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Alzheimer Disease in Women and the Role of Estrogens

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IN MANY WAYS, WOMEN AGE SUCCESSFULLY. IN virtually all species in which there is a difference in longevity, the female lives longer than the male. In humans, as a result of the additional seven to eight years of life span for a woman, two-thirds of the U.S. population are female by the age of 75, with increasing proportions as people approach 100 years of age.

Alzheimer disease (AD) is one of the most frequent obstacles to successful aging, affecting an estimated 4 million people in the United States. Although age-specific incidence rates are fairly similar for men and women, approximately two-thirds of all AD patients are women (prevalence), reflecting their greater numbers in the elderly population and their longer life span even when they have AD (1). Differences in the clinical expression, genetics, and treatment of the illness in women have been described. In this chapter we discuss some of these differences and potential new therapeutic options, particularly the estrogenic compounds, for the growing numbers of women with the disease.

DEFINITION, DIAGNOSIS, AND CLINICAL FEATURES OF ALZHEIMER DISEASE

In 1907 Alzheimer described the first patient, a 51 year-old-woman, with the disease that bears his name (2). Until the early 1980s the diagnosis of AD was usually applied only to cases of dementia with onset before age 65; those patients with onset after 65 years of age were classified as having senile dementia. These definitions have changed markedly, and diagnosis is now determined largely by clinical and neuropathologic characteristics rather than by age of onset. A gradually progressive loss of cognitive function for more than six months, affecting memory and at least one other area of cognition (e.g., language, visuospatial skills, praxis, executive function), is consistent with the diagnosis of the dementia syndrome (DSM-IV) (Table 12–1) (3). The differential diagnosis of dementia is extensive. Delirium and other causes of dementia must be excluded in order to consider AD as the etiology of the syndrome (Table 12–2).

TABLE 12–1

DSM-IV DEFINITION OF DEMENTIA

- Loss of cognitive abilities, including:
  - memory
  - one or more of the following:
    - — agnosia
    - — aphasia
    - — apraxia
    - — disturbance in executive functioning
- Significant impairment in social or occupational functioning (decline from a previous level)
- Deficits do not occur exclusively during the course of delirium

TABLE 12–2

DSM-IV DEFINITION OF DELIRIUM

- Disturbance of consciousness with reduced ability to focus, sustain, or shift attention
- A change in cognition (such as memory deficit, disorientation, language disturbance)
- Develops over short periods of time (usually hours to days)
- Tends to fluctuate
- A toxic, metabolic, infectious, or other medical cause can often be identified

At present, the NINCDS-ADRDA criteria (4) allow 85 percent to 95 percent accuracy in clinical diagnosis by detailed history taking, neuropsychological testing, and a relatively limited workup, summarized in Table 12–3. To make a diagnosis of probable AD with these criteria, the patient should have the insidious onset of cognitive loss (generally including memory) with a gradually progressive course, and no other illnesses that could account for the dementia. Documentation by neuropsychological testing is an important component of the diagnosis and allows the physician to follow the patient's clinical course.

In the future, diagnostic criteria for AD may require revision after subtypes (e.g., Lewy body variant) (5,6) or mixed dementias (vascular-AD) (7) are better defined. The establishment of internationally accepted diagnostic criteria has provided investigators with well-defined and homogeneous groups of patients, leading to a much greater understanding of AD. A correct clinical diagnosis is also important for the practicing physician. On the one hand, it avoids missing potentially treatable conditions by classifying them as AD. On the other hand, as our understanding of AD expands, additional information on prognosis, expected clinical course, and management can be passed on to caregivers. New treatments are being developed and are likely to become increasingly specific for AD as our understanding of its pathophysiology improves.

An extensive description of the variety of clinical manifestations in AD is beyond the scope of this chapter, and there are many excellent reviews of the subject (8,9). Table 12–4 outlines some of the common clinical manifestations of AD. In the sections that follow, we focus on aspects that are pertinent to women, from their cognitive difficulties to their behavioral and psychiatric complications.

