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Menopause and Cognitive Function: Hospitalized Female Patients with Depression

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Abstract

Objectives: Although forgetfulness is a common complaint among depressed menopausal women, there remains debate on the relationship between memory impairment and menopause. The aim of this study was to examine whether menopause is related to cognitive decline among women with depressive disorders. We hypothesized that postmenopausal depressed woman would show generally poorer performance than premenopausal depressed women on various cognitive function tests

Methods: Using a retrospective chart review, we identified a total of 87 female patients (45 premenopausal patients and 42 postmenopausal patients) who were hospitalized with depressive disorders from 2000 to 2016. Demographic and clinical variables and cognitive test results were compared between the two groups.

Results: Years of education was greater in the premenopausal group as compared to the postmenopausal group, whereas clinical characteristics (illness duration, recurrence, and symptom severity) and mean IQ were similar between the two groups. The postmenopausal group had longer reaction times for Bender-Gestalt test recall and Trail-Making Test A and B. After controlling for age and education, there was a significant difference in Bender-Gestalt test recall (p=0.029).

Conclusion: The postmenopausal state may be related to decline of visuo-spatial memory function, in particular, among depressed female patients. Other areas of cognitive function including complex attention, verbal memory, auditory memory, working memory might be interpreted with consideration to age and education level.

Keywords: Menopause; Cognitive function; Depression

Introduction

Menopause is a period in which sudden changes occur. Women often experience physical and mental confusion as the ovaries start to dysfunction [1]. Often, this is a period in which women not only experience physical symptoms such as flushing and perspiration but also psychiatric symptoms such as depression and anxiety, increased forgetfulness, and declines in concentration not experienced before menopause [2] In particular, decline in memory is reported very frequently in about 42% of women experiencing menopause [3] However, whether there is a direct correlation between menopause and decline in cognitive function remains undetermined.

Paganini-Hill and Henderson [4] found that Alzheimer's disease in elderly women is related to estrogen deficiency, and suggested that estrogen alternative remedies may aid in preventing or delaying dementia. Laws et al. [5] also suggested that women may experience greater decline in cognitive function as compared to men with equal disease severity because of decreased estrogen among postmenopausal women. On the other hand, Henderson et al. [6] found that memory function is not affected by the menopausal transition and is maintained without relation to the progressive stage of menopause. Further, Woods et al. [7] found that perceived memory functioning is related more too perceived health, perceived stress, or feelings of depression as opposed to age or menopause.

However, despite these contradictory research findings, it remains common to find middle-aged women coming into psychiatric care stating that their memory declined following menopause [8,9]. Numerous psychophysical symptoms during menopause, especially depressive symptoms, are widely known to affect cognitive functioning [10]. Patients diagnosed with depression for the first time and starting their treatment in menopause are often observed in the psychiatric department [11,12]. However, no research has been conducted regarding the effects of menopause in depressive patients with regard to their prevalence and related decline in cognitive function. This research aimed solely to determine whether menopause is related to differences in cognitive function among women receiving hospitalized depression treatment.

Methods

Subject and procedure

This study was a retrospective analysis of women between 34 and 64 years who were diagnosed with depressive disorder and received inpatient treatment between January 2001 and February 2016 at the Department of Psychiatry in Incheon St. Mary's Hospital of Catholic University of Korea using medical records and results of clinical psychological tests conducted during hospitalization.

Diagnoses were performed using semi-structured interviews with a clinical doctor during the hospitalization period based on Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) published by the American Psychiatric Association (APA), the revised 4th edition (DSM-IV-TR) and the 5th edition (DSM-5). People who had accompanying psychotic symptoms or severe neurological disease were ruled out.

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Classification of premenopausal and postmenopausal groups was based on self-reported bleeding patterns, and this reflected whether participants considered themselves to be in menopause at the time of the study. According to the Stages of Reproductive Aging Workshop +10 (STRAW +10) [13], reproductive age is classified into four stages:

1. Late reproductive stage: Subtle changes in menstrual flow, cycle length, or both.

2. Early menopausal transition stage: Persistent cycle irregularity, defined as a difference in the length of consecutive cycles of 7 days or more at least twice during the prior 10 cycles.

