficulty with personal hygiene, grooming, or performing household tasks such as cooking or cleaning was noted. Ms A's son reported no psychotic symptoms, changes in personality, or aggressive behaviors.

At the time of the initial clinic visit, Ms A admitted to feeling "depressed." During the course of the interview, Ms A was tearful and had difficulty speaking about some of her concerns. She reported passive suicidal ideation related to the loss of her husband, although she had no plan and no intent. Decreased energy was noted, and her concentration was poor. Ms A reported difficulty falling asleep and multiple awakenings during the night, and she felt tired throughout the day. Her appetite was good. Feelings of guilt were present, with Ms A fearing that her current affective

Clinical Points

- Cognitive changes in depression may mimic a neurodegenerative process but are likely to improve with aggressive treatment of the underlying affective disorder. Therefore, a thorough assessment and continued monitoring are necessary to allow for proper diagnosis and treatment.
- Depression causes changes in the brain, and the cognitive impairment associated with depression may be less likely to reverse with treatment than previously thought. Patients with pseudodementia (ie, depression and cognitive impairment) should receive full dementia screening and continued monitoring of cognitive function.

symptoms were negatively impacting her son and daughter-in-law's relationship.

PAST MEDICAL HISTORY

Ms A had a history of myocardial infarction in 2008, hypercholesterolemia, a depression diagnosis in August 2007, hypothyroidism, migraine with visual abnormalities, hysterectomy, and vaginal prolapse.

ALLERGIES

Ms A had no known drug allergies.

MEDICATIONS

Ms A's medication included escitalopram 20 mg daily, which was started shortly after the loss of her husband; amitriptyline 10 mg qhs "for sleep"; alendronate; levothyroxine; ezetimibe/simvastatin; nebivolol; aspirin; magnesium chloride; calcium; a multivitamin; vitamin B_{12}; vitamin C; and vitamin D.

SUBSTANCE ABUSE HISTORY

Ms A had no history of alcohol, tobacco, or illicit drug use.

SOCIAL HISTORY

Ms A had a 16-year education history. She worked as an administrative assistant and as a substitute teacher for several years and had been retired for 15 years. Ms A lived in her own home with her son and daughter-in-law.

FAMILY HISTORY

There was a history of dementia in Ms A's father, who developed cognitive changes in his 80s; there was no history of Parkinson's disease, strokes, mental illness, or substance abuse.

MENTAL STATUS EXAMINATION

Ms A was a well-groomed white woman appearing younger than her stated age. Eye contact was appropriate. Ms A displayed symptoms of significant psychomotor depression. She was pleasant and cooperative during the examination. Ms A's mood was depressed, and her affect was restricted and dysphoric. Her thought was coherent, logical, and goal-directed. There was no evidence of any homicidal or paranoid ideations. No auditory or visual hallucinations were noted. Ms A did express passive suicidal ideations including the desire to die in her sleep; however, she denied any plan or intent to harm herself. Her speech was of normal volume, rate, and amount, and her judgment and insight were good. Fund of knowledge was normal for age and education level. Ms A was oriented to time, place, and person. Recent and remote memories were grossly intact, as were attention and concentration.

Based on the information so far, do you think a dementia is present?

A. Yes
B. No
C. Not enough information

Your colleagues who attended the Banner Alzheimer's Institute Case Conference answered as follows:

Based on the information so far, do you think a dementia is present?

A. Yes	22%
B. No	45%
C. Not enough information	33%

The conference attendees were in agreement that information regarding Ms A's true functional status was limited and that reporting was strongly affected by the family's focus on her depressive symptoms. The attendees also questioned why the family felt that they needed to live with Ms A. They believed that a more in-depth evaluation would most likely reveal functional deficits and that Ms A's depressive symptoms may have been an early sign of a neurodegenerative process. The attendees felt that a diagnosis of dementia could not be established due to a lack of functional deficits from the history and that the impact of the depressive disorder needed to be explored further. They agreed that additional testing was necessary.

The *DSM-IV* defines dementia as multiple cognitive deficits that include memory impairment and at least 1 of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning. The cognitive deficits must be sufficiently severe to cause impairment in social or occupational functioning and must represent a decline from a previously higher level of functioning. A diagnosis of dementia should not be made if the cognitive deficits occur exclusively during the course of a delirium (American Psychiatric Association, 2000).

REFERENCE

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition. Arlington, VA: American Psychiatric Association; 2000.

Based on the information so far, what would you expect to see on the neurologic examination?

A. Normal
B. Objective neurologic findings (including frontal release signs)
C. Nonphysiological findings (consistent with malingering)

Your colleagues who attended the Banner Alzheimer's Institute Case Conference answered as follows:

Based on the information so far, what would you expect to see on the neurologic examination?

A. Normal	67%
B. Objective neurologic findings (including frontal release signs)	33%
C. Nonphysiological findings (consistent with malingering)	0%

General physical and neurologic examinations were entirely normal. Frontal release signs were not present.

