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Anticipation in Bipolar Disorder: A Comparison Between Two Generations

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Abstract

Objective: *The genetic phenomenon of anticipation is a pattern of inheritance that includes earlier age at onset and increased severity of symptoms in succeeding generations, and is a feature of some neurodegenerative diseases. This phenomenon is suggested to occur in bipolar disorder (BP) as well.*

Method: *Anticipation in children with BP type 1 (s2) (n = 31) and their parents (s1) (n = 31)–consecutive generations–was assessed by analyzing clinical characteristics and prognoses.*

Results: *Age at onset of BP type 1 in s2 (mean: 19.3 ± 4.2 years) occurred earlier than in s1 (mean: 29.5 ± 10.2 years) (u = 345, P < 0.001). There was a direct negative correlation between the s1 and s2 cases (r = –0.554, P < 0.001). The total number of episodes in s1 (13.9 ± 12.3) was greater than in s2 (8.7 ± 7), which had a higher frequency of episodes (0.6 ± 0.3 and 1.5 ± 1.2) (u = 357, P < 0.001). There was a direct correlation between total episodes and the frequency of manic episodes between s1 and s2 (r = 0.312, P < 0.001 and r = 0.365, P < 0.001, respectively). We observed that 72.7% of BP type 1 parents that had episodes with psychotic features had offspring that had episodes with psychotic features.*

Conclusions: *Results of this study show that age at onset was earlier and the frequency of episodes was greater in s2 BP type 1 cases. In addition, episodes with psychotic features might be a marker for genetic anticipation.*

Key Words: *Bipolar disorder, anticipation, early onset*

INTRODUCTION

The prognosis of bipolar disorder (BP) varies case by case (Bellivier et al. 2001). A negative prognosis is related to clinical variables, such as neuropsychological developmental disorders, low academic performance, deterioration of interpersonal relationships, severe progress of illness (frequent and more severe episodes), frequent hospitalization, and poor response to mood stabilizers (Carlson 1984; Strober et al. 1995; Schulze et al. 2002; Yıldız & Sachs 2003). Early age at onset negatively influences the prognosis of BP (Bellivier et al. 2001). Another phenomenon that influences the prognosis of BP, which is related to the age at onset, is genetic anticipation (McInnis et al. 1993).

This phenomenon was first demonstrated in some neurodegenerative disorders, including myotonic dystrophy, fragile X syndrome (FXS), mental retardation related to FXS, Freidreich's ataxia, Huntington's disease, spinobulbar muscular atrophy, spinocerebellar ataxia type 1, spastic paraplegia, dentatorubral-pallidoluysian atrophy, and Machado-Joseph disease (Papadimitriou et al. 2005). It has been indicated that anticipation in these disorders might be connected to a dynamic mutation related to trinucleotide repeat disorders (Li and el Mallakh 1997).

Anticipation represents a different pattern of inheritance (McInnis et al. 1993), in which both early age at onset and increased severity are seen in consecutive generations of individuals affected by BP (Petronis and

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Kennedy 1995). This phenomenon might be related to genetic mechanisms; however, molecular genetic studies conducted to date haven't revealed a valid genetic explanation that can clarify anticipation in BP. Genomic studies that have examined trinucleotide repeat disorders report contradictory findings (Lindblad et al. 1995; O'Donovan et al. 1995; Vincent et al. 1999).

The present study aimed to evaluate genetic anticipation in BP by assessing the clinical characteristics and prognosis of BP in 2 consecutive generations. To the best of our knowledge this is the first study of its kind to be conducted in Turkey.

