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Cognitive Symptoms and Disorders in the Midlife Woman

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Given the high prevalence of cognitive complaints from middle-age women, it is important to identify predisposing factors and to determine when symptoms represent a potentially serious neurologic disorder rather than reflect disturbances of lesser consequence.

Forgetfulness is common during middle age. More than a third of women in the Melbourne Women's Midlife Health Project replied "yes" when asked if they had trouble recalling recent events during the preceding week.[1]

DEMENTIA, MILD COGNITIVE IMPAIRMENT, AND COGNITIVE AGING

In discussing cognitive disorders, one should distinguish among dementia, mild cognitive impairment (MCI), and cognitive aging. Dementia entails major cognitive decline that has a substantial impact on occupational activities and other aspects of usual daily living. It is distressingly common with age. By age 95, about half of the population will have dementia.

Fortunately, midlife dementia is rare. For a woman in her 50s, the estimated incidence is less than 0.1 per 1,000 person-years. Alzheimer disease and frontotemporal dementia are the prime considerations in this age-group. Roughly two-thirds of dementia after age 60 is caused by Alzheimer disease, although the importance of mixed pathologies is increasingly recognized.

Frank dementia is often preceded by a transitional stage of cognitive decline, and the term MCI is applied to patients meeting criteria believed to characterize incipient dementia.[2,3] The inference is that patients with MCI already have brain pathology associated with dementia (eg, the neurofibrillary tangles and neuritic plaques of Alzheimer disease), but the pathologic burden is modest or has not yet overwhelmed intrinsic compensatory mechanisms.

MCI was originally defined by "episodic memory" loss without dementia (Table 1).[2-4] This form of memory is tested by deliberate recollection of recent episodes or events. In the clinic, a patient may be asked to recall a short word list or a paragraph story that had been presented to her some minutes earlier.

Patients meeting criteria for MCI are at heightened risk for dementia due to Alzheimer disease. In a clinical series from the Mayo Clinic, nearly half of elderly men and women with MCI developed Alzheimer disease within a 4-year period.[2]

Declines in other areas of cognitive performance—not just memory—can also be an early indication of dementia from Alzheimer disease, vascular disease, frontotemporal dementia, or some other cause. MCI subtypes have been categorized to accommodate other cognitive domains (Table 1).[3,4]

Cognitive aging differs from MCI. It represents an erosion of existing abilities, beginning almost imperceptibly in middle age and accelerating during old age. Indi-

FOCUSPOINT

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TABLE 1. Mild Cognitive Impairment (MCI): Definition and Varieties[3,4]

MCI (original definition)

- Forgetfulness or memory loss
- Demonstrable memory impairment
- Other cognitive abilities are not impaired
- Daily activities are largely intact (implying the absence of dementia)

Varieties of MCI

- *Amnestic MCI, single domain* (corresponds to original definition) or *multidomain* (affecting cognitive skill[s] in addition to episodic memory)
- *Nonamnestic MCI* (not affecting episodic memory), *single domain* or *multidomain*

vidual rates of change can vary, and many among the very elderly maintain cognitive skills remarkably well. The presumption is that cognitive aging reflects processes largely distinct from those that culminate in defined dementias with characteristic brain pathologies. Not everyone agrees, however, that cognitive aging is easily separated from disease processes that determine MCI and dementia..

MENOPAUSE AND MIDLIFE COGNITION

When forgetfulness emerges during the menopause transition or early postmenopause, one might wonder whether symptoms should be attributed to loss of ovarian hormones. However, the link between circulating levels of estradiol and cognitive impairment is weak, and clinical trials of midlife hormone therapy have not shown improved cognition.[5] This conclusion is supported by cross-sectional and longitudinal research within defined cohorts of midlife women, where evidence indicates that episodic memory performance is similar before and after natural menopause.[4]

Findings from the Study of Women's Health Across the Nation offer a nuanced perspective.[5] In this large study, women in the menopause transition, compared to premenopausal women, showed statistically nonsignificant trends for less improvement (loss of a practice effect) across annual test sessions on some cognitive tasks. By early postmenopause, these subtle trends were no longer present. If indeed learning, as inferred from these trends, is less efficient during the perimenopause, then cognitive symptoms during this time may reflect awareness of cognitive inefficiency, even if measurable effects are small and transient.

Cognitive consequences of menopause induced by bilateral oophorectomy, cancer chemotherapy, or irradiation may differ from outcomes of natural menopause. Immediately after oophorectomy, small short-term trials suggest that estrogen therapy may improve or maintain episodic memory. Moreover, oophorectomy at a relatively young age is associated with increased risk of cognitive impairment or dementia later in life.[6]

As shown by Women's Health Initiative (WHI) researchers, beginning hormone therapy later in life (after age 65) increases the risk of dementia.[7] Observational studies generally imply reductions in Alzheimer disease risk from hormone use. What might account for this discrepancy? Women in observational studies have tended to use hormones at younger ages than participants in the WHI memory trial, raising the important question of whether midlife estrogen use could protect against late-life cognitive impairment.[8] This answer is unknown. Because observational findings could be misleading (recall bias and the healthy user bias tend to favor hormone users), the long-term cognitive implications of midlife hormone use are unresolved. The North American Menopause Society does not recommend hormone therapy for cognitive symptoms or to prevent dementia.[9]

COGNITIVE SYMPTOMS: RELATION TO COGNITIVE DISORDERS

It is understandable if symptoms of forgetfulness raise concern of early Alzheimer disease. However, dementia is rare during middle age, and converging evidence suggests that midlife is not a time of particular vulnerability (Table 2).[10] Memory complaints are common at any age and affect men as well as women.

