Association Between Age at Onset of Schizophrenia and Age at Menarche

Şizofreni Başlangıç Yaşı ile Menarş Yaşı Arasındaki İlişki

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ABSTRACT

Introduction: Increasing evidence from clinical practice, as well as from epidemiological and basic research shows that there are gender differences in clinical features of schizophrenia, and this may be related to estrogens. There may be a relationship between earlier puberty and later onset of the disease, because of the protective effects of estrogens in women with schizophrenia. In this study, our aim was to analyze the correlation between age of menarche and age of onset of schizophrenia and to investigate the protective effects of estrogens in schizophrenia.

Method: In this study, we included 289 patients who were diagnosed with schizophrenia. Those with mental deficiency or organic brain disorders were excluded from the study. All subjects were given a socio-demographic form to determine their personal information, age at menarche, age at first odd behavior, age at onset of the disease and first hospitalization. Data on factors which may affect the association between age at onset of schizophrenia and age at menarche such as family history, head or birth trauma etc. were recorded on the information form.

Results: We found out that age at menarche was negatively associated with age at first odd behavior and age at first psychotic symptoms.

Conclusion: Our study verifies the protective effects of estrogens and shows that the earlier puberty may be the cause of later onset of schizophrenia. A gender-sensitive approach in psychiatry improves our understanding of mental illness and our therapeutic strategies. (*Archives of Neuropsychiatry 2014; 51: 211-215*)

Key words: Schizophrenia, gender, menarche age, age at onset of schizophrenia

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ÖZET

Giriş: Epidemiyolojik ve laboratuara dayalı araştırmalar kadar klinik kanıtlar da östrojenin kadınların ruhsal durumu üzerinde anlamlı etkisi olduğunu göstermektedir. Bu konu ile ilgili yapılan araştırmalarda şizofrenide belirli özellikler açısından cinsiyete dair farklılıklar olduğu bilinmekte; bunda östrojenin kadın şizofreni hastalarında koruyucu rolünün etkisi olduğu hipotezi öne sürülmektedir. Bu çalışmada, bizim amacımız kadın şizofreni hastalarında şizofreni başlangıç yaşı ile menarş yaşı arasındaki korelasyonu araştırarak, östrojenin şizofrenide koruyucu etkisini sorgulamaktır.

Yöntem: SCID görüşmesi sonucunda şizofreni tanısı onaylanan 289 hasta çalışmaya dahil edildi. Zeka geriliği ya da bilinen organik beyin hastalığı (epilepsi, inme vb.) bulunan hastalar çalışmaya alınmadı. Verilen sosyodemografik form ile hastaların kişisel bilgileri, ilk tuhaf davranış yaşı, şizofreni başlangıç yaşı, ilk hastaneye yatış yaşı ve ilk adet yaşı hasta ve bir yakını ile görüşülerek belirlendi. Şizofreni başlangıç yaşı ile puberte başlangıç yaşı arasındaki ilişkiyi etkileyebilecek olan veriler (aile öyküsü, kafa veya doğum travması gibi) sosyodemografik forma kaydedildi.

Bulgular: Yaptığımız çalışmada menarş yaşı ile ilk tuhaf davranış ve ilk hastalık başlangıç yaşı arasında anlamlı negatif korelasyon olduğu sonucu ortaya çıktı.

Sonuç: Çalışmamız östrojenin koruyucu etkisiyle ilgili verileri desteklemekte; pubertenin erken başlamasının yani erken östrojen salınımının, şizofreni başlangıcının gecikmesine neden olabileceğini göstermektedir. Psikiyatride cinsiyet odaklı bir yaklaşım hastalıkları ve tedavi yaklaşımlarına olan bakış açımızı geliştirecektir. (*Nöropsikiyatri Arşivi 2014; 51: 211-215*)

Anahtar kelimeler: Şizofreni, cinsiyet, menarş yaşı, şizofreni başlangıç yaşı

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

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Introduction

Interest in the association between female sex hormones and mental diseases is not a new phenomenon. Even at the beginning of the last century, psychiatrists recognized a possible association between schizophrenia and estrogens (1).

Although the risk and the prevalence of developing schizophrenia among males and females are equal, especially in recent years, evidences of gender differences in certain features of the disease are on the increase. In several articles, it has been suggested that the differences may result from estrogen (1,2,3,4).