METHOD

Sample

The study sample consisted of cases diagnosed with BP type 1 (s2) (n = 31) and their mothers and fathers (s1) (n =15 [48.4%] and n = 16 [51.6%], respectively) who were also diagnosed with BP type 1. Offspring with BP type 1 whose mothers and fathers (s= 1) both had BP type 1 were not included in the sample because it might have negatively affected the results of our evaluation (Alda et al. 2000). Patients with a psychiatric or physical disorder that prevented them from being interviewed or hindered the ability to provide accurate information, those that declined participation in the study, and those that didn't provide informed consent (s= 6) were not included in the study. Genetic anticipation has been suggested to occur in schizophrenia; in fact, the KCNN3 gene was reported to be related to an increase in the number of CAG repeats (Saleem et al. 2000). Consequently, another exclusion criterion was a family history of schizophrenia or schizoaffective disorder. Distribution of gender in s1 and s2 were identical (16 male, 15 female). There were no sibling couples among the proband cases that participated in the study. Mean age was 55.2 ± 8.8 years in s1, and 28.8 ± 9.3 years in s2.

Instruments

Turkish versions of the Structured Clinical Interview for DSM Axis 1 Disorders (SCID-I) (Özkürkçügil et al. 1999) and the Structured Clinical Interview for DSM non-patients (SCID-NP) (Sorias et al. 1990) were used for the diagnostic interviews. Sociodemographic data and disease characteristics were collected via a questionnaire created by the researchers. Data collected about BP consisted of age at onset, type of first episode, duration of the disorder, the number of depressive, manic, hypomanic, mixed, and unidentified episodes, total number of episodes, age at first psychotropic and mood stabilizer use, whether there is a shift in the polarity of the episode or not, number of manic or depressive shifts, number of episodes with psychotic features, number of suicide attempts before and after use of mood stabilizers, and number of hospitalizations.

Assessment of Anticipation

In the assessment of anticipation age at onset and episode frequency were considered the first priorities (McInnis et al. 1993). Age at onset was accepted as the age at which the first episode was identified and the criteria for a mood episode were met (Geller et al. 2004). We decided to consider episode frequency instead of the number of episodes because assessing the latter independent of disease duration wouldn't have produced accurate results. Episode frequency was calculated by dividing the total number of episodes (depression, mania, hypomania, mixed, and unidentified) by the time that elapsed from disease onset to interview or date of death (month × 12). In addition, anticipation was also assessed according to other criteria, such as the types and number of episodes, the presence of psychotic features and shifts in the polarity of the episode, hospitalization (H), and any suicide attempts before or after the use of mood stabilizers (MS). Using the frequencies of some of these criteria was thought to be appropriate when they are compared to each other.

Procedure

Participants for this study (mothers and fathers diagnosed with BP type 1, and their offspring, similarly diagnosed) were found by reviewing the archive records and outpatient clinic files at Ege University Medical Faculty Department of Psychiatry, Affective Disorder Unit. The cases were included in the study if they had been followed-up in this unit for at least 1 year. The participants were contacted via phone or mail, provided information about the study, and invited to participate. All the participants provided written informed consent.

Starting with s2, interviews were conducted using SCID-I. In order to determine if the parents were affected as well, SCID-NP was administered to the cases confirmed as BP type 1. Then, SCID-I was used to confirm the diagnosis of each suspected BP type 1 case. Both offspring (s2) and parents (s1) diagnosed with BP type 1 were included in the study.

Data about the disorder was collected from the participants, their relatives that knew the history of the dis-

Table I. Comparison of mean age, years in school, gender, marital status, and level of education.

	s1		s2		
Mean Age	Mean	SD	Mean	SD	P
General	55.2	8.8	28.8	9.3	0
Male	54.2	7.5	29.1	10.5	0
Female	56.3	10.2	28.5	8.1	0
Years in School					
General	9.1	5.3	11.5	3.1	0.094
Male	11.1	5.4	11.9	2.1	0.78
Female	6.9	4.3	11.1	3.9	0.019
General					
Male	16	51.6	16	51.6	1
Female	15	48.4	15	48.4	1
Marital Status					
Married	28	90.3	16	51.6	0.003
Divorced	2	6.5			
Widowed	1	3.2			
Single			15	48.4	
Level of education					
Illiterate	4	12.90%			
Primary or High Sc.	18	58.10%	21	67.80%	0.931
University	9	29%	10	32.30%	

order, and archive records. The study did not include patients whose ability to provide accurate information was doubtful (n = 4).