COGNITIVE DIFFERENCES IN WOMEN WITH NORMAL COGNITION AND WITH ALZHEIMER DISEASE

For a variety of reasons, gender-related differences in cognitive performance in normal persons are difficult to quantify. Neuroanatomic differences have been demonstrated in both volume and neuronal density in the cortex (10–13). For example, women have been shown to have larger left superior temporal and left inferior frontal gyri (Wernicke and Broca areas) and especially the planum temporale, one of the more important regions in language function (13). Such differences may account, at least in part, for the slight verbal superiority of women at all ages that is observed with standard tests of intelligence and memory, with men performing better on visuospatial tasks (14–22). Additionally, in language activation tasks of the frontal cortex, functional imaging studies suggest gender differences in the degree of lateralization of specialized functions, with language less dependent on the left hemisphere and visuospatial functions less dependent on the right hemisphere in women (23).

There are confounding issues, however, in studies of gender-related differences in cognitive performance, including, for example, choice of population and testing batteries. The widely used Mini-Mental State Examination (MMSE) (24) for cognitive function relies heavily on language skills, so that subjects who have poor verbal skills score worse; it is also influenced by demographic factors such as age, education, and socioeconomic status—factors that often are different for women (25–29).

In patients with AD, significant gender differences have been described on the MMSE: geographic orientation items (county, city, and address) and an auditory comprehension item (folding a piece of paper) were performed more poor-

TABLE 12–3

WORKUP FOR DEMENTIA

History

Particularly of events or medical conditions that might cause other dementias or delirium (e.g., strokes, thyroid disease, etc.)

Family History

Of dementia or other neurologic and neurodegenerative diseases

Physical Examination

Particular attention to:

- Hearing
- Vision
- Mental status
- Neurologic examination

Routine Blood Determination

Metabolic screen	CBC	ESR
Thyroid function	B_{12}	RPR/FTA
Renal function	Folate	

Psychometric Testing

Neuroimaging

- CT scan usually sufficient for screening
- MRI is recommended if history and/or examination suggests presence of structural lesions (e.g., tumors, strokes, multiple sclerosis, etc.)

Special Tests

In selected clinical situations additional testing may be necessary

- EEG (suspected seizures or delirium)
- EKG, echocardiogram (cardiac dysfunction, strokes)
- Lumbar puncture (multiple sclerosis, syphilis, meningitides)
- HIV serology (AIDS, dementia, PML)
- Lyme serology (Lyme disease)
- Protein C & S, antithrombin III (multiple unexplained strokes)
- Vasculitis/connective tissue disease workup (multiple strokes)
- SPECT scan (differential diagnosis of frontal dementias, pseudodementia)
- Parathormone, cortisol, etc. (suspect other endocrinopathies)
- Genetic testing (Huntington disease, early onset FAD)
- Brain biopsy (Jacob-Creuzfeldt disease)
- Cancer workup (limbic encephalitis)

TABLE 12–4

CLINICAL FINDINGS IN EACH STAGE OF ALZHEIMER DISEASE

Early Stages

- Memory—new learning defective, remote recall mildly impaired
- Visuospatial skills—topographic disorientation, poor complex constructions
- Language—poor word list generation, anomia
- Personality—indifference, occasional irritability
- Psychiatric features—sadness or delusions in some
- Motor system—normal
- EEG—normal
- CT/MRI—normal

Middle Stages

- Memory—recent and remote recall more severely impaired
- Visuospatial skills—poor constructions, spatial disorientation
- Language—fluent aphasia
- Calculations—acalculia
- Praxis—ideomotor apraxia
- Personality—indifference or irritability
- Psychiatric features—delusions in some
- Motor system—restlessness, pacing
- EEG—slowing of background frequency
- CT/MRI—normal or ventricular dilatation and sulcal enlargement

Advanced Stages

- Intellectual functions—severely deteriorated
- Motor system—limb rigidity and flexion posture
- Sphincter control—urinary and fecal incontinence
- EEG—diffusely slow
- CT/MRI—ventricular dilatation and sulcal enlargement

Adapted from Cummings JL, Benson DF, eds. *Dementia: A Clinical Approach,* 2nd ed. Newton, MA: Butterworth-Heinemann, 1992.

