Onset of Dementia Is Associated with Age at Menopause in Women with Down's Syndrome

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Women with Down's syndrome experience early onset of both menopause and Alzheimer's disease. This timing provides an opportunity to examine the influence of endogenous estrogen deficiency, indicated by age at menopause, on risk of Alzheimer's disease. A community-based sample of 163 postmenopausal women with Down's syndrome, 40 to 60 years of age, was ascertained through the New York State Developmental Disability service system. Information from cognitive assessments, medical record review, neurological evaluation, and caregiver interviews was used to establish ages for onset of menopause and dementia. We used survival and multivariate regression analyses to determine the relation of age at menopause to age at onset of Alzheimer's disease, adjusting for age, level of mental retardation, body mass index, and history of hypothyroidism or depression. Women with early onset of menopause (46 years or younger) had earlier onset and increased risk of Alzheimer's disease (AD) compared with women with onset of menopause after 46 years (rate ratio, 2.7; 95% confidence interval [CI], 1.2–5.9). Demented women had higher mean serum sex hormone binding globulin levels than nondemented women (86.4 vs 56.6 nmol/L, $p = 0.02$), but similar levels of total estradiol, suggesting that bioavailable estradiol, rather than total estradiol, is associated with dementia. Our findings support the hypothesis that reductions in estrogens after menopause contribute to the cascade of pathological processes leading to AD.

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Several lines of evidence suggest that the loss of estrogen in the perimenopausal period and after menopause may play a role in the cognitive declines associated with AD. Before menopause, estrogen promotes the growth and survival of cholinergic neurons,^{1,2} increases cholinergic activity,³ has antioxidant properties,⁴ and promotes the nonamyloidogenic metabolism of the amyloid precursor protein.⁵⁻⁷ In an animal model, ovariectomy led to increased levels of amyloid beta peptides A β 1-40 and A β 1-42 in the brain, and this effect was partially reversible with exogenous estrogen treatment.^{8,9} In some, but not all, observational studies, postmenopausal women who used estrogen replacement therapy (ERT) showed slower declines in cognitive function and decreased risk of AD compared with women who never used ERT.¹⁰⁻²⁰ Alternatively, ERT use may be associated with protective factors such as

higher educational levels and better access to medical care,²¹ and these, rather than ERT use per se, may be the factors that caused these effects. Studies of endogenous estrogen are important to distinguish between these alternatives and to understand the role of estrogen in the pathogenesis of AD. Only a few studies have examined the relationship of endogenous estrogen levels to cognitive decline in healthy women or to risk of AD, and the results have been inconsistent.²²⁻²⁷

The relationship between menopause and AD is difficult to study in the general population because of the extended time period that elapses between menopause, which typically occurs at 51 years of age,^{28,29} and onset of AD, which typically occurs after age 70 years. In contrast, adults with Down's syndrome (DS) have a much earlier onset of AD. Virtually all subjects with DS have the neuropathological changes characteristic of AD,

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including deposition of β -amyloid in diffuse and neuritic plaques, by age 35 years.³⁰ The increased risk of AD neuropathology in DS may be caused, at least in part, by triplication and overexpression of the gene for amyloid precursor protein, located on chromosome 21, leading to the accumulation of cerebral β -amyloid.^{31,32} Women with DS also experience early menopause and have an increased risk for AD onset beginning in their late 40s and early 50s.^{33,34} Thus, many women with DS experience onset of AD more closely in time to their onset of menopause than is typical in the general population. This timing provides an opportunity to examine the influence of endogenous estrogen deficiency, indicated by age at menopause, on risk of AD.

One previous study found a correlation between age at menopause and onset of AD in women with DS,³⁵ but the number of dementia cases was low and supporting hormonal data were not available. In addition, the presence of the apolipoprotein E (ApoE) $\epsilon 4$ allele is associated with earlier age at onset and increased risk of AD in adults with and without DS.^{36–38} Therefore, the relation between age at menopause and onset of AD might be stronger in women with the $\epsilon 4$ allele. This study was designed to examine the relation of age at menopause to age at onset of AD, to determine whether this association is modified by the presence of the ApoE $\epsilon 4$ allele, and to determine the relation of hormone levels to dementia status. We hypothesized that earlier onset of menopause would be associated with earlier onset of AD.