Statistical Analysis

The Mann-Whitney U test was used to compare numerical variables and the chi-square test was used to compare categorical variables. The Spearman test was applied to compare age at onset and frequency of episodes across the 2 groups. Suicide attempts and frequency of hospitalization before and after the use of mood stabilizers were analyzed using Kruskal-Wallis variance analysis. The statistical significance was $P < 0.05$ and all the tests were two-tailed.

RESULTS

Comparison of Sociodemographic Characteristics

Mean score for years in school was higher among women in s2 (u = 121, P = 0.019) (Table I), and 90.3% (n = 28) of the cases in s1 and 51.6% (n = 16) of the cases in s2 were married (x2 = 2145, P = 0.003).

Comparison of Age at Onset with the Number and Frequency of Episodes, in Terms of Anticipation

Age at onset in s2 (mean: 19.3 ± 4.2 years) was less than that in s1 (mean: 29.5 ± 10.2 years) (u = 345, P < 0.001) (Table 2). There was a negative linear relationship between age at onset in s1 and s2 cases (rs = 0.554, P < 0.001).

While the total number of episodes was higher in s1 than in s2 (13.9 ± 12.3 and 8.7 ± 7, respectively), the frequency of episodes was higher in s2 (s1 and s2 respectively, 0.6 ± 0.3 and 1.5 ± 1.2) (u = 357, P < 0.001). Results were similar for the number and frequency of depressive, manic, and mixed episodes (Table II). The number of episodes was higher in s1, whereas the frequency of epi-

Table II. Comparison of age at onset, total number and types of episodes, and the frequency of episodes.

		n	Mean	SD	P
Age at onset	s1	31	29.5	10.2	
	s2	31	19.3	4.2	0.000
Number of episodes	s1	31	13.9	12.3	
	s2	31	8.7	8	0.024
Frequency of episodes	s1	31	0.6	0.4	
	s2	31	1.5	1.9	0.000
Duration of disorder	s1	31	29.8	20.3	
	s2	31	18.4	17.6	0.008
Duration of disorder frequency	s1	31	1.4	1.3	
	s2	31	2.7	2.1	0.003
First use of psychotropics	s1	30	30.2	11.7	
	s2	31	19.7	4.9	0.000
First use of mood stabilizers	s1	27	37.6	11.9	
	s2	31	22.3	6.9	0.000
Number of expressive episodes	s1	31	6.2	5.7	
	s2	31	3.5	3.7	0.000
Frequency of depressive episodes	s1	31	0.3	0.2	
	s2	31	0.4	0.3	0.050
Number of manic episodes	s1	31	6	5.7	
	s2	31	3.9	4.3	0.332
Frequency of manic episodes	s1	31	0.2	0.2	
	s2	31	0.7	0.8	0.000
Number of hypomanic episodes	s1	31	2.6	5.7	
	s2	31	0.9	1.7	0.184
Frequency of hypomanic episodes	s1	31	0.1	0.2	
	s2	31	0.1	0.3	0.54
Number of mixed episodes	s1	31	0.1	0.5	
	s2	31	0.4	0.7	0.53
Frequency of mixed episodes	s1	31	0.004	0.02	
	s2	31	0.1	0.3	0.031
Frequency of hospitalization	s1	19	0.1	0.8	
	s2	18	0.4	0.5	0.004

sodes was higher in s2 (frequency of depressive, manic, and mixed episodes respectively, P= 0.05, P < 0.001, P = 0.031). There was a linear relationship between the frequency of episodes in s1 and s2 cases (rs = 0.312, P < 0.001).