ly by women, even when controlled for age, duration of symptoms, education, and family history of dementia (30). Many of the MMSE items depend on semantic memory, yet not all showed gender differential performance (e.g., geographic orientation items revealed low scores in women, whereas naming did not). Other studies, however, document a disadvantage in naming abilities in women with AD (31–33). Alzheimer disease affects language more severely in women (34), independent of severity of illness or demographic variables. Although Ripich and associates found no gender differences on language measures in a group of

control elderly individuals, after correcting for demographic variables and duration of illness, women with AD performed significantly more poorly than men on the Boston Naming Test (35) and the Peabody Picture Vocabulary Test-Revised (36), but not in other cognitive domains (37). Similar findings were reported by Padovani and co-workers in a study conducted in Italy, providing additional evidence that this finding is not related to ascertainment bias and cultural and language-related factors (38).

These findings suggest that women have a slight verbal superiority, but in the presence of AD this advantage disappears in the very early stages of the disease. Subsequently, language (and/or semantic memory that heavily relies on language) becomes disproportionately more affected in women. Whether these differences reflect a different pattern of neuronal organization in the two sexes, which in turn might influence patterns of language breakdown, is unclear. Conversely, AD might affect women differently on the basis of the hormonal environment or yet other unexplored factors.

BEHAVIORAL AND PSYCHIATRIC COMPLICATIONS

There is increasing recognition of the noncognitive behavioral and psychiatric problems in AD that contribute to the caregiver's stress and the patient's likelihood of institutionalization (39,40). The reported prevalence rates of disruptive behavior vary largely, depending on the methodology, from 40 percent to more than 80 percent (41–44). Although depression frequently occurs in the early stages of the disease, most studies suggest that other behavioral disturbances are more likely to occur with increasing severity of dementia (43,45–47).

Behavioral Problems

Perhaps in keeping with premorbid gender differences in personality, women have somewhat different behavioral expression of AD symptoms such as agitation, aggression, and psychomotor abnormalities. Mild agitation may be the most common behavioral probem in women, with prevalence as high as 46 percent (46,48). A community-based study by Cohen and associates showed that agitation in women frequently appears concurrently with multiple psychiatric signs and symptoms, including depression, paranoid delusions, and hallucinations (49). Women generally have lower rates of aggression but higher rates of other disruptive behaviors (50). Among nursing home residents, women are likely to show greater functional and cognitive impairment and have a higher prevalence of abnormal behaviors in general (43,49).

Although psychomotor abnormalities are present in as many as 90 percent of community-dwelling AD patients (restlessness, pacing, repetitive sorting of objects, following caregivers, wandering, and hyperkinesia or bradykinesia), no gender differences have been reported (42,43,50–53). Similarly, no clear gender differences have been described in the vegetative disorders that affect 75 percent to 85 percent of AD patients, including urinary incontinence, hypo- or hypersexuality, restless sleep, and appetite changes (50).

Psychopathology

Depressed mood is one of the most frequent behavioral complications, particularly in the early stages of AD (54–56), and occurs more commonly in women (49, 56–58). Although 10 percent to 30 percent of AD patients meet criteria for Major Depressive Disorder (56,59,60), the diagnosis is problematic. Symptoms of decreased concentration, vegetative changes and apathy, abulia, and psychomotor retardation may be present irrespective of a comorbid depressive syndrome. Low mood and dysphoria in AD are often inconstant and are sensitive to modifications in the environment (46, 61). Families report the presence of depressed mood more commonly than do patients themselves (55,62). Depression can adversely affect the patient's functional and cognitive status (60, 63–65) and should be treated aggressively with medications and other measures.

Changes in personality, disorders of thought content, and perceptual disturbances have all been reported in AD, but no clear gender differences are reported (50,66).

Delusions may be more common in women (46), but generally no gender differences are reported in the prevalence of hallucinations, which are most commonly visual.

GENETIC FACTORS

Family History of Alzheimer Disease in Women

The risk of developing AD in first-degree relatives is increased, with estimates ranging from 23 percent to 81 percent greater than in those without a family history. In

several series, the risk of developing AD appears to be higher for female relatives (67–70). Alzheimer disease has been classified as sporadic and familial. Familial AD (FAD) (having an affected first-degree relative) may account for up to 50 percent of all cases (71–73), but the described mutations on chromosomes 21,14, and 1 account for less than 5 percent of all AD cases (74–84).

