Cognitive Impairment in Postmenopausal Women

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ABSTRACT

Background: Plasma level of sex hormones is expected to affect different aspects of cognition in postmenopausal females and increase risk of dementia in women than in men. Objective: To assess the relation between estrogen and progesterone levels and cognition in postmenopausal females. Methods: Seventy subjects (30 postmenopausal females, and 40 premenopausal females) were subjected to the following: thorough history, medical and neurological examination, full routine laboratory investigations, serum estrogen and progesterone level, a battery of neuropsychological tests including MMSE, Beck’s questionnaire for depression, Digit span forward and backward of Wechsler, Benton visual retention test, picture completion and picture arrangement from Wechsler, paired associate learning test, word recognition test, verbal fluency test. Results: Mean estrogen and progesterone levels in post-menopausal females were 14.58±10.12 pg/ml and 0.72±0.21 ng/ml respectively. Whereas their levels in premenopausal females were 190.7±91.18 pg/ml and 6.25±5.21 ng/ml respectively. There is a significant difference between them and premenopausal females in other cognitive domains studied. Positive significant correlation between estrogen level and verbal memory in postmenopausal females. Progesterone level showed non significant correlation with all neuropsychological tests in postmenopausal females. Significant correlation between age of onset of menopause, duration of menopause and verbal memory. Conclusion: Postmenopausal females had worse performance in different domains of cognition, so early and repeated assessment of cognition in this period is recommended. Also the use of hormonal replacement in postmenopausal period should be investigated. [Egypt J Neurol Psychiat Neurosurg. 2011; 48(3): 265-270]

Key Words: Estrogen, progesterone, cognitive function, postmenopausal females

INTRODUCTION

The associations of endogenous sex hormones in postmenopausal females and risk of cognitive impairment or even dementia are not well known¹. Authors suggest that, there is an evidence for a tendency of menopausal women with estrogen deficit to present an impairment of cognitive functions in the form of mild cognitive impairment (MCI) or dementia, particularly when compared with the controls, which is keeping with the hypothesis that an estrogen deficit could be a risk factor for Alzheimer's disease (AD) or even for some other types of dementia².

Studies of endogenous estrogen and cognitive functions are inconclusive, some report harmful associations, some protective, and many fail to identify any clinically meaningful association between estrogen level and cognitive ability³,⁴. The aim of this study was to find an association between female sex hormones and cognitive functions in postmenopausal females.

SUBJECTS AND METHODS

This study was conducted on seventy female subjects over 18 month period between 2008 and 2010. Subjects included were divided into two groups: Group I which included thirty postmenopausal females with a mean age 54.2±4.47 years and Group II including forty premenopausal control subjects with a mean age of 35.87±4.03 years. Excluded from the study, females over 60 years old, evidence of major depressive disorder, medical diseases causing dementia and females with memory deficits caused by any concomitant medications or neurological disease as AD, Parkinson disease (PD), stroke, epilepsy.

All females were subjected to thorough medical history, general and neurological examination, Beck’s questionnaire to exclude depression, scoring of 6-9 indicate minimal depression, 10-17 mild depression, 18-29 moderate and 30-40 severe depression. All subjects included must have a score of less than 9 as minimal symptoms of depression could be allowed. Laboratory work up for all females including: routine labs as blood glucose level, serum lipogram, serum electrolytes, liver and kidney functions and thyroid hormonal assay.

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Specific laboratory tests: serum estradiol (E₂) and serum progesterone which were both measured by automated chemilumine using IMMULITE® analyzer (immunometric assay).

Neuropsychological assessment using the following battery of psychometric tests:

- Mini-Mental State Examination (MMSE): as a measure of global brain functions. Confounding factors as age and educational level have to be considered in the interpretation of MMSE, score below which is considered abnormal as follows:
  - In illiterate subjects, 26 in age of 30-39 years, 23 in age of 40-60 years.
  - In subjects with medium education, 26 in age of 30-34 years, 27 in age of 35-60 years.
  - In subjects with high education, 30 in age of 30-49 years and 29 in age of 50-60 years.

- Digit span forward and backward from the Wechsler Memory Scale-Revised (WMS-R): which assess short term memory (working memory). It consists of 2 parts involving presentation of random number sequences read aloud at a rate of one number per second.

- Benton visual retention test: It assesses visual memory. Ten cards are introduced, every card for 10 seconds and the candidate is instructed to draw each of them. Marks given according to the difference between expected and real degree, if it is ≥4, test result is considered abnormal.