3. Late menopausal transition stage: Interval of amenorrhea of 60 days or longer.

4. Early post-menopause stage: The first 12 months after FMP. In this study, participants who were in late reproductive stage were classified into pre menopause group. And, participants who were in early menopauseal transition, late menopauseal transition, and early post-menopause were classified into post menopause group. Therefore in this study, peri-menopausal period, which is defined as encompassing three stages (early menopauseal transition, late menopauseal transition, and early post-menopause), was simplely included in postmenopausal group.

This study was conducted with approval from the ethics committee of Incheon St. Mary's Hospital of Catholic University of Korea (IRB No. OC16RISI10115).

Evaluation Tools

Self-report evaluation tools

Beck Depression Inventory (BDI): The Beck Depression inventory (BDI) is a self-reported evaluation tool developed by Beck et al. to assess the existence of depressive symptoms and its severity [14]. It includes of 21 questions on the psychological, cognitive, motivational, and physiological symptoms of depression, and each question is rated from 0 to 3 on four scales. The total score is rated from 0 to 63, and higher scores represent more severe depressive symptoms. In this study, the version standardized by Lee and Song [15] was used.

State-Trait Anxiety Inventory (STAI): Spielberger's State-Trait Anxiety Inventory (STAI) [16] assesses state and trait anxieties, and it contains 20 questions in the State Anxiety Inventory (SAI) and 40 questions in the Trait Anxiety Inventory (TAI). Each question is rated from 1 to 4 on four scales. The total score ranges from 20 to 80 for the SAI and 40 to 160 for the TAI. Higher scores represent higher anxiety. In this study, the version standardized by Han et al. [17] was used.

Clinical psychological tests

Korean Wechsler Adult Intelligence Scale (K-WAIS): The Korean Wechsler Adult Intelligence Scale (K-WAIS) [18] is a version of the most widely used individual intelligence assessment, the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [19], standardized in Korean. In this study, the K-WAIS and K-WAIS-IV [20] were used.

Bender-Gestalt test (BGT): The Bender-Gestalt test (BGT) [21] is an assessment that assesses cognition, emotion, and personality. Test takers are presented with nine stimulation cards with geometrical figures one at a time and told to copy them down on paper. Then, they are told to recall and redraw the shapes from the previous step. This assessment is useful when diagnosing patients with brain damage. In this study, the time it took to copy and recalls the images was measured to compare the degree of cognitive function.

Trail-Making Test and B (TMT-A/TMT-B)

The original version of the Trail-Making Test (TMT) [22] was developed to analyze visual conceptual tracking and visuomotor tracking and has been widely used in the field of neuropsychology since its development in 1944 for the US army [23]. The TMT is assessed in two ways. First, there is an A type where the task is to connect numbers from 1 to 25, which are randomly distributed on a piece of paper, in order (1→2→3…). Second, there is a B type where the task is to interchangeably connect characters switching between numbers (1 to 13) and letters (A to L) in order (1→A→2→B…). TMT-B, which requires more complex functioning than does the TMT-A, has been confirmed for its clinical usefulness as a sensitive tool in assessing frontal lobe damage [24]. The results are calculated using the time it takes to reach the "end" from the moment the pencil touches the paper,as well as by the number of errors. Higher scores mean that more time was spent finishing, reflecting lower cognitive functioning.

Wechsler Memory Scale (WMS)

The Wechsler Memory Scale (WMS) [25] is a tool for assessing memory function of subjects between the ages of 16 to 69 that consists of subscales such as general cognitive screener, logical memory, verbal paired associates, design memory, visual reproduction, spatial addition, and symbol span. It can measure auditory memory, visual memory, visual working memory, immediate memory, and delayed memory, and these scores are assessed by converting them to a memory quotient (MQ).

Statistical analysis

In order to compare the socio demographic and clinical factors as well as cognitive functioning between the two groups, independent t-tests and chi-square tests were used for continuous and categorical variables, respectively. Then, analysis of covariance (ANCOVA) was used to compare cognitive functioning while controlling for confounding variables. The level of significance was set at $p<0.05$ using a two-tailed test. All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

Demographic and clinical characteristics

Of 87 patients, there were 45 premenopausal (51.7%) and 42 postmenopausal patients (48.3%). The average age was 40.82 ± 4.53 for premenopausal patients and 54.31 ± 4.57 for postmenopausal patients. The level of education was higher for premenopausal patients than it was for postmenopausal patients ($p<0.001$, 13.02 vs. 10.98 years). There were no differences in duration of illness ($p=0.565$), recurrence of illness ($p=0.254$), BDI score ($p= 0.709$), SAI score ($p=0.511$), or TAI score ($p=0.832$) between the two groups (Table 1).