Of particular relevance to women, mutations in mitochondrial DNA (Mt-DNA) genes, which code for various enzymes of the respiratory chain, have been described in aging and AD (85,86), and indeed oxidative metabolism in AD brains is impaired (87). Mt-DNA is inherited mostly and directly from the mother. Maternal inheritance could, in part, explain the unusual pattern of inheritance seen in many families (85). Mt-DNA, however, is likely to accumulate mutations during the lifetime of the cell because its repair mechanisms are less efficient than those of genomic DNA. Mutations in Mt-DNA therefore may be a consequence, rather than the cause, of cellular aging.

The Risk Represented by ApoE in Women

From a population standpoint, one of the most important genetic discoveries in recent years has been the description of an overrepresentation of the e4 allele of the apolipoprotein E gene (ApoE) in AD (88–90). The gene coding for ApoE, a lipid transport protein, localizes on chromosome 19 and has three alleles, e2, e4, and e3, the last being by far the most frequent (91). Almost 50 percent of sporadic cases of AD (90) and more than 65 percent of late-onset FAD cases (88) carry the e4 allele, compared with 15 percent to 20 percent in the normal population (88,92–94). The risk of AD appears to increase and the age of onset to decrease with the number of e4 alleles carried by an individual (92,95), and this effect is maximal for cases with onset before age 70 (96).

In one family history study, women heterozygous for the e4 allele had twice the risk of developing FAD than did heterozygous men, a risk comparable to that of homozygous women and men (97). In a cohort of late-onset AD patients with both familial and sporadic AD, women had a reduced age of onset if they were positive for the e4 allele and had a family history of dementia. For the e4 positive probands, the number of sisters and mothers affected was significantly greater than the number of affected brothers or fathers. Additionally, the e4 positive probands were more likely to inherit the disease from their mothers than from their fathers (98). These findings suggest that gender may be an independent risk factor mostly in FAD and not in sporadic AD, which might explain some of the discrepancies of previous epidemiologic studies. Interactions between gender and ApoE genotype may also affect the duration of survival in patients with AD. We found that the presence of the e4 allele is associated with shorter survival in men but not in women (99).

THE ROLE OF ESTROGENS IN ALZHEIMER DISEASE

Estrogenic compounds hold promise for the prevention and possible treatment of Alzheimer disease. Results from recent epidemiologic studies suggest that the risk of developing AD may be 45 percent lower in women with a history of estrogen replacement therapy (ERT) compared with women without such a history (100,101). In nondemented postmenopausal women, ERT seems to ameliorate age-associated declines in cognition and to improve memory in women diagnosed with AD. Moreover, a growing body of scientific data suggests a number of biologic mechanisms through which estrogen could protect against the development of AD.

Epidemiologic Studies

Evidence that ERT may protect against the development of AD comes from recent, large sample, case control studies demonstrating that women with AD are less likely to have received ERT than are women without the disease. This has been documented in four studies in which ERT use was documented after disease onset (102–105) and, more convincingly, in three of four studies in which ERT use was documented before disease onset (100,101,106). The fourth study found no protective effect when both oral and vaginal forms of treatment were considered, but it did find a mild protective effect when only oral conjugated equine estrogens were considered (107). The only one of these studies to investigate women with ischemic vascular dementia found that they were also less likely to have received ERT treatment (105). The risk for AD may decrease with increased dose (106) and may be lower in women who have a history of ERT and smoking (104).

Two cohort studies provide perhaps the most compelling evidence that ERT protects against AD. In both studies, ERT history and dementia status were ascertained prospectively. Tang and colleagues (101) followed an ethnically diverse cohort of 1,124 women from a

community-based study of aging in Manhattan and concluded that ERT lowers the risk of the disease by delaying disease onset. The risk was especially lowered in those receiving ERT for longer than a year. Kawas and colleagues (100) also found a lower risk of AD in women with a history of ERT in a well-educated, mostly white cohort of 514 women observed for up to 16 years in the Baltimore Longitudinal Study of Aging.

Although these studies suggest that ERT may lower the risk of AD, more conclusive support from intervention studies is lacking. Data from the Women's Health Initiative will greatly enhance our understanding of the relationship between ERT and AD. The influence of dose, duration, and type of ERT on AD has not been clearly established, although increases in dose and duration seem to lower the risk of AD, and most studies suggest that conjugated equine estrogens provide protection against the disease.