Different dementias may be associated with various physical examination findings. However, most often, the physical examination is normal in the early stages. Some subtle general findings can include frontal release signs such as a positive snout, glabellar, or palmomental reflex (Links et al, 2010).

REFERENCE

Links KA, Merims D, Binns MA, et al. Prevalence of primitive reflexes and parkinsonian signs in dementia. *Can J Neurol Sci*. 2010;37(5):601–607.

Based on the information so far, what would you expect the Mini-Mental State Examination (MMSE) score to be?

A. 26–30
B. 21–25
C. 16–20
D. 11–15
E. Lower than 11

A MMSE (Folstein et al, 1975) score generally correlates with disease severity. Scores ≤ 9 can indicate severe dementia, between 10–20 can indicate moderate dementia, and a score > 20 can indicate mild dementia (Mungas, 1991). MMSE scores vary by age and education. MMSE scores and age have an inverse relationship, with scores ranging from a median of 29 for people aged 18 to 24 years, to a median of 25 for individuals over the age of 80. MMSE scores and years of education have a direct relationship. Those with 0 to 4 years of education have a median MMSE score of 22, whereas those with at least 9 years of education have a median MMSE score of 29 (Crum et al, 1993).

REFERENCES

Crum RM, Anthony JC, Bassett SS, et al. Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA*. 1993;269(18):2386–2391.
Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.
Mungas D. In-office mental status testing: a practical guide. *Geriatrics*. 1991;46(7):54–58, 63, 66.

Your colleagues who attended the Banner Alzheimer's Institute Case Conference answered as follows:

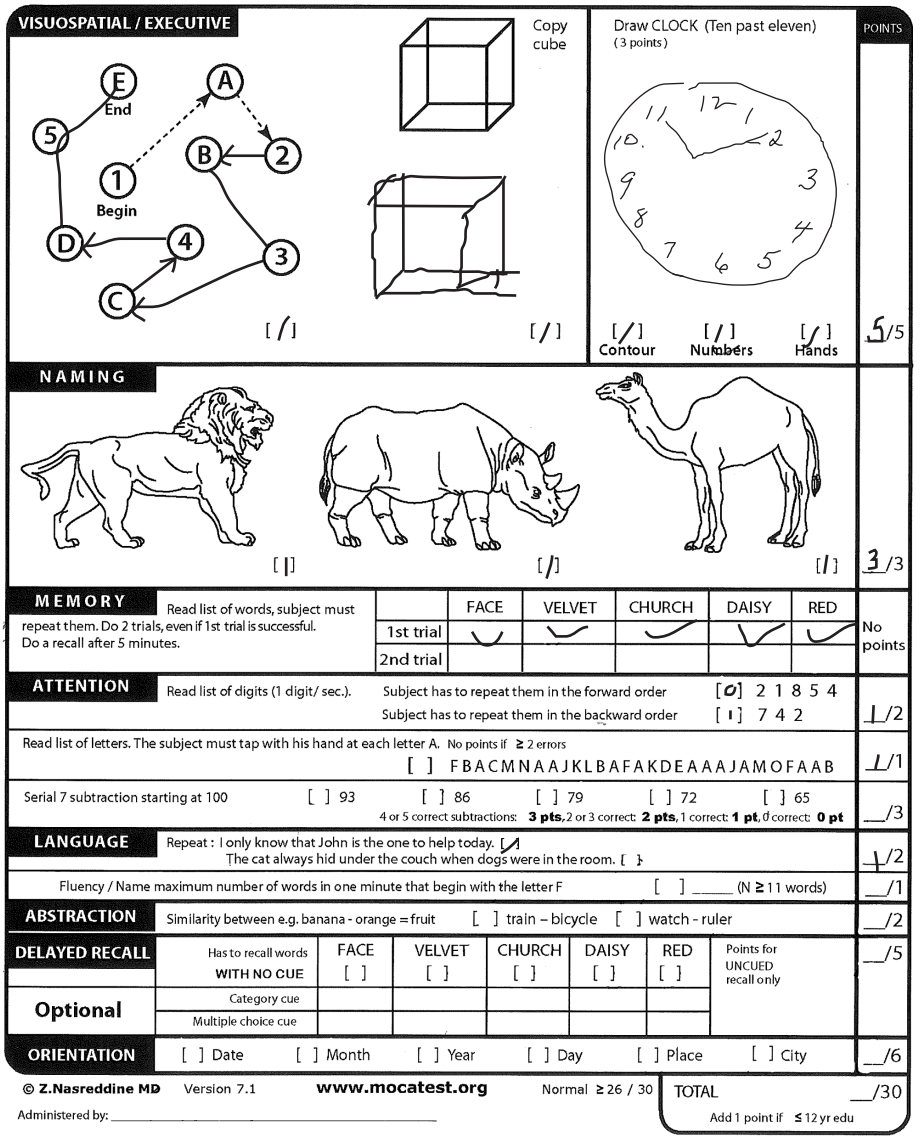
Based on the information so far, what would you expect the MMSE score to be?

