

## Menopause: Case Report

# Menopause-Related Cognitive Impairment

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**BACKGROUND:** Identifying the cognitive changes associated with the menopausal transition prevents misattribution of symptoms to more ominous causes such as neurodegenerative disease.

**CASE:** Two women with cognitive loss and objective evidence of menopause-related cognitive impairment are presented, misattributed to Alzheimer's disease in one case and frontotemporal dementia in the other. Neurocognitive testing, neuroimaging, and laboratory findings are reviewed. Both women were diagnosed with menopause-related cognitive impairment and were stable in follow-up over 4 or more years.

**CONCLUSIONS:** Recognizing the cognitive changes associated with menopause and distinguishing from cognitive impairment resulting from other etiologies—including neurodegenerative diseases such as Alzheimer's disease—has important clinical implications both for treatment and for prognosis.

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Men and women experience cognitive difficulties with aging from myriad sources, including medications, endocrine changes, environmental stressors, nonpathologic age-associated memory impairment, or of a more portentous nature from mild cognitive impairment to dementia.

Across cultures, as women transition into menopause, 34–62% report memory changes. Their subjective

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### Teaching Points

1. Cognitive symptoms and signs are common during the menopausal transition.
2. Features may mimic those seen early in the course of dementias.
3. Awareness of these changes prevents misdiagnosis.

tive memory symptoms correlate with poorer performance on objective neurocognitive testing with reductions in verbal memory skills, verbal fluency, and executive function.<sup>1–4</sup> These disturbances persist despite controlling for concomitant symptoms, such as hot flashes with associated sleep deprivation, depression, and anxiety, and mimic deficits seen early in dementias such as Alzheimer's disease.<sup>1</sup>

In 1871, the English physician Tilt described these changes in 500 menopausal women.<sup>5</sup> “There is almost always,” he wrote, “a partial paralysis...of cerebral power...(women) lose confidence in themselves...unable to manage domestic or other business...feeling as if a cloud or a cobweb required to be brushed from the brain...forget where they have put their purse...some forget their way home...”

Because laboratory indicators of impending menopause may not occur until late in the transition, women with cognitive changes without concomitant, well-recognized symptoms of menopause such as hot flashes may become alarmed that symptoms signify another condition such as dementia. Physicians not cognizant of these changes may misdiagnose these patients, with unfortunate consequences.

The term menopause-related cognitive impairment is proposed to differentiate this condition from mild cognitive impairment, often synonymous with a dementia prodrome.

### CASE 1

Ms. A was a 55-year-old administrator who, 6 years earlier, at the age of 49 years, began developing attentional problems; trouble managing her time; difficulty multitasking; losing documents, keys, wallets; and getting lost in her large office building. She was referred to a university memory disorders center at age 52, where a diagnosis of Alzheimer's disease was made based on progression of cognitive dysfunction on serial neurocognitive testing over 2 or more years. Her working memory was at the 9th percentile compared with age-matched peers, her magnetic resonance imaging (MRI) and electroencephalogram results

were normal, and two positron emission tomography scans showed progressive mild decline in metabolism in the mesial temporal, temporoparietal, and cerebellar lobes, initially reported as a medication effect.

The patient's medical history was significant for bipolar disorder, type 2, for 15 years. She became menopausal at age 46 years and started hormone therapy (HT) a year later for dyspareunia. Her general and neurologic examination results were normal. Her standardized neurocognitive evaluation showed overall abilities at the 96th percentile compared with aged-matched peers, with list learning at the 36th percentile and verbal fluency at the 51st percentile. Her presentation was consistent with menopause-related cognitive impairment. However, given the preexisting diagnosis of Alzheimer's disease, cerebrospinal fluid  $\tau$  and  $\beta$ -amyloid analysis was performed, and the results were normal. Repeat neurocognitive testing 3 years after presentation, at age 58 years, showed maintenance of functioning.

At age 61 years, 6 years after the erroneous diagnosis of Alzheimer's disease, the patient remained functional and independent. However, she was unable to return to work, saying, "I lost my confidence," after her Alzheimer's diagnosis and remains on disability.

## CASE 2

Ms. H, a 55-year-old headmistress, was referred by her therapist with possible frontotemporal dementia given a year-long history of progressive memory and behavioral issues. She previously had a prodigious memory but now repeated herself, was disorganized with daily tasks, lost objects, became increasingly irascible, and had executive functioning problems, refusing, in one instance, to change grossly soiled clothing. Recently retired, she denied cognitive issues were the reason.

Her medical history was significant for depression of 4 years' duration. She had undergone menopause a year earlier. Results of routine laboratory tests and a brain MRI were normal. Her father had developed Parkinson's disease in his 70s, and her maternal grandmother had developed dementia of unknown type in her 60s.