Between-groups comparison in cognitive functioning

The average full scale intelligence quotient (FSIQ) was similar between the two groups ($p=0.157$; Table 1). Scores on the BGT recall ($p=0.037$), TMT-A ($p=0.002$), and TMT-B ($p=0.012$) were lower in the postmenopausal group than they were in the premenopausal group, but when differences in education and age, which may affect cognitive functioning, were adjusted, only BGT recall ($p=0.029$) showed a significant difference (Table 2).

Discussion

The purpose of this study was to examine whether menopause

Variables	Pre-menopause (n = 45)	Post-menopause (n = 42)	p-value
Age	40.82 ± 4.53	54.31 ± 4.57	0.001
Education (years)	13.02 ± 2.26	10.98 ± 1.87	0.001
Marital status (n %)			
Never married	2 (4.4)	0 (0)	0.242
Married	37 (82.2)	37 (88.1)	
Widowed	1 (2.2)	3 (7.1)	
Divorced	5 (11.1)	2 (4.8)	
Clinical factors and Diagnosis (n %)			
MDD	31 (68.9)	32 (76.2)	0.521
Depressive disorder, NOS	13 (28.9)	10 (23.8)	
Dysthymia	1 (2.2)	0 (0)	
Illness duration (weeks)	22.75 ± 16.16	20.62 ± 18.01	0.565
Recurrence (n %)			
First onset	16 (35.6)	20 (47.6)	0.254
Recurrence	29 (64.4)	22 (52.4)	
BDI	28.04 ± 11.08	27.19 ± 10.12	0.709
SAI	54.44 ± 9.78	53.07 ± 9.60	0.511
TAI	54.69 ± 10.29	54.22 ± 10.13	0.832

MDD: Major Depressive Disorder, BDI: Beck Depression Inventory, SAI: State Anxiety Inventory, TAI: Trait Anxiety Inventory

Table 1: Clinical characteristics by menopausal status.

Variables	Crude analysis			Adjusted analysis*		
	Pre-menopause (n = 45)	Post-menopause (n = 42)	p-value	Pre-menopause (n = 45)	Post-menopause (n = 42)	p-value
FSIQ	96.80 ± 12.14	100.48 ± 11.48	0.151	96.80 ± 12.14	100.48 ± 11.48	0.521
BGT						
Copy (sec)	245.57 ± 160.47	301.5 ± 137.26	0.086	241.43± 32.95	305.91± 34.14	0.274
Recall (sec)	114.42 ± 55.81	145.38 ± 79.15	0.037	101.01± 14.68	159.77± 15.48	0.029
TMT						
A (sec)	44.60 ± 18.54	59.45 ± 23.95	0.002	50.51 ± 4.23	53.118 ± 4.46	0.732
B (sec)	107.51 ± 48.86	158.31 ± 95.03	0.012	108.42 ± 15.41	157.03 ± 20.09	0.123
MQ	104.05 ± 16.79	96.33 ± 16.21	0.054	103.82 ± 3.74	96.60 ± 4.17	0.302

FSIQ: Full Scale Intelligence Quotient, BGT: Bender Gestalt Test, TMT: Trail Making Test, MQ: Memory Quotient
*Results from analysis of covariance after adjusting for age and education.

Table 2: Comparison of cognitive test scores between the pre-menopausal and post-menopausal groups (adjusted by education and age).

affects cognitive functioning in depressed female inpatients. The postmenopausal group perfomed poorer on BGT recall and TMT A and B compared to the premenopausal group, and when differences in education and age were adjusted for, BGT recall showed a significant difference. Therefore, in the postmenopausal group, more time was taken to complete the BGT recall as compared to the premenopausal group.

In the BGT test, the difference between recall scores demonstrates that visuomotor memory declined to a greater extent in the postmenopausal group as compared to the premenopausal group. If BGT copy is to be considered a valid indicator for assessing brain functioning through geometric perception and copying abilities [26], BGT recall can be said to reflect memory capacity, as it measures free recall of visual reproduction [27]. The decline in cognitive function for postmenopausal depressive women may be explained by estrogen differences. The central nervous system is one of the target organs for estrogen [28]. In particular, estrogen receptors are distributed in the hippocampus, amygdala, and cerebral cortex [29,30]. It is suspected that due to decline of estrogen following menopause, hippocampal function declines, thereby affecting memory and learning ability, which are implicated in hippocampal function. This might explain the observed decline in memory recall [31,32].