A. 26–30	89%
B. 21–25	11%
C. 16–20	0%
D. 11–15	0%
E. Lower than 11	0%

Ms A scored 28 out of 30 on the MMSE. She lost 1 point on comprehension and 1 point on recall. An additional cognitive screening battery was performed. Due to time constraints, only a partial Montreal Cognitive Assessment Test (MoCA) was performed (Figure 1).

The MoCA (Nasreddine et al, 2005) is a 30-point test that assesses several cognitive domains. Because it is more challenging than the MMSE, it has greater sensitivity for mild cognitive impairment and early stages of dementia. With a cutoff score < 26, the sensitivity for detecting mild cognitive impairment (N = 94) was found to be 90% and the specificity 87%.

Figure 1. The Patient's Montreal Cognitive Assessment (MoCA) Results[a]



[a]Reprinted with permission from Nasreddine Z.

REFERENCE

Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–699.

Based on the information so far, do you think this is dementia?

A. Yes
B. No

Your colleagues who attended the Banner Alzheimer's Institute Case Conference answered as follows:

Based on the information so far, do you think this is dementia?

A. Yes	0%
B. No	100%

Most of the clinicians felt that although a neurodegenerative disorder was most likely present, full criteria for dementia were not met. Laboratory studies available at the time of the visit, including complete blood count (CBC), comprehensive metabolic panel (CMP), thyroid-stimulating hormone (TSH) level, and vitamin B_{12} level revealed no clinically significant

abnormalities. A brain magnetic resonance image scan was unremarkable.

IMPRESSION

At the end of the visit, the clinician's impression was as follows: Ms A is a very pleasant 81-year-old widowed woman presenting to the Memory Disorders Clinic for evaluation of cognitive impairment of approximately 1 to 1 1/2 years' duration. Currently, Ms A displays limited cognitive impairment as well as no significant functional impairment. Symptoms began after a significant psychosocial stressor, namely the death of her husband and the patient's change in living environment. Ms A continues to suffer from undertreated depression that may in part be contributing to her cognitive symptoms. However, at this time, it is unclear whether an underlying neurodegenerative disorder resulting in a mild cognitive impairment (MCI) may be present or whether Ms A's symptoms are solely a result of a depressive disorder affecting her memory. Further workup is indicated.

What should the next step be?

A. Neuropsychological testing
B. Repeat laboratories (CBC, CMP, TSH level, vitamin B_{12} level)
C. Repeat structural brain scan
D. Positron emission tomography (PET) scan
E. B and C
F. A, B, C

Your colleagues who attended the Banner Alzheimer's Institute Case Conference answered as follows:

What should the next step be?

A. Neuropsychological testing	100%
B. Repeat laboratories (CBC, CMP, TSH level, vitamin B_{12} level)	0%
C. Repeat structural brain scan	0%
D. PET scan	0%
E. B and C	0%
F. A, B, C	0%

All of the clinicians felt that neuropsychological testing would be the most appropriate next step in diagnosis, as it would help elaborate whether the pattern of strengths and weakness in cognitive domains was consistent with a neurodegenerative process and would establish a baseline for monitoring of future changes in cognition. However, some of the clinicians present questioned whether repeat structural neuroimaging might also be of benefit given the somewhat more rapid decline over the past 6 months. They felt that volumetric assessment of the hippocampi over time might be helpful in assessing progressive neurodegeneration.

In order to better isolate which of the patient's abilities may have been compromised or affected, a series of tests known as a *neuropsychological battery* may be administered by a neuropsychologist. A typical neuropsychological evaluation might focus on measuring various abilities including general intelligence, attention and concentration, learning and memory, motor and sensory functioning, auditory and visual processing, language functions, thinking, planning and organization, speed of processing, executive functioning, expressive functions, and emotions and personality (Lezak et al, 2004).

A neuropsychological evaluation can achieve the following:

1. Provide a baseline for future testing
2. Aid in the differentiation of the various dementia-causing presentations
3. Identify compensatory strategies
4. Assist in helping to judge if deficits are organic or psychiatric in nature
5. Aid in earlier detection of "preclinical" dementia such as MCI
6. Describe patterns of cognitive weakness and strengths
7. Assist in choosing treatments and preventative/postponing measures.

REFERENCE

Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. Fourth edition. Oxford University Press: New York, New York; 2004

Does the presentation warrant initiation of a cognitive enhancer like a cholinesterase inhibitor?

A. Yes
B. No
C. Uncertain

Your colleagues who attended the Banner Alzheimer's Institute Case Conference answered as follows:

Does the presentation warrant initiation of a cognitive enhancer like a cholinesterase inhibitor?

