

Family History in Patients with Bipolar Disorder

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ABSTRACT

Introduction: In this study, we aimed to better understand the genetic transmission of bipolar disorder by examining the family history of patients.

Methods: Sixty-three patients with bipolar disorder and their families were included. The final sample comprised 156 bipolar patients and their family members. An inclusion criterion was the presence of bipolar disorder history in the family. The diagnosis of other family members was confirmed by analyzing their files, hospital records, and by calling them to the hospital.

Results: Sixty-five patients were women (41.6%) and 91 were men (58.3%) (ratio of men/women: 1.40). When analyzing the results in

terms of the transition of disease from the mother's or father's side, similar results were obtained: 25 patients were from the mother's side and 25 patients were from the father's side in 63 cases.

Conclusion: The results of our study support the fact that a significant relationship exists between the degree of kinship and the heritability of bipolar disorder and, furthermore, that the effect of the maternal and paternal sides is similar on the transmission of genetic susceptibility.

Keywords: Bipolar disorder; family history; genetic transmission

INTRODUCTION

Bipolar disorder is a serious and chronic disorder, which continues with recoveries and relapses and causes significant morbidity and mortality. It not only causes a destruction in the social and professional life of the affected individual but also imposes serious financial burdens on the communities they reside in. Studies reveal that the prevalence of bipolar disorder is 0.5% to 1.5%, that the disease is generally diagnosed between 18 and 30 years of age, and that its prevalence in men and women is similar (1,2,3). The familial transition of bipolar disorder is known by clinicians, patients, and their families. The risk of prevalence in first-degree relatives of patients with bipolar disorder is increased approximately 10-fold over the normal community, and the rate of prevalence is 5–10% in siblings and 10% in dizygotic twins and above 50% in monozygotic twins (3,4,5,6,7). Bipolar disorder is one of the psychiatric disorders where complex and multifactorial heritage is most effective at a rate of 60–80% (8).

According to the information obtained from familial, twin, adoption, linkage analysis, and molecular genetic studies aimed at understanding the genetics of bipolar disorder, it has been concluded that the heredity of the disorder does not comply with the classical Mendel laws and rules (autosomal dominant, autosomal recessive, or gender-related heredity), and that there may be many gene loci and many types of heredity issues related to the disorder (4,5,9,10). In these studies, a single gene responsible for the disorder associated with bipolar disorder could not be identified, and though all studies did not fully support each other, some chromosomal disorders, gene loci, and abnormalities standing as predisposing causes of bipolar disorder were reported (such as some gene loci located on the 4th, 12th, and 18th chromosomes) (2,4,5,9,11).

Methodologic problems faced in determination of genes related to bipolar disorder include that there are many effective genetic and environmental factors involved and also relate to the cost of the methods used and also that their results are not as efficient as expected, which taken together highlight the difficulty in conducting genetic studies in general (12). At this point, biologic predisposition markers (endophenotypes), which are related to disease genes and that are more frequently seen in unaffected family members than in the community and that can be determined by biochemical tests as well as familial studies, may serve as guiding lights (13). There are only a few studies in the literature detailing familial studies in bipolar disorder. Previous studies have reported that in bipolar disorder, familial history may affect the progress of the disorder and the spouse prevalence rates. It has been reported that patients with familial history catch bipolar disorder at an earlier age, have more frequent seizures, have a higher rate of hospitalization, and are more depressed, anxious, and irritable and that more disorders



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Received: 04.07.2014 **Accepted:** 30.09.2014

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are reported in the cognitive functions of patients with familial loading where the number of suicide attempts is also higher. Furthermore, familial history is associated with rapid cycling (8). Familial history studies may thus shed a light on the form of heredity of the disease (4).

This study aimed to review and examine the familial histories and family trees in patients with bipolar disorder, thus studying the relationship between genetic disposition and the degree of kinship on one side and bipolar disorder on the other side to better understand the risks caused by kinship on the disease.