Subjects and Methods

Subjects

A community-based sample of 163 postmenopausal women with cytogenetically confirmed DS, 40 to 60 years of age, and residing in New York State was ascertained from the statewide service system and recruited with the help of state and voluntary service provider agencies. Subjects were eligible to participate in the study if they had a family member or correspondent who could provide informed consent. Informed consent was signed by a parent or correspondent, and subjects also signed a form acknowledging their willingness to participate. The participation rate was 74.6%. Recruitment, informed consent, and study procedures were approved by the institutional review boards of the New York State Institute for Basic Research in Developmental Disabilities and Columbia Presbyterian Medical Center and Columbia University Health Sciences.

Clinical Assessment

Clinical assessments included evaluation of cognition and functional abilities, and ascertainment of psychiatric conditions and health status. Assessments were repeated at 14 to 18-month intervals for two to three cycles of data collection to document declines over time. Cognitive status was evaluated with a test battery used to assess cognitive functions that are typically affected in AD, using standardized instruments for detecting dementia in adults with mental retardation. The cognitive assessment battery consisted of the Down Syndrome Mental Status Exam,³⁹ the IBR Mental Status

Exam,⁴⁰ a modified Selective Reminding Test,⁴¹ the Peabody Picture Vocabulary test,⁴² Verbal Fluency Test,⁴³ Visual-Motor Integration test,⁴⁴ the WISC-R Block Design,⁴⁵ and the Test for Severe Impairment.⁴⁶ Adaptive and maladaptive behaviors were assessed in caregiver interviews using the AAMR Adaptive Behavior Scale,⁴⁷ the Dementia Rating Scale for Mentally Retarded Persons,⁴⁸ and the Reiss Screen for Maladaptive Behavior.⁴⁹ Past and current medical records were reviewed for all participants. Structured interviews were conducted with caregivers to collect information on changes in cognitive function, adaptive behavior, and medical history. Participants showing declines in cognition or in adaptive behavior were evaluated by the study neurologist to determine the presence of dementia and determine the presence or absence of medical or psychiatric conditions other than AD that might result in or mimic dementia. These procedures were consistent with recommendations developed by the Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Intellectual Disability.⁵⁰

Classification of Age at Menopause

Age at menopause was ascertained by medical record review, interviews with caregivers and family members, and survey of the participants' primary care physicians and gynecologists. The medical records included menstrual charts documenting the date and duration of menses. The correlations between age at menopause ascertained from the different sources were substantial, suggesting that ascertainment of age at menopause was reliable. The correlation between age at menopause ascertained from medical records, including menstrual charts, and from physician survey was 0.99; the correlation between age at menopause ascertained from medical records and from informant interviews was 0.77; and the correlation between age at menopause ascertained from physician survey and from informant interview was 0.80. The mean difference in age at menopause from the different sources ranged from 0.21 years (± 2.8) for the difference between age at menopause ascertained from medical chart and from physician survey to 0.38 years (± 2.9) for the difference between age at menopause ascertained from medical charts and from informant interview. We used a consensus age at menopause, with greater weight given to age at menopause ascertained from medical records, then physician survey, then informant interviews. In keeping with convention, we classified age at natural menopause as the age at the last menstrual period preceding cessation of menses for 12 months, in the absence of known causes of amenorrhea (eg, surgery). The median age at menopause was 46.0 years (range, 35–52). For analysis of AD risk associated with age at menopause, we split at the median to classify women as experiencing "early" (≤ 46 years) or "late" (> 46 years) age at menopause. Sixteen women had menopause at age 46 years, and they were all included in the "early" menopause group. Ascertainment of age at menopause was done blind to dementia status, and any misclassification of age at menopause is likely to have been nondifferential for dementia status.

