

## Hormonal Risk Factors for Dementia in Women with Down Syndrome

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### *Estrogen and Alzheimer's disease (AD).*

Several lines of evidence suggest that loss of ovarian steroids after menopause may play a role in the cognitive declines associated with AD. The improved performance on memory tasks and the lower risk of AD in women who have received estrogen replacement therapy observed in epidemiologic studies of women in the general population supports the hypothesis that reductions in estrogen associated with menopause may contribute to the etiology of AD (Honjo et al., 1989; Sherwin, 1994; Henderson et al., 1994; Mortel & Meyer, 1995; Tang et al., 1996). As Toran -Allerand et al. (1992) noted, conditions associated with gonadal steroid deficiency, such as menopause, may contribute to the atrophy or death of cholinergic neurons, accelerating the development of AD. Jaffe et al. (1994) suggested that estrogen acts by stimulating the activity of a nonamyloidogenic pathway for APP metabolism; this could decrease deposition of amyloid, delaying the onset of AD.

**Obesity.** Nutritional status and obesity have been associated with variation in age at onset of menopause (Stanford et al., 1987; Willet et al., 1983). Dr. Chicoine and his colleagues have found that obesity is common in adults with Down syndrome (DS) (Fujiura et al., 1997; Rubin et al., 1998). Cauley et al. (1989) found that estrone levels of obese postmenopausal women were about 40% higher than the levels of non-obese postmenopausal women. Because fat cells can store and release estrogen, obesity might delay onset of AD.

### **Nutrition and Obesity**

Nutritional status and obesity have been associated with variation in age at onset of menopause.



***Psychoactive and anti-epileptic medications.*** Neurotransmitter systems in AD are characterized by a severe deficiency of acetylcholine and decreased choline acetyltransferase activity in several forebrain nuclei (Bowen et al., 1982; Wilcox et al, 1983). Many psychoactive drugs have potent central nervous system anticholinergic activity which may accelerate or aggravate the symptoms of Alzheimer's disease (Larson et al., 1987; Gedye, 1998). Psychotropic medications can interfere also with a number of hormonal and metabolic functions. Seizures and anti-epileptic drugs (AEDs) may also influence memory and cognition through changes in neuroendocrine function and long-term AED therapy has been associated with primary gonadal dysfunction (Richens 1984; Morrell, 1991). We hypothesize that a history of psychotropic or antiepileptic medications which have anticholinergic properties or which influence hormonal regulation will accelerate the development of AD.

***Prevalence of chronic medical conditions in adults with and without DS.*** We used standardized morbidity ratios to compare the frequency of medical disorders in 278 adults with mental retardation (MR) to that in the general population (Kapell et al., 1998). Adults both with and without DS had a frequency of common age-related disorders such as diabetes, ischemic heart disease, stroke and ulcers that was similar to that in the general population, but showed an increased frequency of thyroid disorders, heart rhythm disorders and sensory impairment.

***Prevalence of obesity among adults with DS.*** We have documented the high prevalence of obesity among adults with DS (Chicoine et al., 1994; Fujiura et al., 1997; Rubin et al., 1998). This finding is consistent with the results of Prasher (1998) from a community based where the prevalence of obesity among adults with DS was 52%. In contrast, the prevalence of obesity in the general population is approximately 31% (Flegal, Carroll, Ogden, & Johnson, 2002).

## **Study Purpose and Objectives**

- 1) Determine whether age at menopause is associated with cognitive decline and age at onset of AD. We hypothesize that earlier age at menopause will be associated with earlier decline in cognitive performance and adaptive behavior and with earlier age at onset of AD.
- 2) Determine whether postmenopausal estrogen or hormonal replacement therapy (ERT/HRT) can delay the onset of AD in postmenopausal women with DS. We hypothesize that women receiving estrogen or hormonal replacement therapy have later age at onset of AD and that longer use of ERT or HRT will be associated with greater protection.
- 3) Determine the effect of common risk factors, including obesity and psychotropic or antiepileptic medications, on age at onset and risk of AD.
- 4) Determine whether they modify the influence of estrogen deficiency on decline in cognition and age at onset of AD.

## **Sample Population and Methodology**

The project conducted analyses of previously collected data that examine the effect of menopause on cognitive decline and dementia in DS.

## **Data Analysis**

An Alzheimer's protocol based on the selected tests used in the existing battery was formulated. One purpose of the study was to examine the efficacy of developing a cognitive measure that accurately assessed cognitive function in adults with Down syndrome. To accomplish this task an instrument, the Fuld, was adapted and used together with a well-standardized cognitive measure, the Woodcock-Johnson. Our intent was to investigate the extent to which the Fuld would be more sensitive to cognitive decline than the Woodcock-Johnson. That is the Fuld was being tested to determine whether it was a better

measure for assessing changes in cognitive function than other standardized measures in which persons with Down syndrome frequently “bottomed out” leaving almost no changed data available.

Additional analyses included: 1) The influence of antiepileptic and antipsychotic medications on age at menopause, and 2) Effect of menopause on cognitive function and the influence of obesity.