A weak relationship was observed between age at on-

Table III. Comparison of shifts in the polarity of the episodes, existence psychotic features, suicide attempts, and response to mood stabilizers.

		n	%	s	%	P
	s1	17	54.8	14	45.2	
Presence of shifts in the polarity	s2	17	54.8	14	45.2	0.456
	s1	11	35.5	20	64.5	
Presence of episode with psychotic features	s2	15	48.4	16	51.6	0.303
	s1	6	19.4	25	80.6	
Suicide attempts	s2	5	16.1	26	83.9	0.740
	s1	5	16.1	26	83.9	
Suicide attempts prior to the use of mood stabilizers	s2	5	16.1	26	83.9	0.1
	s1	2	6.5	29	93.5	
Suicide attempts after the use of mood stabilizers	s2	3	9.7	28	90.3	0.641
	s1	19	61.3	12	38.7	
Hospitalizations	s2	18	58.1	13	41.9	0.796
	s1	16	59.3	11	40.7	
Hospitalizations prior to the use of mood stabilizers	s2	15	50	15	50	0.403
	s1	10	38.5	16	61.5	
Hospitalizations after the use of mood stabilizers	s2	12	41.4	17	58.6	0.825

set and total episode number frequency (rs = –0.254, P = 0.023).

Comparison of other Clinical and Prognostic Characteristics

The difference in the rates of depressive and manic episodes in s1 (n = 21, 67.7% and n = 10, 32.3%, respectively) and s2 (n = 16, 51.6% and n = 14, 45.2%, respectively) were not statistically significant in terms of the type of first episode (P = 0.249). While in s2, one of the cases' (3.2%) first episode type was mixed, in s1 no one's first episode was the mixed type.

The difference between s1 and s2 was not statistically significant when manic or depressive shifts (s1: 54.8%; s2: 54.8%; P = 0.456) and having an episode with psychotic features (s1: 35.5%; s2: 48.4%; P = 0.303) were evaluated. Psychotic features were observed in only 8 parent-offspring pairs (25.8%). Psychotic features were observed in both parents (n = 11) their offspring (n = 8) among 8 s1-s2 pairs (72.7%). On the other hand, while the parents in 7 s1-s2 pairs (35%) did not have psychotic features their offspring did (n = 20).

When s1 and s2 were evaluated in terms of attempted suicide (s1: 19.4%; s2: 16.1%; P = 0.740) and hospitalization (s1: 61.3%; s2: 58.1%; P = 0.796) there were no statistically significant differences between the groups. The frequency of hospitalization was higher in the s2 BP type 1 cases (0.4 ± 0.5) than in s1 cases (0.1 ± 0.8) (P = 0.004).

Age at first psychotropic (s1: 30.2 ± 11.7 years; s2:

19.7 ± 4.9 years) and mood stabilizer use (s1: 37.6 ± 11.9 years; s2: 22.3 ± 6.9 years) was earlier in s2 cases, as compared to s1 cases ($P < 0.001$ and $P < 0.001$) (Table III). The rate of attempted suicide and hospitalization before and after mood stabilizer use did not differ between the s1 and s2 BP type 1 cases. On the other hand, when the difference between the rates of attempted suicide and hospitalization before and after mood stabilizer use sere compared, the difference was higher in the s1 cases ($P = 0.035$ and $P = 0.027$).

DISCUSSION

To the best of our knowledge the present study is the first study conducted in Turkey that investigated genetic anticipation in BP. This study evaluated individuals (s2) that were diagnosed with BP and that had 1 parent (s1) that was also diagnosed with BP, and compared the clinical variables of BP in both generations. The most significant limitation of this study was the retrospective evaluation of the BP cases. On the other hand, the inclusion criterion that each case had to have been followed-up for at least 1 year, and our attempts to collect information from the unit records and interviews with the individuals and their relatives were implemented in order increase the reliability of the results.