Classification of Alzheimer's Disease

Classification of AD was made in consensus conferences during which the presence or absence of dementia was determined and a cause of dementia was assigned. To ascertain the occurrence of AD, we reviewed information from all available sources, includ-

ing cognitive test scores, medical history, neurological evaluation, and informant-based interviews. We used International Classification of Diseases–10 criteria for dementia.⁵¹

We classified participants into three groups. (1) Participants were classified as demented if there was a history of progressive memory loss, disorientation, and functional decline over a period of at least 1 year, if no other medical or psychiatric conditions that might result in or mimic dementia were present (eg, untreated hypothyroidism), and if a clinical diagnosis of AD had been made by a neurologist or psychiatrist familiar with this population ($n = 33$). To be classified as demented, participants had to meet criteria for dementia based on the cognitive assessment. These included a decline of at least 20% on the Selective Reminding Test, a decline of at least 15% on the Adaptive Behavior Scale, and evidence of decline in one other area of cognition. (2) Participants were classified as nondemented if they were without cognitive or functional decline and without a clinical diagnosis ($n = 104$). (3) Participants were classified as uncertain if they showed some cognitive or functional decline but had no clinical diagnosis or caregiver concern; if there was caregiver concern about decline in function but only small declines in cognitive test performance or adaptive abilities ($n = 18$) or if they had other conditions that might cause dementia (ie, untreated hypothyroidism, brain tumor, schizophrenia, stroke, depression/anxiety, $n = 8$). Age at clinical diagnosis was used to estimate age at onset of AD, recognizing that it is difficult to document the onset of initial symptoms in this population with precision. However, this is unlikely to influence our findings systematically because classification of AD was made without knowledge of age at menopause or hormone levels.

Apolipoprotein E Genotypes

ApoE genotyping was conducted as described in a previous study.³⁷ A 10ml sample of whole blood was collected in an EDTA lavender-top tube. ApoE genotype was determined by a standard polymerase chain reaction restriction fragment length polymorphism method using *Hha*I (*Cfo*I) digestion of an ApoE genomic polymerase chain reaction product spanning the polymorphic (cys/arg) sites at codons 112 and 158. Acrylamide gel electrophoresis was used to assess and document the restriction fragment sizes. Women were classified according to the presence or absence of an ApoE ϵ 4 allele.

Serum Hormone Levels

All laboratory studies were conducted without knowledge of age at menopause or dementia status. Blood samples were collected between 10:00 AM and 3:00 PM. Blood was centrifuged in a refrigerated centrifuge and, after separation, sera were frozen at -20°C until assay. Total estradiol and estrone (free + bound) were measured by a no-extraction solid-phase ¹²⁵I-radioimmunoassay using commercial kits (Diagnostic Systems Laboratories, Webster, TX). Sensitivity or minimum detection level for estradiol was 4pg/ml, and intraassay and interassay coefficients of variation were 3.8 and 15.2%, respectively. Sensitivity or minimum detection level for estrone was 11pg/ml, and intraassay and interassay coefficients of variation were 6.3% and 15.8%, respectively. Human follicle-stimulating hormone (FSH), progesterone, dehydroepiandrosterone sulfate (DHEAS), and sex-hormone binding globulin (SHBG) were measured by immunometric assays using Immulite systems (Diagnostic Products Corporation,

Los Angeles, CA). We used two commercial controls for the SHBG assays, the first with a mean level of 4.8nmol/L and the second with a mean level of 82nmol/L. Sensitivity was 0.1mIU/ml for FSH, 0.2ng/ml for progesterone, 30 μg /dl for DHEAS, and 0.2nmol/L for SHBG. Intraassay and interassay coefficients of variation were 6.4 and 7.5%, respectively, for FSH, 8.0 and 9.3% for progesterone, 8.2 and 12% for DHEAS, and 6.4 and 8.7% for SHBG.

Potential Confounders

Potential confounders, in addition to age, were level of mental retardation, body mass index (BMI), and past or current hypothyroidism or depression. Level of mental retardation was classified into two groups: mild/moderate (IQ 35–70) and severe/profound (IQ <34), based on IQ scores obtained before onset of dementia. Nutritional status and BMI have been associated with increased serum estradiol and estrone levels in postmenopausal women^{52,53} BMI was computed as weight in kilograms divided by height in square meters (kg/m^2) and was measured at each assessment. The history of past or current of hypothyroidism and depression was ascertained by medical record review. All women with a history of hypothyroidism were being treated with synthroid.