## Results

***Influence of antiepileptic and antipsychotic medications on age at menopause.*** We hypothesized that antiepileptic and antipsychotic medications might influence onset of menopause through stimulation of prolactin. However, hormone data on 130 pre- and post-menopausal women from Dr. Schupf’s study of Women’s Health in Down Syndrome showed no elevations of prolactin and we saw no influence of prolactin levels on age at menopause. We decided to discontinue work on this topic, because it was unlikely that our hypothesis would be supported.

***Effect of menopause on cognition and the influence of obesity.*** We conducted preliminary analyses of the effects of menopause and obesity, using domain scores from the Woodcock-Johnson test to assess cognitive function. We found that menopause affected primarily verbal, and had less effect on visual/spatial function in women with Down syndrome. We also examined the influence of obesity on cognitive function in premenopausal women with Down syndrome. We classified women as non-obese (BMI < 25), moderately obese (BMI 25.2 – 29.9) or severely obese (BMI > 30) based on Metropolitan Life Insurance Company tables.

We found that degree of obesity was associated with cognitive performance in most domains. Severely obese women performed significantly better than normal weight women, adjusting for age and level of mental retardation. The performance of women with moderate obesity was intermediate to that of

normal women and severely obese women. These findings were consistent with hormonal data on women with Down syndrome showing that estrone levels were significantly higher and follicle stimulating hormone (FSH) levels significantly lower in severely obese compared with moderately obese or normal weight women (N. Schupf, Women’s Health Study).

We conducted preliminary analyses to compare the cognitive profiles of men and women with Down syndrome. We hypothesized that differences in cognitive function may be related to differences in hormonal function between men and women with Down syndrome that are distinct from those in the general population. Among women in the general population, menopause is marked by dramatic declines in estrogen levels whereas in men peripheral aromatization of testosterone results in relative preservation of estrogens. Estrogen replacement therapy is associated with decreased risk and later age at onset of Alzheimer’s disease, suggesting an important role for estrogens in the cognitive declines associated with Alzheimer’s disease. Both men and women with Down syndrome showed elevations of follicle stimulating hormone (FSH) and luteinizing hormone (LH) at puberty indicative of primary gonadal dysfunction, which appear to progress with age and be more frequent in men than in women. Thus, adult men with Down syndrome may not benefit from the relative preservation of estrogen proposed to account for lower risk of Alzheimer’s disease in men in the general population. Consistent with these data, we found no

### **Obesity, Menopause, Cognition and Down syndrome**

Degree of obesity was associated with cognitive performance in most domains in that women with severe obesity performed significantly better than normal weight women, adjusting for age and level of mental retardation.



difference in cognitive function in post-menopausal women compared with men matched for age and level of mental retardation. Some of our findings are published in *Cognitive Neuroscience and Neuropsychology*.

The following secondary data analyses were conducted. The content of these analyses are organized into three areas of interest namely, obesity, musculoskeletal, and depression. Although we retained a focus on hormonal risk factors within these areas, we expanded our analyses to include other related hypotheses during these years.

**Depression.** We used a data set that had a substantial amount of information about depression and persons with Down syndrome. When the research protocol for our data set was being designed and instruments were selected or designed, we decided to collect data on depression because of this disorder's known association with dementia. Clinically, one of the most important differential diagnoses is between dementia and depression. The problem of depression in persons with Down syndrome has been studied in conjunction with the manifestation of dementia. Investigators who conduct research in this area tend to include the problem of depression more often than other types of mental illness because of its high prevalence rate and its assumed relationship to dementia in this and other groups of individuals who are old. Even though depression is more likely to be studied than other forms of mental illness, there remains a dearth of findings in this area and the findings from the available literature are frequently contradictory.

We used our data set to study some of the probable underlying reasons that we have contradictory findings in regards to adults with Down syndrome and depression. The first and perhaps the most profound reason is that most of the studies in this

area are theoretical. A primary tenet used in most cases when developing a research project is that it be theory driven. Relatedly, the selection of variables, instruments and hypotheses are developed in tandem with the study's theory. A major series of analyses were those that model different theories of depression.

A primary concern related to conducting these analyses was how to operationally determine the dependent variable of depression. We decided to empirically develop a dependent variable(s) of depression by analyzing our data from items that came from diagnostic scales that measured depression and other mental disorders. Most of the items addressed whether particular symptoms of depression, many of

which are listed in the DSM-IV-TR and the ICD-10, were present. To understand what hypothetical constructs might emerge from the depressive symptoms represented by items from our scales, we

### **Endogenous Estrogen Levels**

Higher endogenous estrogen levels may lower risk of cognitive decline and dementia.

conducted factor analyses. Two independent scales emerged from our analyses, both of which have alpha reliabilities in the high .8 range. One scale contained items that were typically associated with the cognitive symptom construction of depression, while the second included items that were mostly associated with the affective symptom construction of depression. A frequently voiced concern is that the presentation of depression in persons with Down syndrome might differ from that which occurs in the general population. The two scales developed from factor analyses were based on responses specifically targeted for persons with Down syndrome. As a result, these scales might represent depression in this group better than a scale that was developed from responses about persons without Down syndrome.