METHODS

Patients

The study included 63 independent families including a bipolar disorder I (BD I) patient. The sample consisted of 156 bipolar disorder I patients in total. Patients were collected from among the inpatients of two Faculties of Medicine and two state hospitals, or were outpatients of psychiatry polyclinics. Four psychiatrists and one research assistant were involved in the collection of patients for the study. Study data were interpreted by psychiatrists, geneticists, and statisticians. The study inclusion criteria were the existence of a BD I story in the patient's family, and registration in the relevant study centers. Familial history was asked about with the patients or their relatives. The diagnosis of other family members was confirmed by analyzing their files and hospital records and by calling them to the hospital. The first diagnosed patient of each family (index case, proband) was accepted as a reference. Other disorders in the schizophrenia spectrum and psychosis, and schizoaffective disorder, and bipolar and related disorders caused by substance/drug, and bipolar and related disorders associated with another healthcare situation were not included in the study. Approval of the local ethical committee and an informed consent form of the patients were taken for the study.

Statistical Analysis

Descriptive statistics for continuous variables were determined as the average, standard deviation, minimum and maximum values, while descriptive statistics for the categorical variables were determined as the number and percentage. The Z test was used for comparing the ratios for categorical variables. In calculations, the statistical significance level was taken as 5%, and the Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) (version 13) and the MINITAB (version 14) statistics package programs were used for the calculations.

RESULTS

As regards the distribution of sexes, out of 63 proband bipolar disorder patients included in the study, 27 were women (42.9%), and 36 were men (57.1%) (ratio of men/women: 1.33). Out of all the patients (156 patients), 65 were women (41.6%) and 91 were men (58.3%) (ratio of men/women: 1.40) (Table 1). A disorder was detected in first degree relatives (mother, father, siblings, and children) for 57 of these patients, and in second degree relatives (grandmother, uncles, aunts, and nieces/nephews) for 22 patients, and in third degree (10 patients) and above (4 patients) relatives (cousins, father's uncle, father's cousins, etc.) of 14 patients (Table 2). The differences between the number of first degree relatives and the number of second degree relatives and between the number of second degree relatives and the number of third degree relatives were statistically significant (respectively, $p=0.001$ and $p=0.012$). Furthermore, 1 patient was detected in the families of 43 patients, and 2 patients were detected in the families of 12 patients, and 3 or more patients were detected in the families of 9 patients. The bipolar disorder starting age average was 23.23 ± 10.24 (range: 14–52).

Table 1. Comparison of patients and their relatives in terms of gender

	Men	Women	Men/ women	p
Patients	36/63 (57.1%)	27/63 (42.9%)	1.33	0.105
Relatives of patients	55/93 (59.1%)	38/93 (40.8%)	1.44	0.011
Total	91/156 (58.3%)	65/156 (41.6%)	1.40	0.003

Table 2. Comparison of degrees of kinship

		p*
Number of 1 st degree relatives	57	0.001
Number of 2 nd degree relatives	22	0.012
Number of 3 rd degree relatives	10	0.085
*comparison with the next degree		

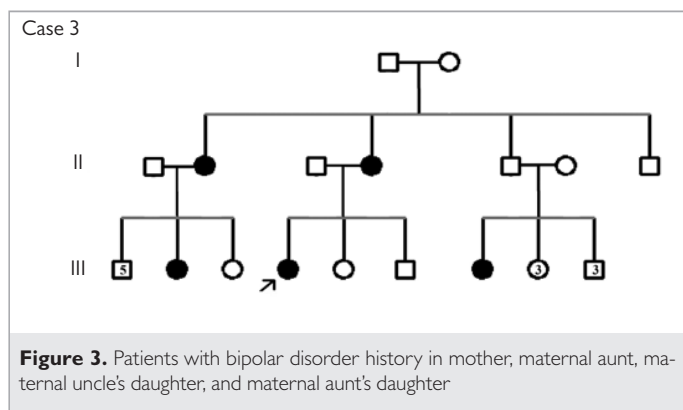
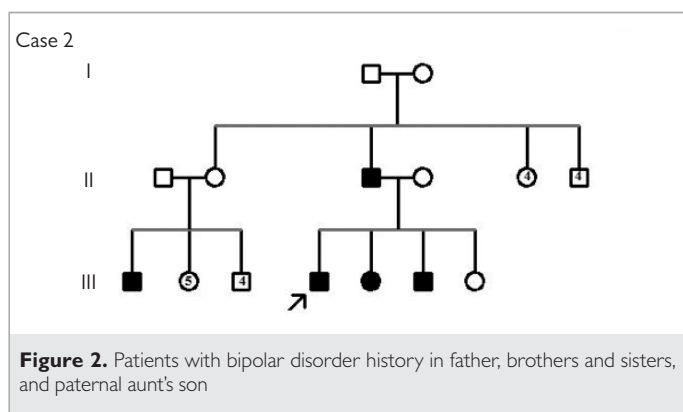
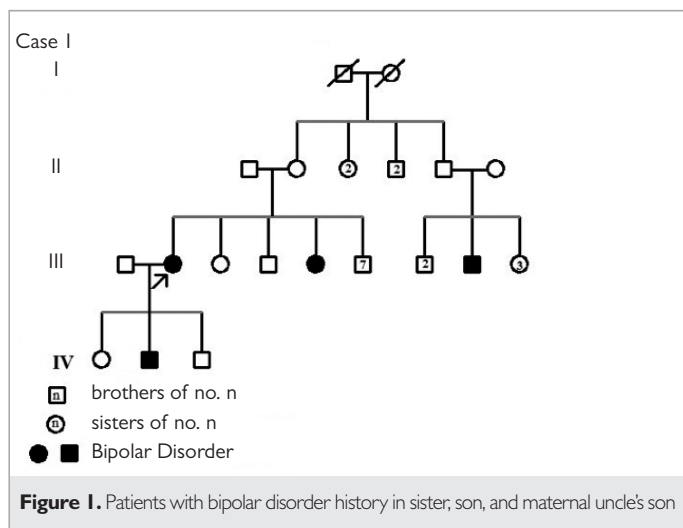
Table 3. Comparison of mother's-side relatives to father's-side relatives of patients