Statistical Analyses

We excluded from the analysis women who had never menstruated ($n = 3$), women with other causes of dementia ($n = 8$), those with uncertain dementia classification (ie, with signs or symptoms of cognitive decline consistent with mild cognitive impairment: $n = 18$), and those for whom we were unable to obtain age at menopause ($n = 23$). The final sample comprised 81 nondemented postmenopausal women and 30 demented postmenopausal women. Blood samples for hormone analyses were available for 93 women (84%), and ApoE genotypes were available for 96 women (86%). Among women without a blood sample, 66% were missing a blood sample for both hormone assays and ApoE genotyping. Women with and without a blood sample did not differ in age or BMI (mean age 50.9 vs 50.7 years, respectively, and mean BMI 28.8 vs 29.0, respectively), but the proportion of women with severe mental retardation was higher among those without a blood sample than among those with a blood sample (65 vs 45%; $p = 0.03$). We used Student's t test for continuous variables and χ^2 tests for categorical variables to compare characteristics of demented and nondemented women. We used Kaplan–Meier life table methods and Cox proportional hazards models, adjusted for age, level of mental retardation, BMI, hypothyroidism, and depression to estimate cumulative incidence of AD and the rate ratio (RR) for AD in women with early versus late onset of menopause.⁵⁴ These analyses were repeated in strata defined by the presence or absence of an ApoE ϵ 4 allele. Multivariate analysis of covariance was used to compare the six measures of hormone levels by dementia status, adjusting for age, level of mental retardation, and BMI. Partial correlations and linear regression analysis were used to estimate the relation of age at menopause with age at onset of AD among demented women, adjusting for level of mental retardation. All analyses were conducted using SPSS version 11.⁵⁵

Results

Women with dementia did not differ significantly from women without dementia in age, level of mental retardation, BMI, or history of depression. The frequency of the ApoE $\epsilon 4$ allele was twice as high in demented as in nondemented women (33.3% vs 15.3%, $p = .055$) (Table 1) and demented women were significantly more likely to have a history of hypothyroidism than nondemented women (73.3 vs 48.1%, $p = 0.01$; Table 1). The mean age at menopause was similar in those with and without an ApoE $\epsilon 4$ allele (44.8 vs 45.5, respectively) and in those with and without a history of hypothyroidism (45.5 vs 45.3, respectively). The mean age at onset of AD was 50.9 (± 3.2) years, with an average interval between age at menopause and clinical diagnosis of AD of 5.3 (± 3.2) years. Women with early onset of menopause (≤ 46 years) had earlier onset of dementia compared with women with onset of menopause after 46 years (RR, 2.7; 95% CI, 1.2–5.9, Table 2, Fig 1). The median age at onset of dementia was 49.5 and 53.5 years in women with early and late onset of menopause, respectively. The presence of an ApoE $\epsilon 4$ allele was associated with earlier onset and increased risk for AD (RR, 3.0; 95% CI, 1.2–7.1). However, the relation between age at menopause and onset of AD was similar in those with and without an $\epsilon 4$ allele (RR, 3.1; 95% CI, 0.6–17.6 in those with an $\epsilon 4$ allele and RR = 2.9; 95% CI, 1.0–8.6 in those without an $\epsilon 4$ allele). A history of hypothyroidism was also associated with increased risk for dementia (RR, 2.6; 95% CI, 1.1–6.3), but, as for ApoE, the relation between age at menopause and onset of AD was similar in those with and without a history of

Table 1. Demographic Characteristics

Characteristic	Nondemented	Demented
No. of participants	81	30
Age (mean $\pm$ SD)	49.8 (3.9)	51.8 (3.0)
Level of mental retardation (n, %)		
Mild/moderate	39 (48.1)	18 (60.0)
Severe/profound	42 (51.9)	12 (40.0)
Body mass index (mean $\pm$ SD)	28.4 (6.9)	27.6 (5.5)
Apolipoprotein E $\epsilon 4$ allele (n, %)		
None	61 (84.7)	16 (66.7)
≥ 1	11 (15.3)	8 (33.3) ^a
History of hypothyroidism (n, %)		
No	41 (51.2)	7 (26.7)
Yes	39 (48.8)	22 (73.3) ^b
History of depression (n, %)		
No	73 (90.1)	26 (86.7)
Yes	8 (9.9)	4 (13.3)

^a $p = 0.055$.

^b $p = 0.01$.

SD = standard deviation.