Age at onset of schizophrenia in females is later than in males (2,3,4,5,6). Estrogen, due its antidopaminergic effect, protects women against schizophrenia, however, in women whose reproductivity is over, estrogen production decreases, thus, leading to the second peak (2). It has been observed that functionality in women is better than in men before the disease develops (2,7,8). There are differences in the brain structures of schizophrenic patients due to sex differences. It has been found that the decrease in the volume of cortical gray matter and the enlargement of cortical sulcus and ventricles are higher in males than in females (9). Therefore, estrogen influences neuropsychological functioning in schizophrenia with differential effects on specific domains of cognitive functioning and neurological signs (10,11).

In another study carried out on individuals with schizophrenia, although the association of metabolic syndrome with age, age at onset of illness and duration of illness was not detected, men had a higher prevalence of metabolic syndrome than women (12). However, there are also studies showing higher prevalence of metabolic syndrome in women (13,14).

It has been reported that clinical symptoms in male and female patients may differ (15,16). Prognosis and the termination of the disease are better in females than in males (17,18). Several studies also found that there are differences between the two sexes in terms of response to the treatment (1,2,3,19). It has also been determined that antipsychotic dose at which females respond to the treatment is lower when compared to males (17). Sexual functions and prolactine levels in schizophrenia patients under antipsychotic medication also differs between the two genders (20). In addition, due to antidopaminergic effect of estrogen, females need less medication than do males. The fact that females need higher antipsychotic doses after menopause is regarded as evidence supporting this hypothesis and it has been hypothesized that this results from the decrease in estrogen levels (17). There are more reliable data on acute estrogen deficiency during episodes of schizophrenia. It has been fixed that there is an inverse association between negative symptoms of schizophrenia and estradiol levels. It has been seen that when estradiol levels increase, the level of symptom decreases and vice versa (21,22,23,24,25).

It has been determined that estrogens, 17 β - estradiol in particular, have a protective and regulative effect on neurons. 17 β - estradiol plays a role in the development of male and female embryonic brains which affect physiological and behavioral sexual differentiation (26).

The finding that there may be an association between age at puberty and age at onset of the disease in female schizophrenic patients is consistent with the hypothesis that estrogen has

a protective effect against schizophrenia. On the other hand, while some studies found a negative correlation between age at puberty and age at the onset of schizophrenia (27), some other studies failed to find such an association (28,29).

In this study, our aim was to analyze the correlation between age at menarche and the age of onset of schizophrenia and to investigate the protective effect of estrogens in schizophrenia.

Method

Subjects

Schizophrenia patients, who were hospitalized and treated in the psychiatry clinic and the outpatient department of İzmir Atatürk Training and Research Hospital and other psychiatry clinics in İzmir, were evaluated and interviewed in accordance with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). At the end of the interviews, 289 patients who were diagnosed with schizophrenia were included in the study.

Those with mental retardation or organic brain disorders, such as epilepsy, stroke, etc. were excluded from the study.

Written informed consent was obtained from all participants.

Instruments

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was developed by First et al. and is used for making the major DSM-IV Axis I diagnoses (30). The Turkish validity study was performed by Çorapçıoğlu (31). Following the SCID-I interview, all patients diagnosed with schizophrenia were sub-grouped according to DSM-IV.

Socio-demographic information form: A data form, which was prepared by the researchers was used in order to obtain the socio-demographic variables such as age, education, vocational status, marital status, the number of children they had and the duration of the disease. Age at menarche was also inquired in the sociodemographic form. In the studies about age at menarche, it has been found that when schizophrenic and non-schizophrenic patients were asked their age at menarche, the answers given by them and by their mothers were coherent and it was concluded that questioning only the age at menarche would be reliable and adequate in reflecting the onset of puberty and estrogen secretion (28,32,33).

Data which may be related with the age at onset of schizophrenia were recorded on the information form: Whether the patient;

- Had a family history of schizophrenia or other psychotic disorders
- Experienced head trauma
- Experienced a birth trauma during the delivery
- Had alcohol or drug abuse or addiction

In order to investigate the onset of schizophrenia retrospectively, we attempted to determine three topics:

- 1) Age at the first symptom of odd behavior
- 2) Age at onset of first psychotic symptoms
- 3) Age at first hospitalization

In order to determine the age at onset of the disease precisely, we decided to interview both the patient and one of the

family members. Data about age at first odd behavior onset was obtained from direct interviews with mothers. Data about age at first psychotic symptoms were obtained from the interviews with patients. Data about age at first hospitalization was obtained from hospital records.