	Mother's side	Father's side	p
Mother and father themselves	9/63	11/63	0.626
Mother's and father's relatives	16*/63	14**/63	0.675
Total of mother's and father's sides	25/63	25/63	1.00
*Maternal uncle, maternal aunt and their children; **Paternal uncle, paternal aunt and their children.			

When analyzing the results in terms of the transition of disease from the mother's side or the father's side, similar results were obtained. There was a bipolar disorder in the mother of 9 patients (14.2%), in the father of 11 patients (17.4%), in the sisters/ brothers of 31 patients (49.2%), in maternal uncles, maternal aunts, or their children of 16 patients (25.3%), and in paternal uncles, paternal aunts, or their children of 14 patients (22.2%). There were 25 patients from the mother's side and 25 patients from the father's side (Table 3). Figures 1, 2, and 3 show the examples of family trees of three bipolar disorder cases. Figure 1 presents bipolar disorder patients with regard sister, son, and maternal uncle's son, while Figure 2 presents bipolar disorder patients in the father, both brother and sister, and paternal aunt's son, and Figure 3 presents bipolar disorder patients in the mother, maternal aunt, and daughters of the maternal uncle and aunt.

DISCUSSION

In our study, it was found that the prevalence of bipolar disorder is higher in males than females (approximately 1.3–1.4 times higher), and the numbers of patients from the mother's side and from the father's side are similar. In some studies studying the mother and father effects in bipolar disorder, transition from the mother has been reported to be higher than transition from the father (10,14). In a study conducted on 31 families with genetic loading, it was reported that the prevalence of disease in children of sick mothers was approximately 2.3–2.8 times higher than for the children of sick fathers (10). The same study also demonstrated that the number of sick relatives from the mother's side is significantly higher than the number of sick relatives from the father's side. However, contradictory findings have been reported in subsequent studies (15,16). Furthermore, epidemiological studies have not supported the finding that the transition from the mother's side is higher (14).



Though some other publications, just like our study, do not support the finding that the transition from the mother's side is higher, it is asserted that mitochondrial heredity may play a role in bipolar disorder (14). Mitochondrial DNA (mtDNA) is a molecule that is inherited solely from the mother's ovum and it plays a role in determination of the sensitivity of an individual to environmental stresses (10). Defects in mitochondrial DNA sequences may contribute to a predisposition to such complex diseases as diabetes and bipolar disorder. Therefore, if all bipolar disorder patients have mitochondrial predisposition genes, then the transition of bipolar disorder from the mother's side would be higher. However, mitochondrial heredity types have not been shown in bipolar disorder (4,10).

It has also been reported that another mechanism underlying the transition from the mother's side may be genetic imprinting. Imprinting means

that the relevant mother-father gene cannot be transcribed and remains silent, and therefore, other mother-father allele appears in phenotypes. For instance, if and when the father's relevant gene cannot be transferred to mRNA, this probably results in allele's not being transcribed, and other active single allele's being effective in the genotype. If the bipolar disorder predisposition gene comes from the father, and the allele from the mother remains silent, then the father's phenotype would be determined in the child (4,10). Though imprinting cannot be demonstrated in bipolar disorder, it is listed among one of its probable causes.