Fig 1. Cumulative incidence of Alzheimer's disease (AD) by age at menopause group in women with Down's syndrome.

hypothyroidism (RR, 3.2; 95% CI, 1.2–8.6, and RR, 2.9 95% CI, 0.5–17.1, respectively).

Mean serum levels of estradiol, estrone, progesterone, FSH, and DHEAS, adjusted for age, level of mental retardation, and BMI did not differ significantly in demented and nondemented women (Table 3). Women with dementia had a 52% increase in mean serum levels of SHBG compared with women without dementia (86.4nmol/L vs 56.6nmol/L, $p = 0.02$; see Table 3).

Among demented women with DS, age at menopause was significantly correlated with age at onset of AD (Pearson $r = 0.54$, $p = 0.003$; Fig 2). Linear regression analysis indicated that age at onset of AD increased by approximately half a year for each yearly increase in age at menopause ($\beta = 0.53$, $p = 0.003$).

Discussion

Evidence to support the hypothesis that higher concentrations of endogenous estrogens may prevent cognitive decline and delay onset of AD has been inconsistent. In one study, healthy nondemented women older than 65

Table 2. Rate Ratio for Dementia by Age at Menopause in Women with Down Syndrome

Menopause Group	N	Demented	Rate Ratio ^a	95% CI
Age at menopause ≤ 46 yr	65	18	2.7	1.2–5.9 ^b
Age at menopause > 46 yr	46	12	1.0	Reference

^aCox proportional hazards model, adjusting for age, level of mental retardation, body mass index, and history of hypothyroidism or depression.

^b $p = 0.016$

CI = confidence interval.

Table 3. Hormone Levels by Dementia Status in Postmenopausal Women with Down Syndrome

Hormone ^a	Nondemented, N = 69 (mean $\pm$ SE)	Demented, N = 24 (mean $\pm$ SE)
Total estradiol (E ₂) level (pg/ml)	35.8 (4.8)	45.6 (8.2)
Estrone (E ₁) level (pg/ml)	31.1 (3.9)	42.0 (6.5)
Progesterone level (ng/ml)	0.30 (0.05)	0.49 (0.09)
FSH level (mIU/ml)	49.2 (3.4)	48.6 (5.9)
SHBG level (nmol/L)	56.5 (6.4)	86.5 (10.9) ^b
DHEAS level (μ g/dl)	91.8 (8.2)	79.6 (14.0)

^aMultivariate analysis of covariance, adjusting for age, level of mental retardation, and body mass index.

^b $p = 0.02$.

SE = standard error; FSH = follicle-stimulating hormone; SHBG = sex hormone binding globulin; DHEAS = dehydroepiandrosterone sulfate.

years of age with high serum concentrations of non-protein-bound and bioavailable estradiol were less likely to develop cognitive impairment than women with low serum estradiol concentrations.²⁴ Two studies reported lower serum estradiol levels in patients with AD than in age-matched controls.^{25,26} However, other studies have found no relation of serum estrogen levels to cognitive function.²² Our results are consistent with the hypothesis that reductions in estrogens after menopause can contribute to the cascade of pathological processes leading to AD and accelerate the development of AD in women at high risk for AD. We found that earlier age at menopause was associated with earlier age at onset of AD, and the relation of age at menopause to onset of AD did not change after accounting for level of mental retardation, BMI, and history of hypothyroidism or depression. Both

Fig 2. Age at onset of Alzheimer's disease (AD) by age at menopause in demented women with Down's syndrome.

the presence of an ApoE $\epsilon 4$ allele and a history of hypothyroidism were independent risk factors for AD but did not modify the association between age at menopause and age at onset of AD. The median age at onset of AD was approximately 4 years earlier in those with early onset compared with those with late onset of menopause. Levels of SHBG were significantly higher in demented than in nondemented women. SHBG binds strongly and specifically to estradiol, reducing its ability to bind to receptors and initiate responses. The high SHBG levels in demented women suggest that bioavailable or free estradiol levels, the components of serum estradiol available to exert biological activity, may be lower in demented than in nondemented women and are associated with AD. These findings are consistent with studies showing a neuroprotective effect for estrogen and point to disturbances in SHBG production or regulation, leading to reduced bioavailable estradiol, in patients with AD.

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