- Picture completion and picture arrangement tests from Wechsler memory scales: It assess executive functions, picture completion subtest consists of 20 pictures each missing an important detail and subject has to figure out the missing detail. Normal score ranges from 10-15. Picture arrangement subtest, consists of scrambled cartoon pictures and subject must be able to arrange them in a sensible order. Standard normal score is between 10-21.

- Paired associate learning test: To assess verbal memory. The examiner says 10 associated pairs, after one minute the examiner says one of the words and the candidate must say the other paired word. Normal score for women aged 30-39 years is 13:19, aged 40-49 years is 11:17, aged 50-60 years is 8:15.

- Word recognition test: To assess auditory memory. The examiner says 50 words in front of the candidate, then the examiner says 2 words and the candidate should know which word she heard from the list. Normal range extends from 31:43.

VERBAL FLUENCY TEST: “Free association test”10: To assess language. Participants have to say as many as possible from a category in a given time (usually 60 seconds). This category can be semantic, such as animals or fruits or phonemic such as words begin with letter P. Cut-off scores of 9 for illiterates and 13 for educated subjects.

**Statistical Methods:**

The Statistical Package of Social Sciences (SPSS) was used. Descriptive statistics (i.e. frequency, percentage, mean and standard deviation) were calculated. Testing significance between the two study groups was applied using the unpaired t-test. Qualitative data were compared by correlation (r) test according to expected frequencies.

**RESULTS**

This study included 30 post-menopausal females (group I) with their age ranging from 45-60 years (mean age of 54.2±4.47 years) and 40 pre-menopausal volunteers (group II) with their age ranging from 30-45 years (mean age of 35.87±4.03). 18 postmenopausal females (60%) were illiterate, 5 females (16.7%) had medium education and 7 females (23.3%) with high education whereas 15 premenopausal females (37.5%) were illiterate, 14 subjects (35%) had medium education and 11 females (27.5%) with high education.

In group I, 24 females (80%) had natural menopause whereas 6 females (20%) had operation menopause. Duration of menopause ranged from 1 to 13 years with a mean of 7.44±4.65 years.

In postmenopausal females, serum estrogen level was 14.58±10.12 pg/ml (range 0.2-34.8 pg/ml) and serum progesterone level was 0.72±0.21 ng/ml (range 0.37-1.2 ng/ml). Whereas in premenopausal females, they were 190.75±91.1 pg/ml (range 27-380 pg/ml) and 6.25±5.21 ng/ml (range 0.6-18 ng/ml) respectively.

On comparing the postmenopausal females (group I) and the pre-menopausal ones (group II) regarding the different neuropsychological tests done (Table 1), group I showed a decrease in scores of different tests measuring different aspects of cognitive abilities in these females but with no statistical significance except for the paired associate test which measures verbal memory (p<0.05).

Positive correlation between serum estrogen level, progesterone level and different neuropsychological tests measuring different aspects of cognition on studying postmenopausal females but with no statistical significance except for the positive correlation between estrogen level and paired associate test measuring verbal memory showing statistical significance (p<0.05) (Table 2).
The age of starting menopause correlated positively as well as the duration of menopause correlated negatively with different neuropsychological tests, as the younger the age of female starting menopausal period and the longer the duration of menopause, the worse was the measure of different cognitive domains with no significant value except for the correlation between age of onset of menopause (r = 0.24, p<0.05), duration of menopause (r = 0.18, p=0.05), and the paired associate test measuring verbal memory.

Table 1. Comparison between post-menopausal females (group I) and pre-menopausal females (group II) regarding different neuropsychological tests.

<table>
<thead>
<tr>
<th>Neuropsychological test</th>
<th>Group I</th>
<th>Group II</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>MMSE</td>
<td>23</td>
<td>76.7</td>
<td>7</td>
</tr>
<tr>
<td>Digit span forward and backward of Wechsler</td>
<td>22</td>
<td>73.3</td>
<td>8</td>
</tr>
<tr>
<td>Word recognition</td>
<td>27</td>
<td>90</td>
<td>3</td>
</tr>
<tr>
<td>Paired-associate learning test</td>
<td>24</td>
<td>80</td>
<td>6</td>
</tr>
<tr>
<td>Benton test</td>
<td>25</td>
<td>83.3</td>
<td>5</td>
</tr>
<tr>
<td>Wexler</td>
<td>Picture completion</td>
<td>26</td>
<td>86.7</td>
</tr>
<tr>
<td>Picture arrangement</td>
<td>25</td>
<td>83.3</td>
<td>5</td>
</tr>
<tr>
<td>Free association test</td>
<td>24</td>
<td>80</td>
<td>6</td>
</tr>
</tbody>
</table>

*p<0.05 = significant

Table 2. Correlation between serum estrogen and progesterone levels and results of neuropsychological tests in postmenopausal females.