In some studies studying the parental effects in bipolar disorder; the father's effect is also reported. In a study conducted with a large sample, the prevalence of disease was found to be higher in children of fathers with bipolar disorder than in the children of mothers with bipolar disorder (15). These results lead us to think that bipolar disorder may be a paternal disease. On the other hand, there are some studies asserting that bipolar disorder may be inherited through X on the basis of cases of transmission from father to son, but serious criticisms have been raised against the methodologies utilized in such studies (16). The analyses make us think that inheritance through X may only be relevant in a small group of cases (1).

Another field where the parental effects in bipolar disorder are studied is in the linkage studies. Bipolar disorder linkage studies have shown that some gene loci in the 18th chromosome may be associated with the disease (17). These studies have further studied the parental effects. In spite of the existence of many studies indicating that transition from the father's side is higher; there are also studies where none of the sides was found to be higher than the other (18,19). Failure to fully clarify the pathophysiology of the disease is shown as one of the reasons for the different results obtained in the linkage studies (17).

One of the key questions attempted to be answered in the familial studies is whether the lifelong disease prevalence rates in the first degree relatives of bipolar disorder patients varied according to the degree of kinship or not. Though it is known whether bipolar disorder concentrates in some families, the question of whether the lifelong disease prevalence rates of relatives of probands are associated with the degree of kinship or not has come to mind. According to our study, as the degree of kinship increases, the prevalence risk of the bipolar disorder also increases (Table 2). It is reported that the mother-father and sibling distribution of female patients is similar to that of male patients in bipolar disorder. In a study conducted on 187 patients, it was found out that the father was also ill in 65% of the patients' cases, while the mother was also ill in 6.4% of patients' cases (14). Similar to our results, this study also reported that transition from the mother's side was almost identical to transition from the father's side. Again, in another study conducted on bipolar disorder 2 patients, no parental effect was been shown to be higher than the other (16).

Besides the studies reporting that the prevalence risk in siblings is higher than the prevalence risk in the mother, father, and children, the same authors later reported different results, and it has been said that the small sample size may have played a role in obtaining such contradictory results (1). In addition, there are also studies reporting that the relative risk of bipolar disorder for siblings increases 8–9 times (19). Also in our study, while the prevalence rates of bipolar disease in the mother and father were found to be similar (14.2% and 17.4%), this rate was very much higher in siblings (49.2%). In bipolar disorder; the lifelong disease risk among the relatives of patients is reported not to be different between genders (1). The results of our study are not coherent with this finding. As shown in Table 1, when the patients and their relatives were compared in terms of gender; it can be noted that the number of males is higher (1.3–1.4 times higher).

As a conclusion, there exists a significant relationship between the degree of kinship and bipolar disorder. The risks of the transmission of disease predisposition genes from the mother's side or from the father's side seem to be similar. For bipolar disorder heredity patterns, though single gene transition comes to mind for some families, this fails to clarify many cases. Many genetic mechanisms may constitute a complex inheritance form. Non-Mendelian hereditary mechanisms, such as mitochondrial inheritance and non-imprinting, may play a role in the complex genetics of bipolar disorder.

Many limitations may be listed for this study. First, the relatively low number of patients may prevent generalization of the findings. The inclusion of only bipolar disorder I patients to the study, and the non-use of structure clinic interviews (SCID I) may be listed among other limitations of this study. For these reasons, the findings of this study should be supported by new studies to be performed on larger groups of patients and on different ethnic populations.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yüzüncü Yıl University School of Medicine (B.30.2.YYU.0.01.00.00/82).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – O.Ö., S.C.; Design – O.Ö., S.C., E.A.M., S.K.; Supervision – E.A.M., P.G.Ö., S.K.; Resources – O.Ö., P.G.Ö.; Materials – O.Ö., S.C., E.A.M.; Data Collection and/or Processing – P.G.Ö., E.Y., A.A., E.A.M.; Analysis and/or Interpretation – O.Ö., S.C., S.K.; Literature Search – O.Ö., A.A., E.Y.; Writing Manuscript – O.Ö., S.C., S.K.; Critical Review – S.C., E.A.M.; Other – E.Y., P.G.Ö., A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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