Procedure

In order to verify schizophrenia diagnosis, patients diagnosed with schizophrenia were evaluated with SCID-I. Following the SCID interview, all patients were sub-grouped according to DSM-IV.

All subjects were given the defined socio-demographic form.

Statistical Analysis

The data obtained was assessed using SPSS (Statistical Package for Social Sciences) version 10.0 for Windows. Pearson's correlation analysis was performed to determine the association between age at menarche and age at onset of schizophrenia. Patients with postmenopausal onset and premenopausal onset were compared via independent samples t-test and chi-square test. In order to compare the numerical variables between different schizophrenic subtypes, ANOVA was employed. Significance value was $p \leq .05$ in all analysis.

Results

To investigate the effect of the age at menarche on the age at schizophrenia onset, only the patients with premenopausal onset were included in the statistical evaluation. This group consisted of 259 (88.42%) patients aged between 16 and 84 years. The mean age of these patients was 39.61 ± 11.9 years, the mean duration of education was 6.94 ± 4.2 years. Eighty-one patients (31.3%) were married, 119 (45.9%) were single, 39 (15.1%) were divorced or living separately and 20 (7.7%) were widowed. The mean number of children was $.93 \pm 1.2$. One hundred seventy-one (66%) patients were unemployed, 56 (21.6%) have been working before, but unemployed at that moment, 6 (2.3%) were retired, 1 (.4%) was student.

While the minimum age at onset of the disease was 10, the maximum age was 65 years. The mean age at onset of the disease was 28.45 ± 11.9 years. When the age at onset of the disease was considered, it was seen that the disease peaked twice at 25 and 45 years of age, respectively (Graphic 1). 76.8% of these patients ($n=199$) had been hospitalized at least once. The mean age of the inpatients at their first hospitalization was 29.17 ± 11.6 years.

Duration of the disease varied between 1 and 47 years. The mean duration of the disease was 13.27 ± 10.12 . According to their SCID evaluation, of all the patients, 76.8% ($n=199$) were paranoid type, 14.9% ($n=43$) were undifferentiated type, 7.3% ($n=21$) were disorganized type and 9% ($n=26$) were residual type. When schizophrenia was evaluated in terms of subgroups, the mean age at onset of the disease was 28.69 ± 12.33 in the paranoid type; 25.24 ± 9.50 in the disorganized type, 26.98 ± 11.07 in the undifferentiated type, and 29.33 ± 11.96 in the residual type. It was determined that mean age at onset of the disease was later in the paranoid and residual subgroups than in the disorganized group (Graphic 2). When age at menarche was considered in the subgroups of schizophrenia, it was 13.48 ± 1.38 in the paranoid subgroup, 13.71 ± 1.27 in the disorganized subgroup, 13.53 ± 1.28

in the undifferentiated subgroup and 13.73 ± 1.40 in the residual subgroup. However, the difference between the subgroups in terms of age at menarche and age at onset of the disease was statistically insignificant ($p=.80$, $p=.64$, respectively).

The mean age of the patients at menarche was 13.48 ± 1.3 . Age at first odd behavior, age at onset of the disease and age at first hospitalization were 24.89 ± 9.59 , 26.12 ± 9.6 and 27.39 ± 9.9 , respectively (Table 1).

When the association between these parameters and age at menarche was inspected, it was determined that age at menarche significantly negatively correlated with age at first odd behavior ($p=.000$, $r=-.375$) and age at first psychotic symptoms ($p=.000$, $r=-.382$). However, there was no significant correlation between age at menarche and age at first hospitalization ($p=.004$, $r=-.215$). Since the number of patients who had their menarche at age 9, 10, 11, 16, 17 and 18 was statistically insignificant, the patients were grouped as having their menarche before 12 or after age 15 (Graphic 3).

In patients with postmenopausal onset ($n=30$, 11.58%), age at menarche did not significantly correlated with age at first odd behavior, age at first psychotic symptoms and age at first hospitalization ($p=.612$, $r=.097$; $p=.214$, $r=.234$; $p=.925$, $r=.025$).