Estrogen Replacement Therapy and Cognition in Nondemented Women

Estrogen appears to be important in the maintenance of cognitive abilities and emotional well-being in postmenopausal women, although some studies fail to show such an effect (108,109). After the menopause, estrogen levels drop to approximately 12 percent of the levels found during fertility. Among women with menopause after oopherectomy, those who receive ERT show a preservation of cognitive abilities over time, whereas those who receive placebo show a decline (110,111). Four studies in which ERT was not randomized also demonstrated improved cognitive function in ERT users compared with nonusers (112–115), although one study did not (116). The changes in performance associated with ERT are typically modest—one to two points on a memory test—and occur most commonly on neuropsychological tests of verbal memory, such as tests of paragraph recall and paired-associates. The selective effect of ERT on memory but not on other cognitive abilities suggests that the improvements are not due to improvements in mood or physical symptoms.

Estrogen as a Treatment for AD

Studies of ERT in women diagnosed with AD have involved small numbers of subjects and a limited number of outcome measures, but they do suggest that ERT may be a useful treatment for AD. The seminal investigation (117) suggested that Estrace (2 mg per day) may improve cognition in women with mild dementia, low serum levels of ERT, or osteoporosis. Later studies suggested that conjugated equine estrogens (0.625 or 1.25 mg per day) also lead to improved cognition on standardized clinical measure of dementia status, on average in approximately 60 percent of patients studied (118–121). In one study, women who received progesterone for a portion of each cycle showed physical declines during that phase (122). Transdermal estrogen may also be effective in treating AD (123). The combined use of ERT and tacrine may be more effective than estrogen alone in treating the symptoms of AD (124), although confirmation of this awaits clinical trials in which both medications are randomized.

Although the bias against publishing studies that show no treatment effect should temper the conclusions drawn from these few, small-scale studies, the extant literature suggests that ERT may be effective in treating the symptoms of AD and that progesterone may be ineffective or deleterious. ERT has not received FDA approval for the treatment of AD.

The Influence of Estrogen on the Brain

A growing body of the literature documents the effects of estrogen on neurons in brain regions that are involved in the pathogenesis of AD (125). Like tacrine and donezepil, the two FDA-approved treatments for AD, estrogen seems to enhance cholinergic transmitter activity. In the basal forebrain, estrogen receptors colocalize with nerve growth factor receptors (126), and estrogen administration promotes the development of cholinergic neurons (127). In this way, estrogen may enhance survival and growth of neurons vulnerable to AD. Hippocampal neurons respond to estrogen with increases in choline acetyltransferase activity (128), increases in the density of dendritic spines (129), and prolongation of long-term potentiation (130). Deficits in choline acetyltransferase activity in the hippocampus and frontal cortex of ovariectomized rats occur with deficits in memory and learning tasks but are offset by treatment with ERT (131).

The mechanisms by which estrogen may serve to prevent and treat AD extend beyond its effects on cholinergic transmission. It acts on other neurotransmitters, including serotonin (132), norepinephrine (133), and dopamine (134). Estrogen affects the cerebrovasculature by increasing cerebral blood flow (120), most likely by inhibiting endothelin, a powerful vasoconstrictor, and by stimulating endothelial-derived relaxing factor, a vasodila-

tor (135). Women with a history of ERT show a lower rate and extent of white matter hyperintensities on magnetic resonance imaging (MRI) (136). Estrogen lowers apolipoprotein E levels in plasma (137). Estrogen may reduce the formation of senile plaques by modifying the processing of amyloid precursor protein to diminish the deposition of insoluble beta amyloid in neurons (138). The antioxidant effects of estrogen (139) are noteworthy in light of theories that oxidative stress contributes to the development of AD. Any one or a combination of these factors may contribute to the apparent decreased risk of AD associated with ERT.

CONCLUSION

Patients with the diagnosis of AD are more likely to be women, many of whom have outlived their spouses. Recent research, including research on hormonal replacement, is providing important information that may ultimately prevent, or at least delay, the devastation that is AD in men and in women.

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