In some instances, awareness of mild changes reflective of cognitive aging—or possibly reflective of transient changes occurring during the menopause transition[6]—is misconstrued as a harbinger of dementia.

TABLE 2. Midlife Forgetfulness: Reminders for Worried Patients[10]

- Dementia is rare during middle age
- The perception of forgetfulness is common at other ages
- Levels of estradiol during middle age are unassociated with memory test scores
- The natural menopause transition is unassociated with memory decline
- The perception of forgetfulness during middle age is unassociated with measurable memory decline

The temporary inability to retrieve the name of an acquaintance or movie actor, or forgetting why one has entered a room, does not reflect impairment in episodic memory. These common forms of forgetfulness are of less concern than episodic memory loss, because of the latter's association with Alzheimer disease.

Finally, perceived memory loss is not equivalent to demonstrable memory loss. Indeed, subjective forgetfulness is often not closely linked to objective measures of poor memory. For midlife women, depressed mood, anxiety, and stress may be stronger determinants of cognitive symptoms than objective memory loss.[11,12]

EVALUATION OF MIDLIFE COGNITIVE COMPLAINTS

The evaluation of cognitive symptoms during middle age differs somewhat from the approach during old age, when dementia is far more common. It is useful first to gauge the functional impact of cognitive symptoms. Do cognitive problems interfere with job performance, financial affairs, or social activities? The availability of a family member or other surrogate informant is quite useful in these assessments. When functional deficits are clear-cut, a family history of midlife dementia raises suspicion of Alzheimer disease or frontotemporal dementia.

Although most gynecologists and primary practitioners have neither the time nor staff for detailed cognitive testing, it is sometimes useful to screen episodic memory skills, impairments of which are a clue for early Alzheimer disease. (Personality and behavioral change, rather than memory loss, are more common early presentations for frontotemporal dementia.) Memory screening should consider the richness and apparent accuracy of details provided by the patient as she conveys her recent medical history. More formally, the clinician can administer a brief test of episodic memory. This might include providing a list of words or a name and address for later recall. Short cognitive batteries such as the familiar Mini-Mental State Examination, apart from items that assess episodic memory, are of modest added value when impairments are mild and are unaccompanied by functional decline.

More detailed evaluation by a neuropsychologist is useful when the medical history raises concern of functional impairment or when screening procedures suggest objective memory impairment. Neurologic consultation is helpful when cognitive loss is clear-cut or when there are other neurologic symptoms or signs.

It is equally useful to consider factors that might contribute to cognitive complaints (Table 3). Among these, midlife stressors are worth exploring. Occupational demands, adolescent children, the "empty nest" syndrome, aging parents, marital accommodations, personal health concerns, and financial challenges are inherently stressful. Such stressors affect mood and sleep, as can menopausal vasomotor symptoms. Depressed mood in turn affects the perception of one's cognitive abilities; both daytime

TABLE 3. Factors Affecting Memory Symptoms During Midlife

- Cognitive aging
- Stress
- Fatigue
- Depression
- Sleep disorders
- Hot flashes
- Medication effects
- Medical illness (eg, thyroid disease)

FOCUSPOINT

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sleepiness and depressed mood can blunt mental acuity.

When anxiety or depression is detected, psychologic or psychiatric referral can be helpful. When a sleep disorder is suspected, referral to a specialized sleep disorder center should be considered. Other forms of career, lifestyle, and marital counseling are warranted on occasion.

PREVENTION: INTRODUCTION TO AN APPROACH

Cognitive impairment and dementia are linked to health and lifestyle factors. Although associations are largely based on observational research, these factors suggest areas for intervention. Midlife, before the usual ages of MCI or dementia, is none too soon to begin. In the WHI memory study, women ages 65 to 79 were far more likely to develop dementia if baseline cognitive function was low prior to treatment randomization. One approach to the reduction of late-life cognitive disorders is thus to devise strategies to maintain cognitive skills through midlife and into old age.

Especially worth emphasizing are physical activity, mental activity, and social engagement. The cognitive reserve hypothesis of dementia predicts that boosting these activities would augment brain reserve capacity.[13] The net effect may be to enhance neural efficiency and enable coping mechanisms that mitigate effects of aging and disease predisposing to dementia. Proper nutrition is also important. Disappointing results in some nutritional supplement trials suggest that the complex combination of nutrients in natural foods are usually more effective than vitamin, mineral, fatty acid, protein, and phytonutrient supplements.

Perhaps the best preventive strategy for cognitive maintenance hews closely to common wisdom: Eat right, exercise (physical and mental), minimize stress, and strive for balance in a socially fulfilling life.

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