A. Yes	0%
B. No	100%
C. Uncertain	0%

Cholinesterase inhibitors are currently not approved for treatment of MCI. Furthermore, it is unclear if Ms A has evidence of a neurodegenerative condition.

PLAN

The clinician's plan of care at the initial visit was as follows:

1. Order neuropsychological testing to help clarify Ms A's pattern of cognitive strengths and weaknesses and assist in the differential diagnosis between MCI due to an underlying neurodegenerative disorder and an affective disorder affecting cognition. The neuropsychological testing will also establish a current baseline of cognitive function and will allow for objective monitoring of changes in cognition.
2. Advise Ms A to undergo psychotherapy in addition to antidepressant treatment due to recent major psychosocial stressors. Ms A was resistant to the idea.

FOLLOW-UP

Ms A underwent neuropsychological testing that revealed relative weaknesses in her memory and concentration abilities. Her ability to immediately recall verbal information was above average, as reflected in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Immediate Memory Index scores in the 87th percentile for her age group. However, after a delay, Ms A's ability to recall both verbal and visual information was below average, resulting in RBANS Delayed Memory Index scores in the 14th percentile. It was noteworthy that Ms A displayed impaired performance on a measure of recognition memory that required her to identify previously presented words from among a list of distracters. Recognition memory is typically intact in affectively driven memory disorders. It is noteworthy that, although memory was a relative weakness for Ms A, her scores were still essentially within normal limits for her age group.

Ms A also displayed variations in her attention and concentration skills. For example, her ability to repeat strings of spoken digits forward and backward was relatively low, in the 16th percentile for her age group. However, her ability to solve arithmetic problems without the benefit of pencil and paper was in the 75th percentile. This discrepancy was noteworthy, in that the latter task places higher demands for attention, concentration, and working memory than does the former. This pattern was felt to most likely be a consequence of her depressed mood.

Ms A's areas of relative weakness were against the background of average or better language abilities, visual perception, and executive functioning. The neuropsychological testing gave indication of the presence of a genuine memory disturbance that was not felt to be a result of Ms A's affective state. However, Ms A's concentration abilities were felt to most likely be adversely influenced by her depression.

REFERENCE

Randolph C, Tierney MC, Mohr E, et al. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol.* 1998;20(3):310–319.

Based on the information so far, what is the most likely diagnosis?

A. Pseudodementia
B. Frontotemporal dementia syndrome
C. Alzheimer's disease dementia
D. MCI
E. Dementia not otherwise specified

Your colleagues who attended the Banner Alzheimer's Institute Case Conference answered as follows:

Based on the information so far, what is the most likely diagnosis?

A. Pseudodementia	0%
B. Frontotemporal dementia syndrome	0%
C. Alzheimer's disease dementia	0%
D. MCI	100%
E. Dementia not otherwise specified	0%

Although most of the clinicians felt that a depressive disorder was present and most likely negatively influencing Ms A's cognitive function, they did not feel that it was solely responsible for her symptoms.

The term *pseudodementia* has been used in the past to indicate a functional impairment in cognition mimicking a dementia but not related to an organic brain disease. The condition was characterized by onset of cognitive impairment in the setting of depression. When the underlying depression was treated, cognitive impairment was believed to fully resolve. However, longitudinal studies indicate that dementia is more likely to develop in elderly persons with depression than in their nondepressed counterparts (Devanand et al, 1996; Sweet et al, 2004). So, depression may place people at increased risk for dementia or may be an early manifestation of dementia. Furthermore, elderly depressed patients with cognitive impairment are more likely to develop dementia than are the elderly depressed patients without cognitive impairment (Alexopoulos et al, 1993). Although the cognitive impairment associated with depression in the elderly often improves somewhat as the depression lifts, recent studies indicate that some degree of cognitive impairment usually persists. These observations in the aggregate suggest that depression in the elderly may uncover or allow the expression of early-stage dementia.

REFERENCES

Alexopoulos GS, Meyers BS, Young RC, et al. The course of geriatric depression with "reversible dementia": a controlled study. *Am J Psychiatry.* 1993;150(11):1693–1699.

Devanand DP, Sano M, Tang MX, et al. Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. *Arch Gen Psychiatry*. 1996;53(2):175–182.
Sweet RA, Hamilton RL, Butters MA, et al. Neuropathologic correlates of late-onset major depression. *Neuropsychopharmacology*. 2004;29(12):2242–2250.

Mild cognitive impairment refers to cognitive impairment that does not meet the criteria for normal aging or dementia because the cognitive impairment does not impair activities of daily living. Several criteria for, and subtypes of, MCI have been proposed (Voisin et al, 2003). Originally, MCI emphasized memory impairment as a precursor state for Alzheimer disease (Petersen et al, 1999). It then became apparent that MCI is a heterogeneous entity that affects other cognitive domains and includes the prodromal stages of other dementias. The diagnostic criteria for MCI are not exact and require subjectivity in determining whether a cognitive impairment is present or what constitutes impairment in activities of daily living.