The study has some other limitations. It is reported that there were confounding factors that created bias in previous studies that suggested genetic anticipation plays a role in BP (Goossens et al. 2001). These confounding factors were as followings: 1. Preferential selection of parents with late onset because parents with early onset have decreased fertility (Bassett and Honer, 1994); 2. The possibility that some offspring were still in the risk period, but did not develop BP at the time of the study, though they might develop the disorder at a later time (Merette et al. 2000); 3. The increase in the amount of knowledge in clinical studies over time resulting in the increased evaluation of disease severity and earlier determination of age at onset (Merette et al. 2000), or the fact that a parent with BP is aware of the disorder and, therefore, is more attentive in observing his/her child, which consequently helps early diagnosis, in addition to a parent's poor memory causing difficulty in determining the date at which the disorder was diagnosed (Goossens et al., 2001); 4. The "cohort effect"; it was reported that the prevalence of BP increased during the 20th century (Gershon et al. 1987). It is stated that especially the first three are considered having confounding effects on the studies, which investigate anticipation (Goossens et al. 2001). When these studies were designed, different combinations of pairs from 2 generations of the family tree should have been formed instead of working only with mothers, fathers, and offspring (McInnis et al. 1993; Macedo et al. 1999). Despite the influence of confounding factors that can be found with every sampling technique, findings should be tested to verify that they are actually measuring the outcome of this phenomenon.

Anticipation in BP was confirmed in the present study based on the findings of earlier age at onset and more frequent episodes in S2. Additionally, the results provide important insights related to the clinical follow-up of the affected offspring of parents diagnosed with BP. The results of this study led us to suggest a theoretical question as well; which one is an indicator of the clinical anticipation, which one is an indicator of the characteristic of the prognosis, and which one is an indicator of the disorder severity? In order to understand whether a clinical variable is the effect of genetic anticipation or not, its relationship with respect to 2 generations and to other variables that influence the severity and prognosis of BP should be explored (Alda et al. 2000).

Groups created based on age at onset are not completely defined because an absolute age at onset cannot be determined retrospectively. In previous studies age at onset has been considered as the age at first hospitalization or the first presentation for treatment (Tsuang 1967); however, with the improvement of diagnostic criteria, age at onset has been acknowledged as the age at the time the first episode that can be identified based on the criteria of a mood episode occurs (Geller et al. 2004). The age at onset has been considered 12 years and below for cases with childhood onset, 13-18 years for cases with adolescent onset, 19-29 years for cases with early adulthood onset, and 30 years and above for cases with late adulthood onset (Leverich et al. 2007).

One study reported that when the first generation was diagnosed with BP, the probability that their second generation would exhibit the disorder was 50%, and the mean age at onset was 25 years (Macedo et al. 1999). It was reported that BP appears in the second generation 8.9-13.5 years earlier, on average (McInnis et al. 1993). Another study revealed that the rate of early onset in second-generation BP cases was 79%-83% (Macedo et al. 1999). In our sample the disorder began 10.2 ± 6.0 years earlier in the second generation. This finding is consistent with previous findings, though on the other hand, the age at onset in the second generation observed in the present study was below the mean reported in previous studies (19.3 ± 4.2 years). In addition, the age at onset

in the first generation was determined as early adulthood (29.5 ± 10.7 years). The rate of early onset was 42% in the second generation, whereas it was 18% in the first generation; therefore, a negative prognosis was not only related to early age at onset, but might have been affected by other factors as well. In fact, the prognosis of BP is affected by age at onset (Kendell 1989); nonetheless, a BP type, which is homogenous in terms of age at onset, cannot be defined (Leboyer et al. 2005). In our sample there was a linear relationship between age at onset in the first and second generations. This finding might suggest genetic anticipation, a hereditary factor. Another variable that was related to age at onset was the frequency of episodes.

It has been shown that the frequency of episodes tends to increase in consecutive generations diagnosed with BP (McInnis et al. 1993). Our study supports this finding as well; however, it is not clear at this point if the frequency of episodes is considered an indicator of phenotype or a characteristic related to severity of the disorder. There was a linear relationship between the frequency of episodes of the s1 and s2 cases. The same linear relationship existed for the frequency of manic episodes. Episode frequency, an indicator of the severity of the disorder, was not related to the other variables that might indicate the severity of the disorder (e.g. presence of a shift in the polarity of the episode, episodes with psychotic features, suicide attempts), except age at onset.