The patient's general and neurologic examination results were normal. On the standardized neurocognitive battery, her overall ability was at the 98th percentile compared with age-matched peers, her working memory at the 39th percentile, and verbal fluency at the 12th percentile. Results of a brain MRI and positron emission tomography scan were normal. The diagnosis of menopause-related cognitive impairment was made, and the patient was placed on HT. Repeat testing 15 months later showed stabilization of cognitive skills, with working memory rising to the 88th percentile and resolution of her behavioral symptoms. She completed a demanding graduate program and, 4 years after presentation, is in another leadership position in education.

## DISCUSSION

These cases illustrate some features of menopause-related cognitive impairment summarized in Box 1.

Prominent in cognitive testing are difficulties in verbal fluency and memory. Cognitive changes accompanying the menopausal transition are not routinely factored into memory disorder assessments by specialists in the field. For instance, there was no mention in Ms. A's extensive medical record of her menopausal status or HT use. A recent meta-analysis found reductions in working memory, phonemic verbal fluency, and verbal delayed memory during the menopausal transition.<sup>2</sup> Because these cognitive changes mimic those seen early in the course of other dementias, including Alzheimer's disease, misdiagnosis becomes a possibility. Although both women experienced chronic depression, a risk factor for cognitive loss in menopause,<sup>2</sup> and were on medications that could affect cognition, their depressive symptoms and medications were stable during this period.

There are several mechanisms for the association of cognitive decline with the menopausal transition.<sup>7,8</sup> Estrogen loss in animals is accompanied by reductions in dendritic spine density and synaptic formation in the hippocampus and basal forebrain regions.<sup>8</sup> Neurochemically, there is reduced cholinergic and serotonergic function. Estrogen modulates serotonergic function in the brain with direct effects on both cognition and mood, and mood disturbances further indirectly exacerbate cognitive dysfunction.<sup>8</sup> Increased levels of cortisol accompanying hot flashes may worsen memory.<sup>7</sup> Estrogen helps maintain cardiovascular health, which may indirectly promote brain health.<sup>7</sup> Estrogen influences function in the hippocampus, striatum, and prefrontal cortex, brain regions responsible for learning, registering, and retrieving information, for language, and judgment.<sup>4</sup>

With regard to treatment of cognitive symptoms during the menopausal transition, the North American Menopause Society recommends HT for treating cognitive symptoms immediately after surgical menopause but not after early natural menopause, given

### Box 1. Menopause-Related Cognitive Impairment

- Subjective change in cognition
- Present in context of persistent change in frequency and quality of menses for at least 12 mo, not related to other factors such as pregnancy or cancer
- Laboratory evidence of perimenopause and menopause such as elevated follicle-stimulating hormone helpful but not necessary for diagnosis
- Objective evidence of cognitive change in one or more cognitive domains, greater than expected for the patient's age and educational background
- No evidence of other medical conditions or dementia

neutral benefits. Furthermore, the North American Menopause Society does not recommend HT “at any age to prevent or treat a decline in cognitive function or dementia,” although it does promote HT for vasomotor symptoms and sleep disturbances, in which relief may indirectly have a salubrious effect on memory and concentration.<sup>9</sup>

Because this report focuses on the identification and treatment of cognitive changes during the menopausal transition, the association among menopause, HT, and future risk for developing dementia is not addressed here.

Two early meta-analyses found HT to improve cognition, but only in cognitively symptomatic women.<sup>10,11</sup> However, the recent KEEPS-Cog and ELITE studies found no cognitive benefits from HT, regardless of time of HT initiation, although neither study evaluated improvement in women with pre-existing symptoms.<sup>12,13</sup>

Screening for menopause-related cognitive impairment is challenging because cognitive screens are not sensitive in this population, yet symptoms correlate well with objective cognitive loss.<sup>3</sup> Nonspecific treatment includes better sleep hygiene and aerobic exercise. Although the North American Menopause Society does not recommend HT for non-surgical cases of menopause-related cognitive impairment, some women in natural menopause experience symptom alleviation with HT. The author therefore uses short-term HT as a first-line treatment for menopause-related cognitive impairment. Cognitive remediation to address deficits may be helpful (Devi G, Marrero C. The effectiveness of cognitive rehabilitation for memory and cognitive loss associated with menopause. Presented at the annual meeting of the North American Menopause Society, October 4–6, 2001, New Orleans, Louisiana). When symptoms persist past the transition, or significantly interfere with function, referral to a specialist may be necessary.

Menopause-related cognitive impairment should be considered in the differential diagnosis of perimenopausal and menopausal women with cognitive

symptoms to prevent misdiagnosis and deleterious consequences. Appropriate treatment and a role for HT or another intervention in at least some women with significant menopause-related cognitive impairment is an area worth exploring.

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