REFERENCES

Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56(3):303–308.
Voisin T, Touchon J, Vellas B. Mild cognitive impairment: a nosological entity? *Curr Opin Neurol*. 2003;16(suppl 2):S43–S45.

What would you do next?

A. Repeat neuropsychological testing in 12 months
B. PET scan
C. Initiate a cholinesterase inhibitor
D. Initiate a *N*-methyl-D-aspartate (NMDA) antagonist
E. Change the antidepressant
F. Have the patient return to the clinic in 6 months
G. D and E

Your colleagues who attended the Banner Alzheimer's Institute Case Conference answered as follows:

What would you do next?

A. Repeat neuropsychological testing in 12 months	0%
B. PET scan	0%
C. Initiate a cholinesterase inhibitor	0%
D. Initiate an NMDA antagonist	0%
E. Change the antidepressant	80%
F. Have the patient return to the clinic in 6 months	0%
G. D and E	20%

The majority of the attendees felt that Ms A's depressive symptoms were severe enough to warrant more aggressive antidepressant treatment. On the basis of recent studies, they also saw no benefit from initiating a cholinesterase inhibitor for mild cognitive impairment. A few of the attendees believed that, in addition to more aggressive antidepressant therapy, an off-label trial of a cholinesterase inhibitor might be beneficial and felt that such an option should be discussed with Ms A and her family.

Currently, there is no US Food and Drug–approved treatment for MCI. Prior clinical trials of cholinesterase inhibitors yielded primarily negative results, showing either lack of benefit of cholinesterase inhibitors altogether or lack of benefit on primary outcomes, with possible benefit on secondary outcomes. For example, Petersen et al (1999) conducted a double-blind study in which 769 subjects were randomly assigned to receive 2,000 IU of vitamin E daily, 10 mg of donepezil daily, or placebo for 3 years. The primary outcome was clinically possible or probable Alzheimer's disease; secondary outcomes were cognition and function. The rate of progression to Alzheimer's disease after 3 years was not lower among patients treated with donepezil than among those given placebo, although some secondary outcomes showed results favoring donepezil. Among carriers of 1 or more apolipoprotein E epsilon4 alleles, donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first 12 months of treatment; however, this retrospective analysis was not sufficient to guide practice. There were no significant differences in the rate of progression to Alzheimer's disease between the vitamin E and placebo groups at any point, either among all patients or among apolipoprotein E epsilon4 allele carriers.

REFERENCE

Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56(3):303–308.

PLAN OF CARE

At the time of the follow-up visit, the results of neuropsychological testing were reviewed with Ms A. She was felt to be suffering from MCI most likely due to a progressive neurodegenerative disease such as Alzheimer's disease in addition to a major depressive disorder. The off-label use of a cognitive enhancer was discussed with Ms A, and she was started on donepezil 5 mg daily. After 1 month, the dose was increased to 10 mg daily. Ms A initially tolerated the medication and noted significant improvement in attention, concentration, energy level, and mood. However, Ms A slowly began to develop dizziness, leg cramping, and vivid nightmares (known side effects of donepezil). The medication was subsequently changed to the rivastigmine patch 4.6 mg daily and titrated to a dose of 9.5 mg, which Ms A tolerated well.

The physician also discussed the adverse influence of depression on cognition, and Ms A was referred to a psychiatrist for brief psychodynamic therapy in conjunction with adjustment of antidepressant therapy. Ms A was advised to stop amitriptyline due its anticholinergic properties.

FOLLOW-UP

Over the course of the next 2 years, Ms A's cognitive symptoms fluctuated significantly. She continued to complain of a subjective sense of cognitive decline involving short-term memory abilities, concentration, and attention. Ms A remained engaged in social activities such as volunteering in a local homeless shelter, outings with friends and family, Spanish classes for seniors, and a book club. No changes in activities of daily living were noted. Ms A continued to work with a psychotherapist to adequately address depressive symptoms and existential issues influencing their development. During times of increased stress, Ms A was noted to display a significant worsening in cognition and mood.

Over the course of the treatment, several discussions with Ms A's family revealed behavioral disturbances that appeared when she was challenged or felt criticized or when she was noncompliant with her antidepressant therapy. Ms A's son brought in a video of his mother during one of these episodes. He described Ms A as "going into a trance-like state." On the video, Ms A displayed repetitive verbalizations and agitation, uncontrollably crying, trembling, and repeating, "I can't do this. I don't wanna do this." Family also noted episodes during which Ms A appeared to be in a dissociative state and would sit rocking back and forth clutching her husband's photo and repeating, "Why did you leave me?" Other symptoms of depression persisted, including increased irritability, that resulted in increased tensions in the home, depressed mood, periods of trance-like states characterized by increased agitation, periods of decreased appetite, and impaired concentration. Ms A stated that she continued to be hard on herself and to call herself names. Considerable feelings of guilt over being a burden were noted during the discussion.

