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Original Article

J Clin Gynecol Obstet. 2018;7(3-4):69-71

Early Menopause Is a Risk Factor for Postmenopausal Depression in Healthy Women, But Are Depressive Episodes a Risk Factor for Early Menopause?

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Abstract

Background: This study investigated whether age of menopause in bipolar women is different from that in healthy women and if there is a relationship between age at menopause and previous depressive episodes.

Methods: We consecutively evaluated 86 euthymic and postmenopausal women who were older than 33 years and were diagnosed with bipolar disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The healthy control group comprised 100 individuals of similar age. After the diagnostic interview, bipolar patients completed the Mood Disorders Diagnosis and Follow-Up Form (SKIP-TURK).

Results: Age at menopause in bipolar women was earlier than that of the controls (P = 0.001). Age at menopause correlated with age of onset of bipolar disorder (r = 0.453). A strong inverse correlation was found between the age of menopause and total duration of depressive episodes (r = -0.542).

Conclusion: Early-onset bipolar disorder is associated with early ages of menopause. Age at menopause seems to be related to duration of depressive period. Considering the effects of hypoestrogenemia on ischemic heart diseases and cognitive impairment, it is important that the risk which is already high for both situations should be reduced, and depressive periods should be prevented.

Keywords: Age at menopause; Depressive episode; Bipolar disorder; Ischemic heart disease; Cognitive impairment

Introduction

Menopause is a new identity process which involves biological, psychological and socio-cultural elements [1]. Seventy-seven percent of women who were diagnosed with bipolar disorder (BD) mentioned worsening in their menopausal or postmenopausal state [2]. These women reported their increased symptomatology as their diseases worsened. An increase of 20% was reported in mood episodes in postmenopausal cases in bipolar women [2].

Several women who did not have a psychiatric diagnosis so far mentioned perimenopausal and postmenopausal changes in their mood. Considering the neuroprotective effects of estrogen, this is not a surprise. The age of menopause in healthy individuals is a risk factor for postmenopausal depression. Jung et al found the risk of depression in cases of 46 years old or younger as high [3]. The same researchers reported an inverse and strong relationship of age of menopause and age of fertility with postmenopausal depression in a meta-analysis [4]. Georgakis et al in a systematic review repeated the same diagnosis in 67,714 women [5]. When they made a comparison between women of age younger and older than 40 years old, they reported that the risk of postmenopausal depression is 50% lower in women aged at 40 years old or younger.

If early menopause increases the risk of postmenopausal depression in healthy individuals, could the frequency and severity of depressive episodes in individuals with BD be related to the age of menopause? The purpose of this study is to understand whether the age of menopause in bipolar women differs in comparison to healthy individuals, and if there is a relationship between the age of menopause and the number, duration and severity of depressive episodes.

Patients and Methods

Sample

In this study, women aged at 33 years old or older including 86 postmenopausal women diagnosed with BD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and in remission and referred to our outpatient clinic for routine follow-up (at least 2 years) were evaluated consecutively. The healthy control group comprised 100 women coming from the same geographic regions as the bipolar patients, had similar mean ages and socioeconomic levels, and had no history of psychiatric referral, treatment or psychi-

Manuscript submitted June 13, 2018, accepted October 25, 2018

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doi: https://doi.org/10.14740/jcgo504w

Table 1. Clinical Features of Bipolar Patients

	BP (n = 126)
Age of onset illness	19.25 ± 5.13
Frequency of total episodes (number of episodes/years)	0.69 ± 0.45
Frequency of manic episodes (number of episodes/years)	0.25 ± 0.23
Frequency of depressive episodes (number of episodes/years)	0.47 ± 0.18
Duration of total episodes (mount)	21.15 ± 6.6
Duration of manic episodes (mount)	5.50 ± 1.1
Duration of depressive episodes (mount)	15.65 ± 3.7

Data are expressed as mean ± SD.

atric symptoms.

Measures

Structured Clinical Interview for DSM-Axis 1 Disorders (SCID-I): DSM-IV structured clinical interview form for axis 1 disorders Turkish version [6].

Structured Clinical Interview for DSM-Axis 1 Disorders–non-patient (SCID-NP): DSM-III-R structured clinical interview form for axis 1 disorders for non-patients Turkish version [7].

Mood Disorders Diagnosis and Follow-Up Form (SKIP-TURK): age at disorder onset, duration of the disorder, age at treatment initiation, physical and sexual abuse in patient history, academic and social functioning, age at menarche, premenstrual syndrome, the type of the first episode, severity of the episode, postpartum onset, seasonality, depression subtype, psychotic episode, suicide, hospitalization, duration of the episode, the number of the episodes, dominant course pattern, acute onset and remission, chronicity and rapid cycling, shifts, cigarette smoking and substance use were asked to the participants [8].