When patients with postmenopausal onset were compared with patients with premenopausal onset, there were no

Graphic 1. Age at onset of the disease

Graphic 2. Age at onset of the disease in subgroups of schizophrenia

statistically significant difference between the groups for the duration of education ($p=.256$), the duration of the disease ($p=.086$), and age at menarche. In the postmenopausal onset group being married, and being unemployed was more common than the other group ($p=.000$, $p=.001$). Between the two groups, there were no significant difference in history of birth trauma, family history of schizophrenia or other psychotic disorders and having alcohol or drug abuse or addiction ($p=.614$, $p=.679$, $p=.660$, respectively). In the postmenopausal onset group, head trauma history was significantly more frequent than in the premenopausal onset group ($p=.008$).

Discussion

When the association between age at menarche and age at first odd behavior, age at onset of schizophrenia, and age at first hospitalization in schizophrenic patients was inspected, it was determined that age at menarche negatively correlated with age at first odd behavior and age at first psychotic symptoms.

The number of the research which are consistent with the hypothesis that estrogen has a preventive effect and which have investigated the association between early puberty age and late onset of the disease in female schizophrenic patients is rather few. In their study, Cohen et al. investigated the association between age at onset of puberty and age at onset of schizophrenia and found a significant negative correlation between the three measurements (first strange behavior, first psychotic symptoms and first hospitalization for psychiatric

reasons), which is consistent with the findings in our study (27). However, a study carried out by Ruiz et al. does not support the view on the relationship between age at menarche and age at onset of schizophrenia (28).

In their study, Hochmann et al. determined that age at menarche did not correlate with age at onset of schizophrenia and age at first hospitalization, but that negative symptom scores were higher in patients who experienced late menarche and that deterioration in functionality was more, which is consistent with the hypothesis on estrogen (29). Cohen et al. in their study, concluded that other factors, such as drug use, head trauma, obstetric complications and family history of schizophrenia do not affect the association between age at onset of schizophrenia and age at onset of puberty (27).

In our study, factors which may affect the age at schizophrenia onset such as birth trauma, family history and alcohol and substance did not differ between the patients with premenopausal and postmenopausal onset. In patients with postmenopausal onset, history of traumatic head injury was significantly more common than in premenopausal onset patients. Therefore, the origin of the disease in this group may be caused by organicity, although they were not diagnosed with organic mental disorder.

Unlike those other studies, in our study, the diagnoses were confirmed with standard interviews and schizoaffective patients were not included in the study group. We included a total of 259 subjects in this study while the number of subjects was 35 in Cohen's study, 22 in Ruiz's and 57 in Hochmann's study. The limitation of our study, similar to that of other studies, the puberty age was retrospectively determined from the responses given by the patient and a relative of the patient. Although the subjects, relatives, and psychiatric records showed high concordance for information that was available from all three sources, corroboration was not available for every data point. Besides, the interviewer was not blind to the hypothesis.

Riecher-Rossler and Hafner emphasized that a gender-sensitive approach in psychiatry improves understanding of mental illness and therapeutic strategies, furthermore comprehensive psychiatry should not be considered as two separate areas called 'biological psychiatry' and 'social psychiatry' (34).

There are a great number of studies reporting that estrogen had a protective effect against psychosis (6,12,22,23,24,25,26). Our study confirmed the view that estrogen has a protective effect, and that early onset of puberty, in other words, early estrogen secretion might delay the onset of schizophrenia. It is known that estrogen

Graphic 3. Association between parameters of age at onset of schizophrenia and of age at menarche

Table 1. Sociodemographic variables and parameters of age at menarche and onset of the disease in patients who developed schizophrenia before menopause and after menopause

	Premenopausal onset group	Postmenopausal onset group	p
Age	39.61±11.9	59.73±8.87	.000*
Duration of education	6.94±4.24	6±4.68	.0256
Duration of disease	13.62±10.3	10.27±7.57	.086
Age at menarche	13.48± 1.3	13.98±1.32	.062
Age at first odd behavior	24.89± 9.6	48.03±10.24	.000*
Age at onset of the disease	26.12± 9.6	49.80±7.88	.000*
Age at first hospitalisation	27.39± 9.9	50.24±8.24	.000*

antagonizes and potentiates the dopamine system. Today, it is being discussed whether selective estrogen modulators may be added to antipsychotic treatment. Further investigation in this area is needed.

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