In addition to the individual psychodynamic therapy that Ms A was undergoing, the family began to engage in family psychotherapy. This psychotherapy appeared to improve interpersonal relations and Ms A's depressive symptoms. However Ms A continued to complain of subjective worsening of short-term memory abilities. Cognitive screening tests were repeated.

Based on the information so far, what would you expect the MMSE score to be?

A. 26–30
B. 21–25
C. 16–20
D. 11–15
E. Lower than 11

Your colleagues who attended the Banner Alzheimer's Institute Case Conference answered as follows:

Based on the information so far, what would you expect the MMSE score to be?

A. 26–30	100%
B. 21–25	0%
C. 16–20	0%
D. 11–15	0%
E. Lower than 11	0%

All of the attendees felt that Ms A would display only a slight drop in MMSE scores. There was no evidence of any functional decline on history, and, hence, Ms A would still meet criteria for MCI. Nearly 2 years earlier, Ms A had scored 28 out of 30. She was now scoring 29 out of 30.

Based on the information so far, what would you expect the MoCA score to be?

A. 26–30
B. 21–25
C. 16–20
D. 11–15
E. Lower than 11

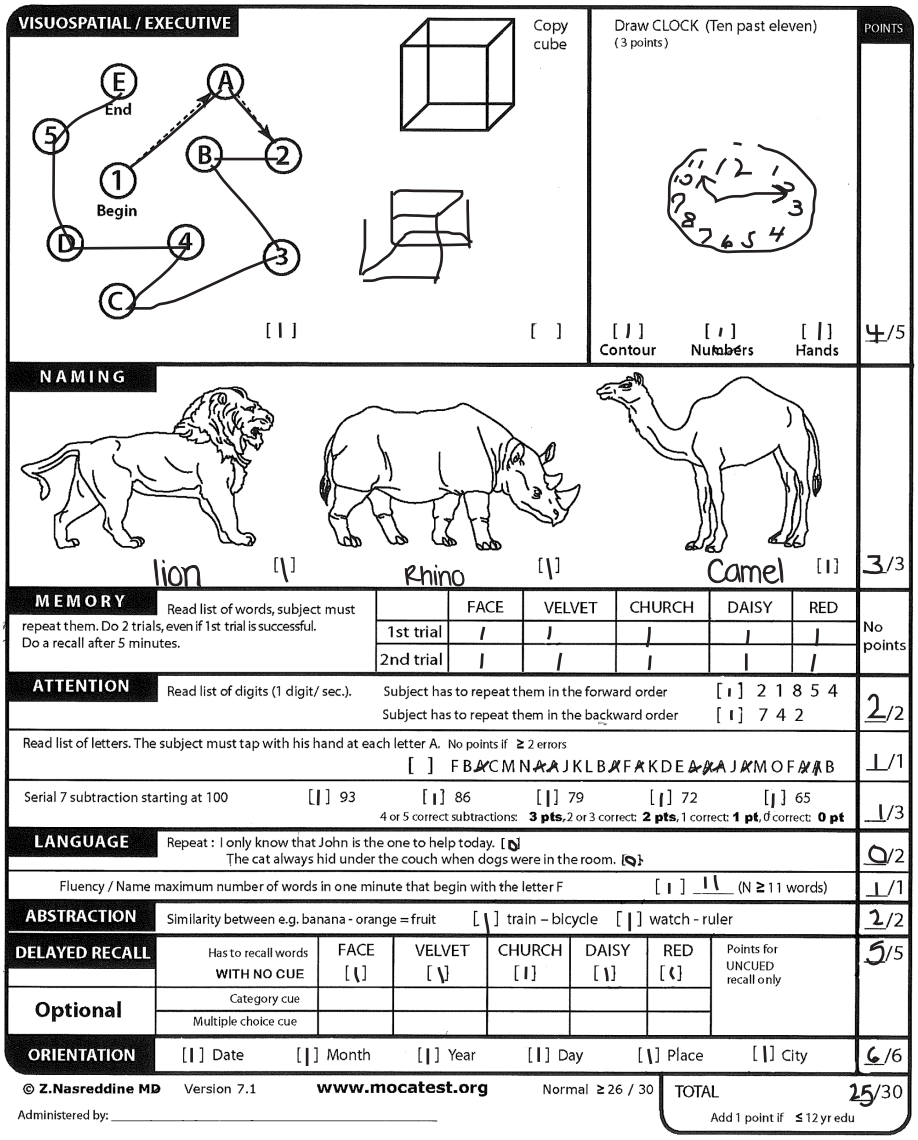
Your colleagues who attended the Banner Alzheimer's Institute Case Conference answered as follows:

Based on the information so far, what would you expect the MoCA score to be?