However, in this study, postmenopausal patients showed a delay in BGT recall, while there was no difference between groups in MQ score. The WMS assessment, which calculates MQ assesses not only visual memory but also visual working memory, auditory memory, immediate memory, and delayed memory, and it is known to be especially sensitive in calculating short-term verbal memory [33]. The fact that there was no difference in the MQ between groups suggests the possibility that there was greater decline in non-verbal and visual memory function in the postmenopausal depressive group as compared to the premenopausal depressive group. Previous research by Resnick et al. [34] in support of the present findings, found that short-term visual memory and visual perception were improved among elderly women after using an estrogen alternative remedy. It has also been reported that even within young males, the level of visual memory is higher for those with higher amounts of estrogen (E2) in the blood [35] Moreover, when estrogen was subcutaneously injected after removing a mouse's ovaries during animal research, visual and spatioperceptual memories increased [36] suggesting the possibility that estrogen affects visual memory in particular among memory functions.

However, many studies have found that menopause affects verbal memory [37-39]. Further, in the Henderson et al. [6] study mentioned above, memory function was found to be steadily maintained following menopause during 8 subsequent years of monitoring and no significant correlation between memory function and blood estrogen concentration has been found. Therefore, more research is needed on

the possible impact of estrogen and menopause on visual memory function.

On the other hand, when age [40,41] and education level [42,43] which may affect cognitive function, are taken into consideration in analyzing the TMT-A and B and MQ scores, which initially showed differences between the two groups, the difference disappeared. Therefore, decline in cognitive functioning in postmenopausal women with depression may be influenced by education level as well, as opposed to menopause itself. In fact, previous findings demonstrate that level of education has a protective effect on cognitive function. Mortimer [44] and Katzman [45] have suggested that a high level of education can have a protective effect against dementia by increasing cognitive reserves [46-48] and this suggests a possibility for application to patients with depression.

Conclusion

Lastly, the decline in cognitive function for women after menopause may have been due to influence from depression [49]. This study compared premenopausal and postmenopausal patients with depression who displayed a similar degree of depressive and anxiety symptoms, and focused on the effect of menopause itself as opposed to that of symptoms. However, it has been reported that senior patients with depression show a decline in cognitive function as a characteristic depressive symptom [50]. Considering this factor, this study compared cognitive function between the two groups while controlling for age. Given that the postmenopausal group was older, a study comparing the group to depressive male patients in the same age group may help in further understanding the relationship between menopause and cognitive function. Moreover, according to previous research, a patient that displayed a decline in cognitive function during a depressive episode did not recover in her cognitive function even after treatment, and it continued to decline [10]. Further research is needed regarding the possibility of recovering cognitive function after depression improves.

There were several limitations to this study. First, the small number of participants underscores elimination in generalizing the results. Second, information regarding menopause was obtained from participants, and the definition of menopause was not specific. In earlier studies, the levels of menopause were subdivided into early peri-menopausal, late peri-menopausal and postmenopausal periods. However, in this study, we simply divided participants into premenopausal and postmenopausal groups, and followed the information regarding menopause given by patients themselves, making the classification of women in the menopausal transition period inconsistent. Third, in this study no discrimination between premenopausal and peri-menopausal periods. Participants who were in peri-menopausal period was simply included in postmenopausal group. Therefore, the effects of peri-menopausal periods may have been overlooked. Fourth, most participants already had meaningful depressive symptoms in the clinical aspect, while in the diagnostic aspect, they were heterogeneous. Major depressive disorder was most common at 72.4% (n=63), followed by depressive disorder not otherwise specified at 26.5% (n=23) and dysthymia at 1.1% (n=1). Finally, this study could not perform precise comparisons before and after menopause because it was a retrospective cross-sectional study.

Even with these limitations, this study has significance in that it demonstrated a possibility of higher decline in visual memory ability for postmenopausal women than premenopausal women among patients with depression. Moreover, it suggests a possible protective effect of level of education on cognitive function after menopause. A more meaningful conclusion is expected to be achieved about ideas surrounding menopause and cognitive function if prospective studies and assessments regarding biological mechanisms are conducted in the future.

Conflict of Interest

The authors have no financial conflicts of interest.

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