The number of episodes with psychotic features was similar in the s1 and s2 cases; however, it was observed that 72.7% of the parents that had episodes with psychotic features had offspring that also had episodes with psychotic features. Additionally, among the offspring of parents that didn't have episodes with psychotic features, 35% had episodes with psychotic features. Studies that explored the relationship between episodes with psychotic features and early onset considered those episodes an indicator of disorder severity, and early onset indicated that more episodes with psychotic features are observed in cases with early onset (Apter et al. 1988; McGlashan 1988; Carlson et al. 2000). In contrast, there are studies which do not support these results (Erkıran et al. 2003). In the present study, when the cases were grouped based on early onset, the cases that had episodes with psychotic features and those that didn't were highly matched. As opposed to studies reporting no difference between cases that had episodes with psychotic features and those that didn't, in terms of the disorder severity (Potash et al. 2001), a study by Bora and colleagues (2007) reported that cognitive functioning in cases that had episodes with psychotic features were distorted, even during periods of well being. In the present study episodes with psychotic features were interpreted as a factor that both indicated disorder severity and contributed to negative prognoses. Another variable in the index, which is related to psychotic features, is the frequency of episodes (Lange and McInnis 2002). The present study's analysis didn't reveal such a finding. Considering its relationship to early age at onset and high rates of occurrence in both generations (parent-child pairs), it is possible to assert that episodes with psychotic features were not only related to disorder severity or predictive of negative prognoses, but were also a hereditary characteristic of the disorder, occurred because of anticipation, or contributed to anticipation.

No difference was observed between s1 and s2 in terms of the type of first episode; however, mixed episodes didn't occur in s1, but did in 3.2% of s2. It is known that mixed episodes, which appear mostly in early onset cases (Krasa and Tolbert 1994) and in cases with a family history (Lish et al. 1994), are related to a negative prognosis (Moorhead and Scott 2000). The presence of shifts in the polarity of the episode and suicide attempts, and their frequency were similar in the s1 and s2 BP cases. There wasn't a relationship between s1 and s2 in terms of shifts of episodes or suicide attempts. It was shown that the cases that attempted suicide had longer disease duration and more episodes. This finding was considered to indicate the relationship between attempted suicide and the severity of the disorder. Shifts were not related to the other variables of severity.

In accordance with previous research, the frequency of hospitalization and duration of disorder were both higher in the s2 cases diagnosed with BP (Erkıran et al. 2003). These 2 variables can be considered indicators of a negative prognosis in the second generation; nevertheless, the results didn't reveal any relationship between s1 and s2 in terms of these variables.

One of the variables, which indicate the severity of BP, is response to mood stabilizers (Strober et al. 1998). The age at first use of mood stabilizers was earlier in s2 then in s1. The number of suicide attempts and hospitalizations, before and after the use of mood stabilizers, was similar in both generations; however, the difference between the number of suicide attempts and hospitalizations before and after the use of mood stabilizers was greater in s1. If these 2 variables are regarded as indicators of the response to medication, then it is possible to state that this response was better in s1.

BP is a disorder that results in social dysfunction be-

cause of its long-lasting nature and a variety of reasons (McElroy et al. 1997). Higher rates of an inability to work and divorce are observed in adult BP patients with early onset compared to those with adult onset. Comparison of such data in the present study would have created erroneous results because of the age difference between the 2 generations. The increase in the education year that was observed among the female participants in s2 is explained by the improvements to educational services that have been made in Turkey.

According to the results of the present study, genetic anticipation in BP was confirmed based on the fact that the age at onset was earlier and the frequency of episodes was higher in s2. In terms of the types of episodes, as an effect of anticipation the frequency of manic episodes increased in s2. Additionally, episodes with psychotic features are proposed as a variable of anticipation. The present study's findings indicate that when BP appears in the offspring of parents diagnosed with BP, the symptoms are going to be more severe, including duration of disorder, and frequency of hospitalization and suicide attempts. Mixed episodes, as observed in s2, as well as a family history, were factors indicative of a negative prognosis, similar to poor response to mood stabilizers.

Additional clinical studies are needed in order to understand the phenomenology of genetic anticipation, and further genetics research is needed to explore BP's hereditary nature.

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