A. 26–30	20%
B. 21–25	80%
C. 16–20	0%
D. 11–15	0%
E. Lower than 11	0%

Most of the clinicians believed that the MoCA test would be better able to reveal subtle cognitive impairments not evident on the MMSE. Ms A scored 25 out of 30, with impairments in visuospatial abilities and language as well as attention, but surprisingly, no impairments in delayed recall (Figure 2).

Figure 2. The Patient's Follow-Up Montreal Cognitive Assessment (MoCA) Results[a]



[a]Reprinted with permission from Nasreddine Z.

Based on the information so far, what is the most likely diagnosis?

A. Pseudodementia
B. Frontotemporal dementia syndrome
C. Alzheimer's disease dementia
D. MCI
E. Dementia not otherwise specified
F. Normal aging

Your colleagues who attended the Banner Alzheimer's Institute Case Conference answered as follows:

Based on the information so far, what is the most likely diagnosis?

A. Pseudodementia	33%
B. Frontotemporal dementia syndrome	0%
C. Alzheimer's disease dementia	0%
D. MCI	67%
E. Dementia not otherwise specified	0%
F. Normal aging	0%

Several attendees began to question the presence of an underlying neurodegenerative disorder due to the lack of objective short-term memory deficits and no clear

evidence of progression. They were also concerned about the worsening depressive symptoms and their link to exacerbation of cognitive symptoms and felt that further workup was indicated.

The majority of the attendees indicated that Ms A continued to meet criteria for MCI and that progression of cognitive deficits was not necessary for the diagnosis. However, they did question whether the MCI was related to an underlying Alzheimer's disease pathology. Some also questioned whether the cognitive enhancer was actually improving or considerably slowing the cognitive decline and recommended discontinuing the rivastigmine patch for a trial period.

PLAN OF CARE

This presentation was felt to be unusual for MCI due to Alzheimer's disease, as over the course of 2 years, some progression of deficits would be expected. Ms A also reported a subjective decline in cognitive abilities, and symptoms tended to fluctuate depending on psychosocial stressors. The clinician recommended a repeat of the neuropsychological testing.

FOLLOW-UP

Neuropsychological testing was repeated and compared to testing from 2 years prior. The results indicated that Ms A gave no indications of cognitive decline. The relative weakness in memory abilities from 2 years before was not seen during the repeat testing. Her Delayed Memory Index score was in the 75th percentile for her age group, whereas before it had been in the 14th percentile. The neuropsychologist felt that such changes would be highly unusual for a progressive neurodegenerative disorder. Ms A also displayed relative weakness on measures of attention and concentration consistent with depression. However, her scores in these areas continued to be within normal limits and had not decreased significantly from the previous evaluation.

Based on the information so far, what is the most likely diagnosis?

A. Pseudodementia
B. Frontotemporal dementia syndrome
C. Alzheimer's disease dementia
D. MCI
E. Dementia not otherwise specified

Your colleagues who attended the Banner Alzheimer's Institute Case Conference answered as follows:

Based on the information so far, what is the most likely diagnosis?

A. Pseudodementia	100%
B. Frontotemporal dementia syndrome	0%
C. Alzheimer's disease dementia	0%
D. MCI	0%
E. Dementia not otherwise specified	0%

The attendees felt that there was overwhelming evidence against a progressive neurodegenerative process. Hence, they believed that affective illness was affecting the patient's cognitive abilities and resulting in a pseudodementia.

What would you do next?

A. Repeat neuropsychological testing as soon as possible
B. Repeat neuropsychological testing in 6 months
C. PET scan
D. Stop the cholinesterase inhibitor
E. Continue current therapy and have the patient return to the clinic in 6 months
F. Have the patient follow up with the psychiatrist
G. D and F
H. E and F

Your colleagues who attended the Banner Alzheimer's Institute Case Conference answered as follows:

What would you do next?

A. Repeat neuropsychological testing as soon as possible	0%
B. Repeat neuropsychological testing in 6 months	0%
C. PET scan	0%
D. Stop the cholinesterase inhibitor	0%
E. Continue current therapy and have the patient return to the clinic in 6 months	0%
F. Have the patient follow up with the psychiatrist	0%
G. D and F	80%
H. E and F	20%

The majority of the conference attendees believed that a cognitive enhancer was no longer indicated since the symptoms appeared to be the result of an underlying affective disorder. They recommended close follow-up by a psychiatrist. Some attendees questioned the beneficial

influence of the rivastigmine patch and recommended that the medication be continued in addition to more aggressive psychiatric treatment.

CLINICIAN'S ASSESSMENT

The clinician felt that the results of the neuropsychological testing were consistent with cognitive disorder not otherwise specified that was unlikely to be a result of a neurodegenerative disorder but rather a result of an affective disorder possibly exacerbated by current psychosocial stressors as well as underlying personality traits. These types of disorders have on occasion been referred to as pseudodementias. However, individuals who develop pseudodementias during times of excessive stress or depression are at a greater risk of developing dementia in the future, and, hence, Ms A was advised to remain vigilant with regard to worsening of symptoms. The cholinesterase inhibitor was stopped, and Ms A was advised to continue to follow up with her psychiatrist.