Our immediate goal for using these scales was to study the relationship among depression, menopause,

and cognitive status. We also included other independent variables in our analyses. These included demographic variables, musculoskeletal pain, and other variables that were in the data set and had been identified in the literature as related to depression. We completed bivariate analyses and used some of these findings to examine different theories of depression. For example, the biological theory was modeled using the differential depression outcomes relative to pre- and post-menopausal women and age-matched males. On the bivariate level, we already learned that the cognitive scale and gender are not related whereas on the affective scale, there was a significant relationship between this scale and women with women being significantly more likely to score higher on this scale than men.

Finally, to examine some theories of depression, we used scales in our data set that had not been previously used. These include the following scales: social support and social activities, a stress index, grief questionnaire, social relationships, a five dimension life satisfaction questionnaire, and a leisure inventory. Respondents for some of these scales were persons with Down syndrome or informants.

**Obesity.** Obesity has been associated with higher levels of serum estradiol and estrone in postmenopausal women, which may protect against estrogen-related loss in neuronal systems important for cognitive function. Because obesity appears to be a feature of the Down syndrome (DS) phenotype and fat cells can store and release estrogen, we hypothesized that obese postmenopausal women with Down syndrome would perform better on test of cognitive function than non-obese postmenopausal women. That is, obesity might be expected to influence the rate of cognitive decline with age and may delay onset of Alzheimer's disease. In our data set 69% of premenopausal women and 45% of their age-matched peers were severely obese (BMI > 30), while 67% of postmenopausal women and 27% of their age-matched peers were severely obese. We tested this hypothesis and indeed found that obese postmenopausal women with Down syndrome performed better on the

Woodcock Johnson than non-obese postmenopausal women. However our sample was quite small and we felt that publishing this finding was premature. Using a different data set, Dr. Schupf and Bindu Patel replicated the finding. Healthy nondemented premenopausal (n = 28) and postmenopausal (n = 48) women with mild and moderate mental retardation, not on ERT, and who could complete the cognitive assessment battery were included in the analyses. Blood samples for hormone analyses were collected in 59 women (78%). We used analysis of covariance to compare the cognitive performance of obese and non-obese women, adjusting for age and level of mental retardation. The cognitive performance of obese and non-obese premenopausal women did not differ. Postmenopausal obese women performed significantly better than postmenopausal non-obese and premenopausal women on tests of selective reminding (episodic memory), language, a measure of mental status and an omnibus measure of cognitive function, but there were no significant differences in verbal fluency, apraxia, and two measures of visio-spatial functioning. Estrone and estradiol levels were significantly higher in obese than in non-obese women and the pattern of cognitive performance was the same when only women with hormonal data were included in the analyses. These findings supported the hypothesis that estrogen deficiency contributes to decline in memory and other cognitive functions.

**Musculoskeletal.** Descriptively looking at our data, we found that a little over 60% or almost two thirds of our total sample had musculoskeletal problems such as hip, spine, osteoarthritis, and musculoskeletal pain. These problems occurred among our younger sample participants who were in their 20's and 30's as well as those who were older. We examined whether musculoskeletal problems, particularly those associated with pain, influence hormones and cognitive decline as well as other factors that are common in this population such as psychotropic and antiepileptic medications, depression, and obesity. Given the information on obesity above, we hypothesized that obesity was associated with delay in cognitive decline whereas psychotropic or



antiepileptic medications were associated with the early onset of cognitive decline. By studying musculoskeletal problems and cognition, we were able to tease out which types of musculoskeletal problems were more likely to be associated with functional problems and cognition. Also we knew that musculoskeletal pain was associated with depression but rarely has obesity, cognitive decline, and hormonal status been included in the analyses, that we completed.

### **Implications for Research and Practice**

In sum, our results suggested that higher endogenous estrogen levels can lower risk of cognitive decline and dementia and had implications for prevention and therapeutic intervention, both in women with Down syndrome and in women in the general population. However, these implications need to be examined with care. Recently, the Women's Health Initiative randomized controlled trial of combined estrogen/progestin reported a moderate but significant increased risk of coronary heart disease, invasive breast cancer, stroke and pulmonary embolism in treated women compared with those on placebo and concluded that the overall health risks of the combined estrogen/progestin regimen exceeded its benefits.

Factors that could influence the efficacy of postmenopausal hormonal replacement treatment include the form and schedule (tonic or cyclic) of estrogen and progestins used, dose, time of initiation in the peri-menopausal or postmenopausal period, and route of administration. These alternatives will need to be evaluated in controlled trials. The development of selective estrogen receptor modulators (SERMs) which can selectively activate specific estrogenic receptors in the brain without adverse effects on cardiovascular and other systems may provide a safer and more efficacious mode of intervention. One study has reported no benefit from the use of raloxifene in women with osteoporosis. Studies with different SERMs may help to identify those most likely to have a role, if any, in preserving cognitive function.

### **Publications and Products**

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Walsh, P.N., Heller, T., Schupf, N., van Schrojenstein Lantman-de Valk, H, & Working Group. (2000). *Healthy Ageing - Adults with Intellectual Disabilities: Women's Health Issues*. Geneva, Switzerland: World Health Organization.

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