Procedure

Local ethics committee approved the study protocol.

Following the diagnostic interviews (SCID-I and SCID-NP), an open-ended interview was undertaken with the bipolar patiens in order to fill in the SKIP-TURK. For the conditions in which a clear evaluation could not be done, information from the relatives of the patient was taken. The age at menarche was an information which was questioned by SKIP-TURK. The age at menopause is defined as the year without regular and consecutive periods [3]. SCID-NP was applied to the control group.

Statistical analysis

Parametric variables were compared with Student's *t*-test (since SD ± mean was < 0.3), while categoric variables were compared with Fisher's exact test. Pearson correlation test was used for correlation analysis. Statistical significance was set at $P < 0.05$ and all tests were two-tailed.

Results

Sample

Mean age of 86 cases with BD (54.81 ± 16.35 years old) is similar to that of healthy subjects (55.34 ± 15.45 years old) ($t = 0.3$, $P = 0.652$). Marriage rates and number of children are similar between the two groups ($\chi^2 = 0.123$, $P = 0.586$ and $t = 0.2$, $P = 0.627$). Age of menarche is similar between the two groups ($t = 0.3$, $P = 0.235$). Clinical characteristics of BD in these cases is outlined in Table 1.

Comparison of age at menopause between bipolar and healthy women

Mean age at menopause in cases with BD (43.25 ± 6.18 years old) is lower than that in healthy women (51.83 ± 5.72 years old) ($t = 2.6$, $P = 0.001$).

Relation between the age at menopause and clinical characteristics of BD

There is a strong correlation between the age of menopause and age at onset of BD ($r = -0.453$, $P = 0.023$). In cases diagnosed with BD, no relation was found between the age at menarche and the number and severity of depressive episode. However, a strong inverse relation was found between the age at menopause and total duration of depressive episodes ($r = -0.542$, $P = 0.007$).

Discussion

This is the first study which investigated the presence of a relationship between the age of menopause and clinical characteristics in affective disorders. There was no study found to investigate the presence of a relationship between depres-

sive episodes and age of menopause or whether this is a risk factor. In a study we conducted in 2016, it showed that there was a relationship between the age of menopause in healthy women and depressive and cyclothymic temperament [9]. Affective temperament was proposed as an endophenotype for mood disorders [10]. The mildest end of mood disorders was defined as subthreshold states. This is an indicator of depressive mood, unipolar disorder, cyclothymic mood and BD [11]. Considering these findings, we proposed that there might be a relationship between subliminal mood disorders and the age of menopause, and therefore, a mood disorder may be a risk factor for early menopause.

In this study, the mean age of menopause in cases with BD was lower than that in healthy women. Presence of a relationship between the age of menopause and BD indicates a relationship between the duration of the disease and the age of menopause. In the question that corresponded to this, the numbers and durations of mood disorder were found to only relate to the age of menopause for depressive episodes. This result may be related to the opportunities of faster diagnosis and treatment of manic and mixed episodes. While the duration of depressive episodes may be an indicator of severity, no relationship was found between the severity of depressive episodes and the age of menopause. In addition to this, no relationship was found in the comparison between the cases with and without postpartum episodes. These results might suggest that the depressive episode had a correspondence in the hypothalamus-hypophysis-gonadal axis. Nevertheless, in our study where we looked for a relationship between the age of menarche and the clinical and mood characteristics of BD, we did not find a difference in terms of the age of menarche in bipolar women and healthy women, while we showed a relationship between the age of menarche and the length of depressive episodes [12]. In the same study, we found a relationship between the age of menarche and scores of depressive and cyclothymic temperament. Considering the results of these two studies, we may talk about a period of premature fertility in bipolar women; however, no relationship was found in this study between the age of menarche and the age of menopause. In addition to its analysis towards the past, the most important limitation of this study was that it did not control the effect of chronic drug usage on the period of fertility in bipolar cases.

According to these findings, the age of menopause is related to the clinical course of affective disorders. Moreover, the age of menopause also seems to be related to traits associated wtih affective disorders. Further studies are required to shed light on this relationship. These findings suggest that the neuroendocrine profiles of affective disorders remain to be discovered. On the other hand, considering the neuroprotective and anti-atherosclerotic effects of estrogen and the increased risks of cognitive impairment and ischemic heart disease, the fast and effective treatment of depression gains importance. Protective treatment of affective disorders and prevention of depressive episodes will serve women's and the public's health.

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