DISCUSSION

The concept of *pseudodementia* or *dementia syndrome of depression* has long been a misunderstood and contentious diagnosis. Physicians frequently grapple with attempting to categorize the cognitive symptoms that they note into a "functional" (ie, affective) versus "organic" (ie, neurodegenerative) category. However, recent evidence as to the physical effects of depression on the brain indicates that this concept no longer holds true. Depression results in genuine biological changes, including pituitary-adrenal overactivity, decreased serotonin receptor activity, and shifts in hippocampal size and prefrontal cortex activity. Therefore pseudodementia, even when it is fully accounted for by depression and reversed when depression lifts, probably involves some organic brain pathology.

Depression can also be a risk factor for the development of Alzheimer's disease dementia, or it can develop secondary to the neurodegenerative process. Longitudinal studies indicate that dementia is more likely to develop in elderly persons with depression than in their nondepressed counterparts (Devanand et al, 1996; Sweet et al, 2004). So, depression may place people at increased risk for dementia or may be an early manifestation of dementia. There is a high prevalence rate (30%–50%) of Alzheimer's disease and depression comorbidity. Elderly depressed patients with cognitive impairment are more likely to develop dementia than are the elderly depressed without cognitive impairment (Alexopoulos et al, 1993). Although the cognitive impairment associated with depression in the elderly often improves somewhat as the depression lifts, recent studies indicate that some degree of cognitive impairment usually persists. These observations in the aggregate suggest that depression in the elderly may uncover or allow the expression of early stage dementia. Therefore, patients with pseudodementia should continue to be closely monitored for development of a neurodegenerative disorder in the future.

Cerebrospinal fluid examination may also be a useful tool for diagnostically challenging cases. Although used routinely in the research setting, cerebrospinal fluid biomarker analysis can be used as an adjunct test in the clinic. β amyloid levels in the cerebrospinal fluid, in particular Aβ1–42 (Aβ42), are reduced by 40% to 50% in patients with Alzheimer's disease compared to normal controls (Thal et al, 2006). Cross-sectional studies have demonstrated that cerebrospinal fluid total tau (T-tau) has a 2-fold to 3-fold elevation in patients with Alzheimer's disease (Hampel et al, 2004). A ratio of T-tau to Aβ42 levels has a high sensitivity (89%) and specificity (90%) (Thal et al, 2006). Cerebrospinal fluid biomarkers may allow for better differentiation between an Alzheimer's disease–type process and a dementia syndrome of depression or pseudodementia.

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DISCLOSURE OF OFF-LABEL USAGE

The authors have determined that, to the best of their knowledge, amitriptyline is not approved by the US Food and Drug Administration for the treatment of insomnia, and rivastigmine and donepezil are not approved for the treatment of mild cognitive impairment.

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Dr Yaari is a consultant for Amedisys Home Health. **Dr Tariot** is a consultant for Acadia, AC Immune, Allergan, Eisai, Epix, Forest, Genentech, MedAvante, Memory Pharmaceuticals, Myriad, Novartis, Sanofi-Aventis, Schering-Plough, and Worldwide Clinical Trials; has received consulting fees and grant/research support from Abbott, AstraZeneca, Avid, Baxter, Bristol-Myers Squibb, GlaxoSmithKline, Elan, Eli Lilly, Medivation, Merck, Pfizer, Toyama, and Wyeth; has received educational fees from Alzheimer's Foundation of America; has received other research support only from Janssen and GE; has received other research support from National Institute on Aging, National Institute of Mental Health, Alzheimer's Association, Arizona Department of Health Services, and Institute for Mental Health Research; is a stock shareholder in MedAvante and Adamas; and holds a patent for "Biomarkers of Alzheimer's Disease." **Drs Burke**, **Seward**, and **Fleisher** and **Mss Brand** and **Dougherty** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the activity.

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CASE CONFERENCE

The Banner Alzheimer's Institute Case Conference is a weekly event in which physicians and staff discuss challenging and/or teaching cases of patients seen at the Institute's Memory Disorders Clinic. These conferences are attended by a multidisciplinary group that includes Banner Alzheimer's Institute dementia specialists, community physicians (internal medicine, family medicine, and radiology), physician assistants, social workers, nurses, medical students, residents, and fellows.

BANNER ALZHEIMER'S INSTITUTE

The Banner Alzheimer's Institute located in Phoenix, Arizona, has an unusually ambitious mission: to end Alzheimer's disease without losing a generation, set a new standard of care for patients and families, and forge a model of collaboration in biomedical research. The Institute provides high-level care and treatment for patients affected by Alzheimer's disease, dementia, and related disorders. In addition, the Institute offers extensive support services for families and many unique and rewarding research opportunities.

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