<table>
<thead>
<tr>
<th>Neuropsychological test</th>
<th>Serum estrogen (r)</th>
<th>Serum progesterone (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>0.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Digit span test</td>
<td>0.23</td>
<td>0.42</td>
</tr>
<tr>
<td>Word recognition</td>
<td>0.07</td>
<td>0.14</td>
</tr>
<tr>
<td>Paired associate-learning test</td>
<td>0.12*</td>
<td>0.07</td>
</tr>
<tr>
<td>Benton test</td>
<td>0.29</td>
<td>0.14</td>
</tr>
<tr>
<td>Picture completion test</td>
<td>0.22</td>
<td>0.13</td>
</tr>
<tr>
<td>Picture arrangement test</td>
<td>0.15</td>
<td>0.09</td>
</tr>
<tr>
<td>Free association test</td>
<td>0.41</td>
<td>0.63</td>
</tr>
</tbody>
</table>

*p<0.05 = significant

**DISCUSSION**

If endogenous estrogen influences cognitive function, this effect might be more apparent during the menopausal transition when estrogen levels are decreased dramatically and 60% of women report memory problems.

This study was conducted on 30 postmenopausal females and 40 pre-menopausal controls, aimed at finding an association between sex hormones in postmenopausal females and cognitive functions.

On performing the MMSE as a measure of global brain function, post-menopausal females showed greater number of females having abnormal test results when compared with premenopausal ones, but this difference didn't reach a significant value. This result was in accordance with many other studies.

Lebrun et al. in their study reported that women in the highest quintile of either estradiol or estrone were 40% less likely to be cognitively impaired (MMSE <27) compared to women in the lowest quintile.
Contrary to our results, Qui et al.\textsuperscript{17} in their first large population based study of post-menopausal females found that women with the highest estrone levels had significantly poorer performance on one of three cognitive function tests at base line and a greater reduction in scores on another over 5 years compared with women with lower estrone levels. These results didn’t support the hypothesis that estrogen preserves brain function.

Den Heijer et al.\textsuperscript{18} found that women with higher bioavailable estradiol levels had significantly poorer memory performance. Whereas, the Rancho Bernardo study failed to identify any consistent cross-sectional association of estrone or total and bioavailable estradiol with performance on 12 cognitive function tests in postmenopausal females\textsuperscript{19}.

Many authors tried to explain the relation between cognitive decline in postmenopausal females and decreased estrogen level. They reported that estradiol may decrease oxidative stress, inhibit neuronal apoptosis and promote synaptogenesis and synaptic plasticity\textsuperscript{13,20}. Also, estrogen raises HDL cholesterol level, reduces atherosclerosis, inhibits endothelin-mediated vasoconstriction, and promotes vasodilatation so improves cerebral blood flow\textsuperscript{21,22}.

Moreover, Chen et al.\textsuperscript{15} mentioned that estrogen reduces the deposition of B-amyloid in the brain and prevents it from inducing a rise in intracellular calcium and prevents mitochondrial damage\textsuperscript{15}.

On analyzing the different domains of cognition, our results revealed significant difference between postmenopausal and premenopausal females as regard verbal memory, moreover, a significant correlation was found between estrogen level, age of onset, duration of menopause and verbal memory. This was in accordance with several preceding studies\textsuperscript{3,18,24}.

Women with greater decline in estradiol level had greater decline in performance on verbal memory tasks\textsuperscript{21}. Others previously found an association of life time estrogen exposure on verbal skills but not on visuospatial skills and attention\textsuperscript{25}.

Wolf and Kirschbaum\textsuperscript{26} studied five cognitive tests measuring verbal memory, spatial memory, verbal fluency, mental rotation and susceptibility to interference in postmenopausal females. Females with lower estrogen levels had worse verbal memory and more susceptibility to interference. This supports the notion that estradiol is protecting verbal memory and possible also frontal lobe mediated functions.

Others\textsuperscript{27} stated that, estrogen replacement therapy improves verbal memory in postmenopausal females as estrogen had its effect on hippocampal synaptogenesis and function.

On the other hand, Erlanger et al.\textsuperscript{28} previously found no effect of menopause status on verbal memory.

Den Heijer et al.\textsuperscript{18} explained the effect of estrogen on verbal memory as the human hippocampus and prefrontal cortex, which serve verbal episodic memory are rich in estrogen receptors. Also estrogen promotes the formation of dendritic spines and synapses and enhances long-term potentiation in the hippocampal region\textsuperscript{29}.

Considering the age of menopause and its duration, an evidence of poorer verbal memory was associated with early age at menopause and with surgical menopause. Moreover, verbal memory was negatively associated with years since surgery and onset of menopause and positively associated with age at surgery\textsuperscript{30,31,32}. This was in accordance with our results.

This finding may be explained by many authors who mentioned that, genetic factors may play a role in the timing of age at menopause and also contribute in postmenopausal cognitive ability. For example, polymorphism in estrogen receptor gene may influence age at menopause and also be associated with cognitive impairment\textsuperscript{3,33}.

On the other hand, others mentioned that cognitive and ovarian function may be linked through hormonal mechanisms controlled by the hypothalamic adrenal axis\textsuperscript{34}. Also women with early menopause have a less favorable cardiovascular risk profile\textsuperscript{22}.

Our results showed non-significant difference between postmenopausal and premenopausal females as regard other domains of cognition. This was in accordance with Drachman\textsuperscript{35}, who mentioned that performance on immediate or primary memory tasks that do not require storage and retrieval of material, such as digit span tasks and memory for remote past events appear to be relatively intact.

On the other hand, different authors have mentioned that post-menopausal women with low estimated levels of estrogen had performed better on the story memory test from Wechsler; verbal memory, naming, abstract reasoning\textsuperscript{36}, digit span forward and backward, logical memory and paired associate subtests\textsuperscript{29} on using the estrogen replacement therapy. These data threw the light on the different domains of cognition which may be affected in postmenopausal females and so they become better on having such estrogen replacement therapy.

Considering the relation of progesterone level in postmenopausal females and different domains of cognition, our results showed a non-significant correlation between progesterone level in postmenopausal females and different domains of cognition studied. This was supported by other studies\textsuperscript{22}.

Whereas, Freeman et al.\textsuperscript{17} previously suggested that progesterone may affect cognitive abilities adversely "decreases in several performance tests including delayed recall and digit symbol substitution tests".
Common environmental or genetic factors, operating through long-term or even life long hormonal mechanisms, may influence the timing of natural menopause and life time cognitive function.  

[Disclosure: Authors report no conflict of interest]

REFERENCES

El-Katan, et al.: Postmenopausal cognitive impairment


الملخص العربي

الاضطراب المعرفي في السيدات بعد انقطاع الطمث

تهدف هذه الرسالة إلى توضيح العلاقة بين مستوى الهرمونات الجنسية وبين الأداء المعرفي للسيدات بعد انقطاع الطمث. هذا وقد أجريت هذه الدراسة على 30 سيدة بعد انقطاع الطمث و 40 أجريت قبل انقطاع الطمث كمجموعة مقارنة، وقد تضمن جميع الس Stout: فحص إكلينيكي شامل، فحوصات عملية روتيناية، قياس مستوى هرمون الأستروجين والبروجستيرون بالدم ومقاييس الأداء المعرفي والتي شملت: قياس فولشتاين لتقويم الحالة الذهنية، مقاييس الاكتئاب بيك، اختيار إعادة الأرقام للأمام والخلف من وكر، اختيار بندون للذاكرة الصرية، اختيار إكمل وترتب الصور من وكر، اختبار التعريف السمعي على الكلمات، اختيار التداسو على الجمل، اختبار تعليم الأزواج المتزوجة.

وقد توصلت هذه الدراسة إلى وجود اختلاف لكن ليس ذو دلالة إحصائية بين أفراد المجموعتين في جميع الاختبارات لقياس مختلف مجالات الحالة المعرفية، فيما عدا اختبار تعليم الأزواج المتزوجة كقياس للذاكرة الكلامية الذي أظهر اختلاف ذو دلالة إحصائية في السيدات بعد انقطاع الطمث.

وجدت علاقة طردية ذات دلالة إحصائية بين نسبة هرمون الأستروجين بالدم في السيدات بعد انقطاع الطمث واختبار تعلم الأزواج المتزوجة (الذاكرة الكلامية)، بينما لم توجد علاقة إحصائية بين نسبة هرمون البروجستيرون بالدم ومقاييس الأداء المعرفي المختلفة لهذه السيدات. كما وجدت علاقة عكسية بين فترة (مدة) انقطاع الطمث ونتائج اختبارات ومقياسات الأداء المعرفي ولكن لم تصل إلى دلالة إحصائية فيما دعا اختيار النهاية الكلامية.

ومن هنا يتضح أن أداء السيدات بعد الانقطاع الطمث في كل الاختبارات المعرفية أسوأ من أداءهن قبل انقطاع الطمث، ولكن لم تصل إلى دلالة إحصائية إلا فيما اختيار الأزواج المتزوجة الذي أجرى كمقياس للذاكرة الكلامية.